EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2022
EMA/CHMP/205556/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Adjupanrix

International non-proprietary name: pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)

Procedure No. EMEA/H/C/001206/II/0074

Note

Variation 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
ATP	According-to-protocol
BF	Booster factor
BI	Boostability index
CBER	Center for Biologics Evaluation and Research (US FDA)
CHMP	Committee for Medicinal Products for Human Use (EMA)
CI	Confidence Interval
CSR	Clinical Study Report
EBV	Epstein-Barr virus
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GMT	Geometric Mean Titre
GSK	GlaxoSmithKline Biologicals SA
HA	Hemagglutinin
HCRT	Hypocretin
HI	Hemagglutination inhibition
IABS	International Alliance for Biological Standardization
LL	Lower limit
MAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MGI	Mean geometric increase
MN	Microneutralization
NIBSC	National Institute for Biological Standards and Control
PBRER	Periodic Benefit Risk Evaluation Report
PDCO	Paediatric Committee
pIMD	potential Immune-Mediated Disease
PIP	Paediatric Investigational Plan
PSP	Paediatric Study Plan (US)
RMP	Risk Management Plan
SAE	Serious adverse event
SCF	Seroconversion factor
SCR	Seroconversion rate
SPR	Seroprotection rate
TVC	Total Vaccinated Cohort
U0	Day 0 in Year 2 for Placebo group who received placebo during Year 1 and Q-PAN H5N1 vaccine at the beginning of Year 2 (Study Q-PAN H5N1-021)
VRR	Vaccine Response Rate
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, GlaxoSmithkline Biologicals SA submitted to the European Medicines Agency on 2 April 2021 an application for a variation.

The following variation was requested:

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

Extension of indication to include use in children from 6 months to <18 years for Adjupanrix based on the results of the studies: study H5N1-013, a phase II, non-randomized, open-label study to evaluate the safety and immunogenicity in children aged 6 to 35 months and study H5N1-032, a phase III, randomized, open, active-controlled study to evaluate the safety and immunogenicity in children aged 3 to 17 years. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 6.6 of the SmPC are updated and the Package Leaflet is updated in accordance. Further, the MAH proposed to update section 4.4 with information on sodium and potassium content in line with the excipients guideline, as well as to add wording on traceability. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.2, the MAH performed minor editorial changes and removed information related to the withdrawn of the Prepandrix marketing authorisation. Version 13 of the RMP has also been submitted.

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

Information on paediatric requirements

Not applicable.

Article 8 does not apply as the authorised medicinal product is not protected by a supplementary protection certificate under Regulation (EC) No 469/2009 or by a patent which qualifies for the granting of the supplementary protection.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did seek Scientific advice at the CHMP in 2018 EMA/CHMP/SAWP/838326/2018 and Procedure No.: EMEA/H/SA/3998/1/2018/PED/II for Pandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted) (EU/1/09/578/001, Adjupanrix).

1.2. Steps taken for the assessment of the product

The CHMP and PRAC Rapporteurs appointed were:

CHMP Rapporteur: Johann Lodewijk Hillege PRAC Rapporteur: Menno van der Elst

Timetable	Actual dates
Submission date	2 April 2021
Start of procedure:	24 April 2021
CHMP Rapporteur Assessment Report	17 June 2021
PRAC Rapporteur Assessment Report	17 June 2021
PRAC Outcome	8 July 2021
CHMP members comments	12 July 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 July 2021
Request for supplementary information (RSI)	22 July 2021
CHMP Rapporteur Assessment Report	18 November 2021
PRAC Rapporteur Assessment Report	18 November 2021
Updated PRAC Rapporteur Assessment Report	30 November 2021
PRAC Outcome	2 December 2021
CHMP members comments	06 December 2021
Updated CHMP Rapporteur Assessment Report	9 December 2021
Request for supplementary information (RSI)	16 December 2021
CHMP Rapporteur Assessment Report	22 March 2022
PRAC Rapporteur Assessment Report	n/a
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	07 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur Assessment Report	13 April 2022
Opinion	22 April 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Adjupanrix is a split virion, inactivated, AS03-adjuvanted H5N1 pandemic influenza vaccine. It is currently indicated for intramuscular use in adults ≥18 years of age and intended for prophylaxis of influenza in the case of an officially declared pandemic.

Disease or condition

Influenza viruses are enveloped negative-strand RNA viruses. The RNA genome of influenza viruses consists of seven to eight gene segments, each coding for at least one protein. Reassortment, the process of influenza viruses combining and rearranging gene segments, can occur when two differing influenza viruses, for example an animal and human subtype, co-infect a cell. This process results in antigenic shift which causes major changes in the influenza type A haemagglutinin (HA) antigen. This in turn can, in rare events, result in strains capable of causing large regional or global pandemic outbreaks.

An influenza pandemic is a global outbreak of influenza disease that occurs when a type A influenza strain to which most or all humans are immunologically naïve emerges to cause clinically apparent illness, and then spreads easily from person to person worldwide. 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

The MAH proposed the following indication:

Adjupanrix is indicated in adults and children from 6 months of age for prophylaxis of influenza in an officially declared pandemic situation.

The use of Adjupanrix should be in accordance with official guidance.

The application was based on safety and immunogenicity data from the one Phase 3 trial, one single-arm Phase 2 trial, one Phase 2 dose finding study and one additional supportive study.

During the procedure it was decided that section 4.1 should not be amended, as vaccines registered through the 'mock-up' vaccine procedure prior the authorisation of a 'pandemic' variation are not

indicated in a prepandemic setting (the indication has been restricted to the use during a pandemic phase). When a pandemic situation is duly recognised by the WHO or the Union, the MAH should submit a variation to include the declared pandemic strain in the pandemic vaccine.

Section 4.1 has therefore not been amended and reads:

Prophylaxis of influenza in an officially declared pandemic situation.

Adjupanrix should be used in accordance with official guidance

Epidemiology

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

Influenza viruses are classified into types A, B and C on the basis of their core proteins. 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

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

Vaccination is the most effective way of preventing and controlling the spread of influenza in the human population. GlaxoSmithKline Biologicals (GSK) has developed H5N1 pandemic influenza vaccines. GSK manufactures split virion seasonal influenza vaccines at two GSK facilities, one in Dresden Germany and the other in Québec Canada (the subsequent vaccines are indicated with the prefix D and Q respectively). The pandemic vaccine H5N1 split virus antigens are produced using a process similar to that used for the production of seasonal influenza vaccine, and are adjuvanted with GSK's AS03 adjuvant system.

2.1.2. About the product

Adjupanrix is a split virion, inactivated, AS03-adjuvanted H5N1 pandemic influenza vaccine. The influenza strain contained in the vaccine is a strain derived from the highly pathogenic avian influenza strain A/Vietnam/1194/2004. This vaccine strain A was developed by a World Health Organization (WHO) collaborating centre [National Institute for Biological Standards and Control (NIBSC), UK].

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

Development programme

The clinical development program for Adjupanrix to support licensure in children 6 months of age and older consists of 1 Phase 3 study, D-PAN H5N1-032, 1 Phase 2 single arm study, D-PAN H5N1-013, the Phase 2 dose-finding study Q-PAN H5N1-023 and the supportive study Q-PAN H5N1-021.

Compliance with CHMP guidance

The most relevant CHMP guidelines applied:

"Guideline on Influenza vaccines; Non-clinical and Clinical Module" (CPMP/VWP/457259/2014)

Scientific Advice

During the course of development, the sponsor sought regulatory and scientific advice from EMA's

Committee for Medicinal Products for Human Use (CHMP) once. This advice is detailed below:

EMEA/H/SA/3998/1/2018/PED/II. The MAH sought advice on the clinical development with regards to the use of half the adult dose in the paediatric population and adequacy of the available data package to support an extension of the indication. CHMP agreed that the clinical data package would suffice for the proposed extension, and it was agreed that study Q-PAN H5N1-024 was not required. In addition, the accumulated immunogenicity data from a combination of D-Pan and Q-Pan studies do support selection of the 1.9µg/AS03$_B$ (i.e. half the adult dose) from the age of 6 months but also suggest that one quarter of the adult dose may suffice and may be safer in children aged < 36 months. Therefore, subject to a full assessment of the data at the time of filing, it may be that the CHMP concludes that a quarter of the adult dose is suitable between the ages of 6-35 months and half the adult dose from 3-17 years. Finally, the application dossier should contain a full review of all the evidence that has emerged from investigations into the possible mechanism(s) underlying the association between narcolepsy and D-Pan-H1N1.

Conclusion of VWP based on the review of the data in connection to the scientific advice

The AS03 adjuvant is linked to substantial local reactogenicity and fever even in adults, which increases with decreasing age. The VWP accepted that the data could support use of half the adult dose down to 3 years of age. In infants and toddler from 6 months to 36 months of age the VWP agreed with the co-ordinators that a quarter adult dose may be preferable since it seemed sufficiently immunogenic (including in cross-immunogenicity studies) and had a slightly better safety profile than the half adult dose.

2.1.4. General comments on compliance with GCP

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

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

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application.

2.3. Clinical aspects

2.3.1. Introduction

Overview of data supporting the posology

- Tabular overview of clinical studies

Study ID **study location**	**Design**	**Population and Schedule of vaccination**	**Study population per group**	**Primary Immunogenicity Objective**
D-PAN-H5N1-013 (109825) Australia / Singapore	Phase II, open-label, non-randomised, single arm Heterologous prime-boost schedule	Unprimed children 6 to 35 Mo of age Primary vaccination: 2 doses (Day 0, 21) of 1.9 μg HA (A/Indonesia strain) + $AS03_B$ Booster vaccination: 1 dose (Day 182) of 1.9 μg HA (A/Turkey strain) + $AS03_B$	113	To assess whether a heterologous booster dose of 1.9 μg A/Turkey (H5N1) haemagglutinin (HA) with $AS03_B$ given 6 months following a 2-dose primary vaccination series with 1.9 μg A/Indonesia (H5N1) HA with $AS03_B$ elicits an antibody response that meets CHMP guidance targets for pre-pandemic vaccine seroconversion rate (SCR), seroprotection rate (SPR) and mean geometric increase (MGI) based on haemagglutination inhibition (HI) responses to A/Turkey (H5N1) 10 days following booster vaccination
D-PAN-H5N1-032 (115115) Philippines	Phase III open-label, active-controlled, randomised study Heterologous prime-boost schedule	Unprimed children 3 to 17 years of age Primary vaccination: 2 doses (Day 0, 21) of 1.9 μg HA (A/Indonesia strain) + $AS03_B$ Booster vaccination: 1 dose (Day 182) of 1.9 μg HA (A/Turkey strain) + $AS03_B$ Active control: Hepatitis A vaccine (Havrix)	H5N1-H5N1: H5N1 primary and booster vaccination N = 156 H5N1-Havrix: H5N1 primary vaccination, Havrix booster N = 156 Havrix – H5N1 Havrix primary vaccination, H5N1 booster N= 104 Havrix – Havrix Havrix primary vaccination and booster N = 104	To assess the superiority of the HI antibody response against A/Turkey (H5N1) 10 days following H5N1 vaccination on Day 182 (1.9 μg A/Turkey [H5N1] HA antigen adjuvanted with $AS03_B$) in subjects previously primed with 2 doses of heterologous A/Indonesia (H5N1) vaccine versus non primed subjects
Q-PAN H5N1-023 (116938) Thailand / Taiwan	Phase II, randomised, controlled, observer-blind study Homologous prime-boost schedule		190_B (1.9 μg HA + $AS03_B$) - reference group N = 38 090_C (0.9 μg HA + $AS03_C$) N = 37	To assess the performance of alternative dosing regimens for primary immunisation with Q-Pan H5N1 vaccine using an immunogenicity-fever index that considers immunogenicity by HI assay /

Study ID **study location**	**Design**	**Population and Schedule of vaccination**	**Study population per group**	**Primary Immunogenicity Objective**
		Unprimed children 6 to <36 Mo of age Primary vaccination: 2 doses (Day 0, 21) of AS03 adjuvanted HA (A/Indonesia strain) - varying antigen and adjuvant dose combinations Booster vaccination: 1 dose (Day 385) of 3.75 µg HA (A/Indonesia strain) (unadjuvanted)	190_C (1.9 µg HA + $AS03_C$) N = 38 375_C (3.75 µg HA + $AS03_C$) N = 37 375_D (3.75 µg HA + $AS03_D$) N = 35	microneutralization (MN) assay 21 days after the second priming dose and fever scores after the first and second priming doses. To assess the performance of dosing regimens for booster immunisation with Q-Pan H5N1 vaccine considering immune response by HI / MN assay 7 days after a 12-month booster dose of 3.75 µg HA Q-Pan H5N1 unadjuvanted antigen
Q-PAN H5N1-021 (114464) United States / Canada / Thailand	Phase II/III, randomised, controlled study The study included 2 parts: *Study Year 1* – an observer-blind, treatment arm and a placebo-controlled arm 2 primary doses at Day 0, 21 of 1.9 µg of HA with $AS03_B$ / Placebo on Days 0, 21 *Study Year 2* – open-label, single- arm, single cross-over 2 doses of 1.9 µg of HA with $AS03_B$ 21 days apart administered to subjects that received placebo during Year 1	Unprimed children 6Mo to <18 years of age at first vaccination Year 1 vaccination: 2 doses (Day 0, 21) of 1.9 µg Q-Pan H5N1 (A/Indonesia) + $AS03_B$ or Placebo (saline) Year 2 vaccination: 2 doses (Day 0, 21) of AS03 adjuvanted HA (Q-Pan A/Indonesia 15 µg/mL) for subjects who received Placebo in Year 1	Year 1: Q-Pan N = 607 Year 1: Placebo N = 231 Year 2: Placebo group during Year 1 who received Q-Pan vaccine during Year 2 N = 155	To assess whether two doses of H5N1 antigen in association with AS03 elicited an immune response, measured by post-immunisation vaccine-homologous virus HI titres, that met or exceeded CBER/CHMP young adult targets for proportion of subjects attaining post-immunisation reciprocal HI titres ≥40 against A/Indonesia.

CBER = Center for Biologics Evaluation and Research (US FDA); CHMP = Committee for Medicinal Products for Human Use (EMA); HA = Haemagglutinin; HI = Haemagglutination inhibition; MGI = Mean geometric increase; MN = microneutralization; SPR = Seroprotection rate.

$AS03_B$: contains 5.93 mg of tocopherol; $AS03_C$: contains 2.965 mg of tocopherol; $AS03_D$: contains 1.4825 mg of tocopherol

The studies were performed in compliance with the paediatric investigation plan (PIP, EMEA-000160-PIP01-07-M05).

The Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014) is applicable for this submission.

2.3.2. Pharmacodynamics

Refer to clinical efficacy section below for immunogenicity data

2.4. Clinical efficacy

The overall objective of the clinical development program was to evaluate the safety and immunogenicity of Adjupanrix administered as a 2-dose regimen in children aged 6 months to <18 years of age.

2.4.1. Dose response study(ies)

With the approval of D-Pan H5N1 products by the European Commission, GSK committed to conduct several paediatric studies using half the adult dose (containing 1.9 µg H5N1 HA antigen adjuvanted with $AS03_B$ [containing 5.93 mg of tocopherol]) as part of the initially agreed D-Pan H5N1 PIP (PIP-EMEA-000160-PIP01-M01). In response to concerns raised by the Paediatric Committee (PDCO) during the review rounds for the PIP on the lack of traditional dose-ranging studies (EMA/PDCO summary report EMA/737469/2010) and to align the paediatric development plans for D-Pan H5N1 in the EU with those proposed for Q-Pan H5N1 in the US, GSK added two additional paediatric studies to the D-Pan H5N1 PIP (EMA decision EMA/480049/2012):.

- Q-Pan-H5N1-023, a dose-ranging study in children 6 months to less than 36 months of age,
- Q-Pan H5N1-024, a dose-confirmatory study in children 6 months to less than 18 years of age.

The addition of both studies was endorsed by PDCO (EMA decision EMA/597267/2013).

Based on CHMP advice (EMEA/H/SA/3998/1/2018/PEDII), study Q-PAN H5N1-024 was cancelled. There was sufficient data available to describe the safety and immunogenicity of half the adult dose from 3 years to 17 years (study D-H5N1-009 [previously assessed not included in current submission], D-PAN H5N1-032 and Q-PAN H5N1-021). These data are considered to support this dose regimen, as immunogenicity was good and the safety profile of a half adult dose is likely better than that of a full adult dose. In children aged 6 months to 36 months, full assessment of the data at time of filing was considered required to conclude on the best dose in this age group. However, the results from study Q-PAN H5N1-023 was considered sufficient to be able to make this assessment, and therefore study Q-PAN H5N1-024 was not considered necessary.

Study Q-PAN H5N1-023

Study Design: Study Q-PAN H5N1-023 was a Phase II, observer-blind, randomized, dose-ranging, multi-center, multi-country study to evaluate safety, reactogenicity and immunogenicity of alternative

dosing regimens with adjuvanted Q-Pan H5N1 vaccine given as a 2-dose primary series in children 6 to less than 36 months of age. All subjects received 3.75 µg HA, unadjuvanted H5N1 vaccine as a booster dose at Day 385. The vaccines were administered intramuscularly in the left anterolateral thigh (Days 0 and 385) or right anterolateral thigh (Day 21).

Treatment: Participants in Study Q-PAN H5N1-023 were randomly assigned to one of 5 study groups in a 1:1:1:1:1 ratio. Subjects received 2 priming doses of adjuvanted H5N1 vaccine (the first at the Day 0 visit; the second at the Day 21 visit) followed by a single dose of unadjuvanted H5N1 vaccine at the Day 385 visit.

The treatment groups were as follows:

- 190_B: 1.9 µg H5N1 HA antigen adjuvanted with $AS03_B$ (containing 5.93 mg of tocopherol)
- 090_C: 0.9 µg H5N1 HA antigen adjuvanted with $AS03_C$ (containing 2.965 mg of tocopherol)
- 190_C: 1.9 µg H5N1 HA antigen adjuvanted with $AS03_C$ (containing 2.965 mg of tocopherol)
- 375_C: 3.75 µg H5N1 HA antigen adjuvanted with $AS03_C$ (containing 2.965 mg of tocopherol)
- 375_D: 3.75 µg H5N1 HA antigen adjuvanted with $AS03_D$ (containing 1.4825 mg of tocopherol)

Study Participants: The study population consisted of healthy male or female children 6 months to less than 36 months old at time of first study vaccination. In total 185 subjects were enrolled. Duration of the study for each subject was approximately 415 days after the first dose of vaccine.

Objectives: The co-primary objectives of the study were to assess the performance of alternative dosing regimens for primary immunization with Q-Pan H5N1 vaccine using an immunogenicity-fever index that considers immunogenicity by HI assay / MN assay 21 days after the second priming dose and fever scores after the first and second priming doses, and to assess the performance of dosing regimens for booster immunization with Q-Pan H5N1 vaccine considering immune response by HI / MN assay 7 days after a 12-month booster dose of 3.75 µg HA Q-Pan H5N1 unadjuvanted antigen.

The secondary objectives of the study were 1) to assess HI immune response to the vaccine homologous virus 21 days after the second dose of each priming regimen, 2) to assess the performance of alternative dosing regimens for primary immunization with Q-Pan H5N1 vaccine considering persistence of immune response by HI and MN assay at Day 385 in terms of persistence index, 3) to assess the performance of the H5N1 vaccine regimens in terms of vaccine homologous and heterologous HI and MN antibody titres on Days 0, 42, 385 and 392, 4) to assess vaccine induced cell-mediated immune response (frequency of CD3+/CD4+/CD8+ T-cells) on Days 0, 42, 385 and 392. and 5) to describe the reactogenicity and safety of the different priming regimens and the safety of the unadjuvanted booster dose.

Demographics: Table 1 presents the demographic characteristics. The mean age of the subjects at vaccination Dose 1 ranged from 20.3 months of age (375_D group) to 22.6 months of age (090_C group). There was an unequal distribution of males and females across groups: fewer females were observed in the 190_B, 090_C and 190_C groups. Overall, most subjects were of East Asian and South East Asian heritages.

Table 1 Summary of demographic characteristics – Total vaccinated cohort (Q-PAN H5N1-023).

		190_B N = 38		090_C N = 37		190_C N = 38		375_C N = 37		375_D N = 35		Total N = 185	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (months) at vaccination dose: 1	Mean	21.9	-	22.6	-	21.6	-	20.8	-	20.3	-	21.4	-
	SD	8.0	-	8.1	-	9.2	-	8.3	-	7.8	-	8.2	-
	Median	20.5	-	24.0	-	21.0	-	21.0	-	20.0	-	21.0	-
	Minimum	8	-	8	-	7	-	6	-	6	-	6	-
	Maximum	35	-	34	-	35	-	35	-	34	-	35	-
Gender	Female	17	44.7	14	37.8	16	42.1	23	62.2	18	51.4	88	47.6
	Male	21	55.3	23	62.2	22	57.9	14	37.8	17	48.6	97	52.4
Geographic Ancestry	African Heritage / African American	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	American Indian or Alaskan Native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - Central/South Asian Heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - East Asian Heritage	21	55.3	21	56.8	22	57.9	21	56.8	19	54.3	104	56.2
	Asian - Japanese Heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - South East Asian Heritage	16	42.1	16	43.2	16	42.1	16	43.2	16	45.7	80	43.2
	Native Hawaiian or Other Pacific Islander	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Arabic / North African Heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - Caucasian / European Heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Other	1	2.6	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5

190_B = 1.9 mcg H5N1 HA adjuvanted with $AS03_B$
090_C = 0.9 mcg H5N1 HA adjuvanted with $AS03_C$
190_C = 1.9 mcg H5N1 HA adjuvanted with $AS03_C$
375_C = 3.75 mcg H5N1 HA adjuvanted with $AS03_C$
375_D = 3.75 mcg H5N1 HA adjuvanted with $AS03_D$
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

Results:

Primary Endpoints

Table 2 presents the observed immunogenicity-fever indices (0 = not desirable, 1 = highly desirable) for the 5 groups.

Table 2 Immunogenicity-fever indices based on HI and Mn assay (Q-PAN H5N1-023)

Group	HI			MN		
	D_{GMT}	**Fever index**	**Immunogenicity-fever index**	**D_{GMT}**	**Fever index**	**Immunogenicity-fever index**
190_B	1.00	0.84	0.92	1.00	0.84	0.92
090_C	0.54	0.91	0.70	0.56	0.91	0.72
190_C	0.57	0.95	0.74	0.57	0.95	0.74
375_C	0.40	0.93	0.61	0.32	0.93	0.55
375_D	0.34	0.94	0.57	0.33	0.94	0.56

An adjusted GMT was constructed, using ANCOVA which was fitted on the log10 transformed HI and MN antibody responses at Day 42, with the vaccine group as a fixed independent variable, adjusted by the log10 transformed pre-vaccination titer and age. The use of pre-vaccination titre and age was not well understood as all children were naïve for H5N1 based on exclusion criteria and pre-vaccination GMTs and randomisation included a minimization procedure accounting for age. In addition, only using body temperature measurements performed from Days 0-2 after each dose to construct the fever index was not understood. Solicited symptoms, such as fever, are collected for 7 days post-vaccination.

The usefulness of this immunogenicity-fever-index for both the HI as well as the MN antibodies is limited.

The totality of all immunogenicity and safety results have been evaluated to determine which dose is considered appropriate for children. Assessment of the totality of evidence have been based on the immunogenicity aspects mentioned in the Guideline on Influenza Vaccines. Please see section on secondary endpoints.

The mean geometric increase (MGI) for HI and MN antibodies at Day 392 (12 days post booster dose) relative to Day 385 (pre-booster dose) is presented in Table 3.

The highest MGI for HI antibodies at Day 392 relative to Day 385 was observed in 090_C group (6.6) followed by 190_B (4.9) for the homologous strain with the GMT values being 98.1 and 476.2 for 190_B group and 61.5 and 407.6 for 090_C group, at Day 385 and Day 392, respectively.

The highest MGI for MN antibodies at Day 392 relative to Day 385 was observed in 090_C group (4.8) followed by 190_B (4.3) for the homologous strain with the GMT values being 250.3 and 1085.0 for 190_B group and 203.6 and 969.1 for 090_C group, at Day 385 and Day 392, respectively.

Table 3 Mean geometric increase (MGI) for vaccine homologous and heterologous for HI antibodies at Day 392 relative to Day 385 (Q-PAN H5N1-023)

Antibody	Group	HI				MN			
		N	**GMT D385**	**GMT D392**	**GMT ratio (95% CI)**	**N**	**GMT D385**	**GMT D392**	**GMT ratio (95% CI)**
Flu A/ Indonesia/5/ 2005	190_B	34	98.1	476.2	4.9 (3.8-6.3)	34	250.3	1085.0	4.3 (3.3 – 5.7)
	090_C	33	61.5	407.6	6.6 (4.9 – 9.0)	33	203.6	969.1	4.8 (3.4 – 6.6)
	190_C	37	72.1	305.4	4.2 (3.4 – 5.3)	37	213.8	674.2	3.2 (2.3 – 4.3)
	375_C	31	79.1	286.2	3.6 (2.9 – 4.5)	31	247.2	681.0	2.8 (2.0 – 3.8)
	375_D	32	59.6	201.0	3.4 (2.8 – 4.1)	32	198.5	489.6	2.5 (2.0 – 3.0)
Flu A/duck/ Bangladesh/ 19097/2013	190_B	33	24.1	125.6	5.2 (3.9 -7.0)	34	102.0	262.5	2.6 (1.9 – 3.5)
	090_C	31	21.8	130.8	6.0 (4.2 – 8.5)	33	79.2	240.9	3.0 (2.3 – 4.1)
	190_C	33	18.1	71.9	4.0 (3.0 – 5.2)	37	76.3	194.8	2.6 (2.0 – 3.2)

Antibody	Group	HI				MN			
		N	GMT D385	GMT D392	GMT ratio (95% CI)	N	GMT D385	GMT D392	GMT ratio (95% CI)
	375_C	31	20.9	70.7	3.4 (2.7 – 4.2)	30	100.7	210.9	2.1 (1.6 – 2.8)
	375_D	30	19.5	53.3	2.7 (2.3 – 3.3)	32	63.0	174.5	2.8 (2.2 – 3.5)
Flu A/Vietnam/1194/2004	190_B	33	26.8	133.9	5.0 (3.7 – 6.8)	34	113.0	323.4	2.9 (2.2 – 3.8)
	090_C	31	22.6	141.4	6.3 (4.5 – 8.7)	33	88.0	256.6	2.9 (2.1 – 4.1)
	190_C	33	18.7	71.2	3.8 (3.0 – 4.8)	37	80.7	235.3	2.9 (2.2 – 3.8)
	375_C	31	21.3	76.5	3.6 (2.9 – 4.5)	31	103.6	270.4	2.6 (2.1 – 3.3)
	375_D	30	20.6	57.2	2.8 (2.2 - 3.4)	32	89.0	216.5	2.4 (1.9 – 3.1
Flu A/ gyrfalcon/ Washington/ 41088-6/ 2014	190_B	33	9.4	42.6	4.5 (3.2 – 6.5)				
	090_C	31	8.1	39.5	4.9 (3.5 – 6.9)				
	190_C	33	7.5	22.9	3.1 (2.3 – 4.2)				
	375_C	31	7.7	22.6	2.9 (2.2 – 3.8)				
	375_D	30	7.2	17.4	2.4 (2.0 – 3.0)				

GMT = geometric mean antibody titer
N = Number of subjects with available results at the two considered time points
95% CI = 95% confidence interval; LL = lower limit, UL = upper limit

At 12 months after the primary vaccination regimen, GMTs for both HI and MN antibodies were numerically higher in group 190-B (half adult dose) compared to the other groups. The homologous GMTs for both HI and MN antibodies were higher in the 190_C group compared to the 090_C group (quarter adult dose), while heterologous GMTs for both HI and MN antibodies were higher in the 090_C group compared to the 190_C group. Lowest responses were seen for groups 375_C and 375_D.

At D392, 10 days after the booster with unadjuvanted A/Indonesia H5N1 vaccine, GMTs for both HI and MN antibodies were highest in group 190-B (half adult dose) followed by group 090_C. However, group 090-C showed the highest GMT ratio (GMT D392/D385) for both HI and MN antibodies, indicating that the boost induced the highest response in this group. Again lowest responses were seen for 375_C and 375_D.

With respect to ability to induce an immune response by the unadjuvanted booster vaccine 1 year after the primary vaccination, group 090_C was able to induced the highest response as measured by GMT ratio followed by 190_B for both vaccine-homologous and -heterologous HI and MN antibodies.

Secondary Endpoints

HI antibodies

A summary of vaccine homologous and heterologous HI antibody parameters, GMT, seroconversion rate (SCR) and MGI for homologous and a selected heterologous antibody (Flu A/Vietnam/1194/2004 H5N1) are presented in Table 4.

At Day 42, all formulations elicited a strong homologous H5N1 immune response by HI assay with SCR (100%), and MGI (range: 101.0 [375_D group] – 219.5 [190_B group]). In addition, non-overlapping CIs for the HI GMTs were observed between the reference group 190_B and the groups 375_C and 375_D, whereas for the 2 other formulations (090_C or 190_C), a trend for a higher immune response in the group 190_B was observed.

At Day 385, one year after the primary vaccination, the vaccine-homologous HI antibody titres declined for all formulations at Day 385. Antibody responses were sustained with seroconversion rate above 40% for all formulations. The reference group, 190_B, had the highest SCR of 97.1% (95% CI: 84.7, 99.9) among all groups.

At Day 385, the MGIs (Day 385/Day 0) were 19.2-fold, 12.0-fold, 14.0-fold, 15.8-fold and 10.5-fold higher_ than baseline for 190_B, 090_C, 190_C, 375_C and 375_D groups, respectively. The 190_B group showed a trend of higher GMTs at Day 385 and Day 392 among the formulations studied

At Day 392, 7 days after antigen challenge (unadjuvanted booster), the seroconversion rate was 100% for all formulations. The MGI (Day 392/Day 0) were 93.3-fold, 79.8-fold, 59.4-fold, 57.2-fold and 35.3-fold higher than baseline for 190_B, 090_C, 190_C, 375_C and 375_D groups, respectively).

In terms of cross-reactivity against heterologous H5 influenza virus isolates, the highest HI antibody titres were observed against the Flu A/duck/Bangladesh/19097/2013 (H5N1) isolate, the clade of which is closest to the vaccine strain, followed by the A/Vietnam/1194/2004 (H5N1) isolate. The 190_B group showed a trend of higher cross reactivity against 3 heterologous strains than the other groups.

Table 4 Summary of vaccine homologous and heterologous HI antibody parameters (GMT, SCR and MGI) – Adapted ATP cohort for immunogenicity (Q-PAN H5N1-023)

Antibody	**Group**	**Day**	**N**	**GMT (95% CI)**	**N'**	**SCR**		**MGI (95% CI)**
						n	**% (95% CI)**	
Flu A/ Indonesia/ 5/2005	190_B	0	36	5.1 (4.9–5.3)				
		42	36	1118.6 (884.4–1414.9)	36	36	100 (90.3–100)	219.5 (172.6–279.0)
		385	34	98.1 (76.7-125.4)	34	33	97.1 (84.7-99.9)	19.2 (14.8-24.9)
		392	34	476.2 (348.4-650.9)	34	34	100 (89.7-100)	93.3 (67.9-128.3)
	090_C	0	33	5.1 (4.9-5.3)				
		42	33	858.8 (659.2-1118.8)	33	33	100 (89.4-100)	168.2 (127.4-222.0)
		385	33	61.5 (47.1-80.3)	33	26	78.8 (61.1-91.0)	12.0 (9.2.-15.8)
		392	33	407.6 (315.0-527.4)	33	33	100 (89.4-100)	79.8 (61.5-103.5)
	190_C	0	37	5.1 (4.9-5.4)				
		42	37	913.6 (672.6-1241.1)	37	37	100 (90.5-100)	177.7 (131.5-240.1)
		385	37	72.1 (51.6-100.7)	37	28	75.7 (58.8-88.2)	14.0 (10.0-19.7)
		392	37	305.4 (227.1-410.6)	37	37	100 (90.5-100)	59.4 (44.5-79.4)
	375_C	0	31	5.0 (5.0-5.0)				
		42	31	640.0 (488.3-839.0)	31	31	100 (88.8-100)	128.0 (97.7-167.8)
		385	31	79.1 (59.2-105.6)	31	28	90.3 (74.2-98.0)	15.8 (11.8-21.1)
		392	31	286.2 (216.0-379.1)	31	31	100 (88.8-100)	57.2 (43.2-75.8)
	375_D	0	35	5.6 (4.9-6.5)				
		42	35	568.4 (442.7-729.8)	35	35	100 (90.0-100)	101.0 (74.8-136.4)
		385	32	59.6 (45.0-79.0)	32	21	65.6 (46.8-81.4)	10.5 (7.6-14.5)
		392	32	201.0 (156.1-258.7)	32	32	100 (89.1-100)	35.3 (25.9-48.1)
Flu A/ Vietnam/ 1194/2004	190_B	0	33	5.3 (5.0-5.7)				
		42	32	128.9 (103.1-161.2)	30	30	100 (88.4-100)	24.3 (19.0-31.0)
		385	34	26.0 (20.0-33.8)	31	12	38.7 (21.8-57.8)	4.7 (3.5-6.2)
		392	33	133.9 (95.5-187.7)	30	29	96.7 (82.8-99.9)	25.1 (17.3-36.4)
	090_C	0	30	5.0 (5.0-5.0)				
		42	27	104.7 (79.0-138.6)	24	22	91.7 (73.0-99.0)	20.1 (15.2-26.7)
		385	32	21.5 (16.8-27.5)	29	8	27.6 (12.7-47.2)	4.1 (3.1-5.3)
		392	32	137.5 (107.3-176.1)	29	29	100 (88.1-100)	27.1 (20.9-35.0)
	190_C	0	35	5.1 (4.9-5.5)				
		42	36	88.9 (63.2-125.0)	34	29	85.3 (68.9-95.0)	16.7 (11.7-23.8)
		385	34	18.4 (13.2-25.7)	32	9	28.1 (13.7-46.7)	3.5 (2.5-5.0)
		392	36	76.2 (53.9-107.7)	35	28	80.0 (63.1-91.6)	14.5 (10.2-20.5)
	375_C	0	25	5.1 (4.9-5.4)				
		42	31	77.2 (59.7-99.9)	25	21	84.0 (63.9-95.5)	15.1 (11.1-20.6)
		385	31	21.3 (16.3-27.9)	25	5	20.0 (6.8-40.7)	3.9 (2.8-5.4)
		392	31	76.5 (56.8-103.1)	25	22	88.0 (68.8-97.5)	14.5 (10.0-21.1)
	375_D	0	30	5.8 (4.7-7.2)				
		42	35	69.0 (51.7-92.0)	30	24	80.0 (61.4-92.3)	11.4 (8.4-15.6)
		385	30	20.6 (14.8-28.7)	27	6	22.2 (8.6-42.3)	3.6 (2.6-5.2)

Antibody	Group	Day	N	GMT (95% CI)	N'	SCR n	SCR % (95% CI)	MGI (95% CI)
		392	32	57.8 (41.5-80.4)	27	20	74.1 (53.7-88.9)	10.1 (6.7-15.2)

GMT: geometric mean titre; MGI: mean geometric increase; SCR: seroconversion rate
SCR is defined as: for initially seronegative subjects an antibody titre ≥40 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects.
N is the number of subjects with results available (GMT)
N' is the number of subjects with both pre- and postvaccination results available (SCR and MGI)

Table 5 presents the percentages of vaccinees with homologous HI antibody titres above cut-off levels on a logarithmic scale at all timepoints for the different groups and the reverse cumulative distribution curve in Figure 1

Table 5 Distribution of vaccine homologous HI antibody titres (Adapted ATP cohort for immunogenicity study Q-PAN H5N1-023)

				<10 1/DIL		>=10 1/DIL		>=100 1/DIL		>=1000 1/DIL	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**N**	**%**
Flu A/Indonesia/5/2005 H5N1 HI	190_B	PRE	36	35	97.2	1	2.8	0	0.0	0	0.0
		PII(D42)	36	0	0.0	36	100	36	100	19	52.8
		PII(D385)	34	0	0.0	34	100	13	38.2	0	0.0
		PIII(D392)	34	0	0.0	34	100	33	97.1	5	14.7
	090_C	PRE	33	32	97.0	1	3.0	0	0.0	0	0.0
		PII(D42)	33	0	0.0	33	100	33	100	16	48.5
		PII(D385)	33	0	0.0	33	100	9	27.3	0	0.0
		PIII(D392)	33	0	0.0	33	100	32	97.0	3	9.1
	190_C	PRE	37	36	97.3	1	2.7	0	0.0	0	0.0
		PII(D42)	37	0	0.0	37	100	37	100	17	45.9
		PII(D385)	37	0	0.0	37	100	14	37.8	0	0.0
		PIII(D392)	37	0	0.0	37	100	31	83.8	2	5.4
	375_C	PRE	31	31	100	0	0.0	0	0.0	0	0.0
		PII(D42)	31	0	0.0	31	100	31	100	10	32.3
		PII(D385)	31	0	0.0	31	100	10	32.3	0	0.0
		PIII(D392)	31	0	0.0	31	100	28	90.3	1	3.2
	375_D	PRE	35	32	91.4	3	8.6	0	0.0	0	0.0
		PII(D42)	35	0	0.0	35	100	34	97.1	5	14.3
		PII(D385)	32	0	0.0	32	100	11	34.4	0	0.0
		PIII(D392)	32	0	0.0	32	100	27	84.4	0	0.0

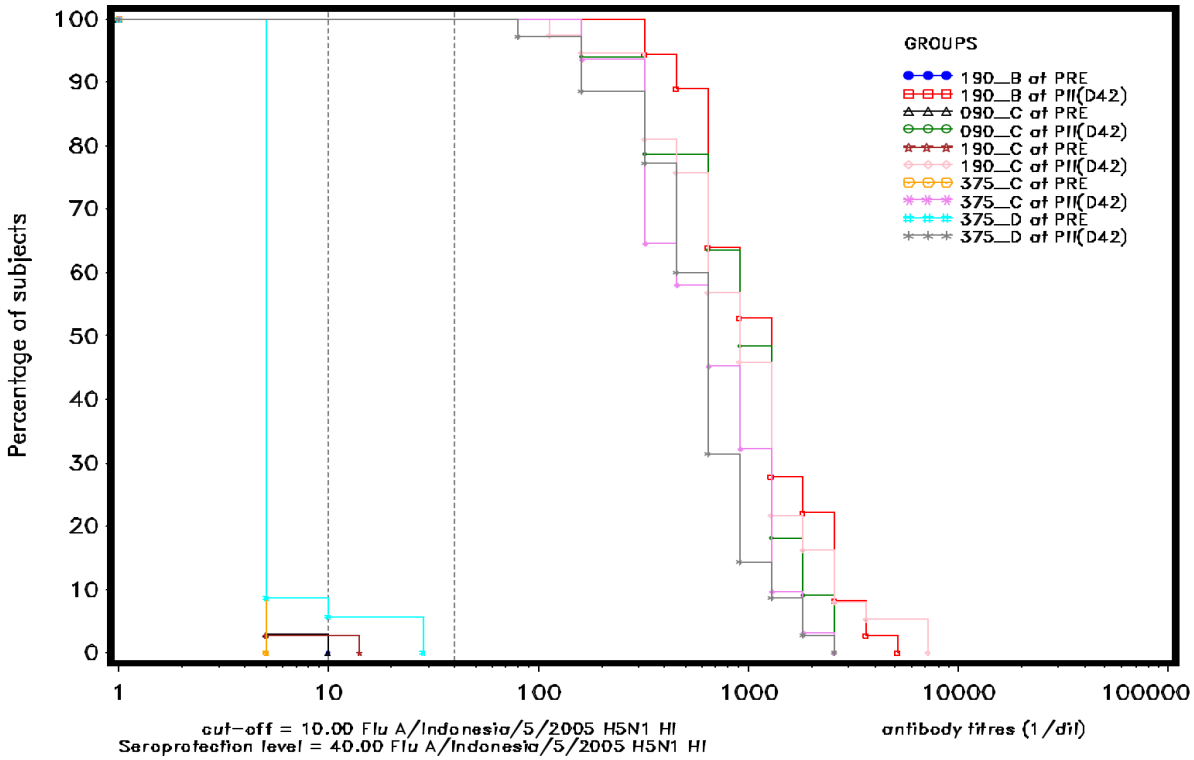


Figure 1 Reverse cumulative distribution curve of Flu A/Indonesia/05/2005 HI antibodies at Day 0 and Day 42 (ATP cohort for immunogenicity at Day 42 study Q-PAN H5N1-023)

Seroconversion rates for vaccine-homologous and -1 heterologous HI antibody (Flu A/Vietnam/1194/2004 H5N1) are presented in Table 6 by serostatus at Day 385.

Table 6 Seroconversion rate for vaccine homologous and heterologous HI antibodies by serostatus at D385 (Q-PAN H5N1-023)

Antibody	Group	Seronegative at D 385			Seropositive at D 385		
		N	n	SCR % (95%CI)	N	n	SCR % (95%CI)
Flu A/Indonesia/ 5/2005	190_B	0	-	-	34	24	70.6 (52.5 – 84.9)
	090_C	0	-	-	33	26	78.8 (61.1 – 91.0)
	190_C	0	-	-	37	23	62.2 (44.8 – 77.5)
	375_C	0	-	-	31	16	51.6 (33.1 – 69.8)
	375_D	0	-	-	32	15	46.9 (29.1 – 65.3)
Flu A/Vietnam/ 1194/2004	190_B	1	1	100 (2.5 – 100)	32	23	71.9 (53.3 – 86.3)
	090_C	0	-	-	31	23	74.2 (55.4 – 88.1)
	190_C	6	1	16.7 (0.4 – 64.1)	27	14	51.9 (31.9 – 71.3)
	375_C	1	1	100 (2.5 – 100)	30	16	53.3 (34.3 – 71.7)
	375_D	2	1	50.0 (1.3 – 98.7)	28	12	42.9 (24.5 – 62.8)

SCR: seroconversion rate
SCR is defined as: for initially seronegative subjects an antibody titre ≥40 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders

The clinical impact of the achieved immune response is unknown as there is no correlate of protection.

Reverse cumulative distribution curves (RCDCs) and tables presenting percentages of vaccinees with titres above a cut-off levels on a logarithmic scale (titres above 1:10, 1:100 and 1:1000) at all timepoints for the different groups were provided upon request. The RCDC curves show that the immune responses are highest in groups 190_B, 090_C and 190_C. For all groups the curves show a similar shape, indicating

a similar response though reduced in some groups, especially in groups 375_C and 375_D. These data are also reflected in the table containing the percentage of participants with titres above cut-off levels.

At Day 42, 21 days after the last vaccination of the primary vaccination series, all formulations induced a substantial vaccine-homologous HI antibody response, as SCR was 100% for all formulations. In addition, SCR for a heterologous H5N1 HI antigen (Flu/Vietnam) was >80% in all groups, indicating that 21 days after a primary vaccination series using all doses, a substantial immune response was generated to a antigenically drifted strain. An immune response to an H5N8 strain could also be detected, leading to SCR of 56.7% in group 190_B, 37.5% in group 090_C, 29.4% in group 190_C, 20.0% in group 375_C and 26.7% in group 375_D.

The H5N1 vaccination induced both vaccine-homologous and -heterologous HI antibody titres in all groups, which declined over time but remained above baseline for 1 year. A booster dose of unadjuvanted vaccine 1 year after the primary vaccination was able to elicit an immune response in all groups, however this response measured after 7 days was lower compared to the initial immune response seen at D42. The highest immune responses were seen in groups 190_B and 090_C. The immune response in group 090_C, receiving a quarter dose, was only slightly lower compared to the response seen for group 190_B, receiving half the adult dose.

All participants in all groups were seropositive for homologous HI antibodies at 1 year postvaccination. For heterologous HI antibodies, seronegative participants did occur, however, for both Flu A/duck/Bangladesh/19097/2013 and Flu A/Vietnam/1194/2004 the maximum number of participants in each group being seronegative was 6. For Flu A/gyrfalcon/Washington/41088-6/2014, the number of seronegatives ranged from 11 to 19. For both group 109_B and 090_C, there was no difference in seroconversion rate in seropositive and seronegative participants, with approximately 50% in both groups being seropositive after the booster dose. For groups 190_C, 375_C and 375_D, the seroconversion rate was higher in seropositive participants versus seronegative participants.

In conclusion, the highest immune response was seen in the 190_B group receiving the half adult dose. However, a quarter adult dose, 090_C, induced an immune response that was only slightly less immunogenic, as seen for example by GMT 95% CI that overlap. At 21 days post primary vaccination, both doses induced SCR of 100% for homologous antibodies and >90% for heterologous antibodies.

MN antibodies

A summary of vaccine homologous and heterologous MN antibody parameters, GMT, vaccine response rate (VRR) and MGI, for homologous and 1 heterologous antibody (Flu A/Vietnam/1194/2004 H5N1) are presented in Table 7.

Results for immune response assessment by MN assay were similar to HI assay. Neutralizing antibody parameters (seropositivity rates, GMT, and VRR) peaked at Day 42 and persisted well above baseline in all vaccine groups at Day 385. The Day 392 immune response results by MN were similar to the HI assay results.

Table 7 Summary of vaccine homologous and heterologous MN antibody parameters (GMT, SCR and MGI) – Adapted ATP cohort for immunogenicity (Q-PAN H5N1-023)

Antibody	**Group**	**Day**	**N**	**GMT (95% CI)**	**N'**	**VRR**		**MGI (95% CI)**
						n	**% (95% CI)**	
Flu A/Indonesia/ 5/2005	190_B	0	36	14.3 (13.7-14.8)				
		42	36	1498.5 (1181.7-1900.1)	36	36	100 (90.3-100)	
		385	34	250.3 (197.1-318.0)	34	34	100 (89.7-100)	17.5 (13.7-22.4)
		392	34	1085.0 (767.5-1533.9)	34	34	100 (89.7-100)	
	090_C	0	32	14.0 (14.0-14.0)				
		42	32	1214.3 (921.3-1600.6)	31	31	100 (88.8-100)	

Antibody	Group	Day	N	GMT (95% CI)	N'	VRR n	VRR % (95% CI)	MGI (95% CI)
		385	33	203.6 (172.8-239.8)	32	32	100 (89.1-100)	14.8 (12.6-17.5)
		392	33	969.1 (710.1-1322.6)	32	32	100 (89.1-100)	
	190_C	0	37	14.0 (14.0-14.0)				
		42	37	1211.6 (881.3-1665.9)	37	37	100 (90.5-100)	
		385	37	213.8 (175.2-260.9)	37	37	100 (90.5-100)	15.3 (12.5-18.6)
		392	37	674.2 (492.3-923.3)	37	37	100 (90.5-100)	
	375_C	0	29	14.0 (14.0-14.0)				
		42	31	707.1 (533.1-937.9)	29	29	100 (88.1-100)	
		385	31	247.2 (201.4-303.5)	29	29	100 (88.1-100)	17.8 (14.3-22.1)
		392	31	681.0 (496.3-934.4)	29	29	100 (88.1-100)	
	375_D	0	35	14.0 (14.0-14.0)				
		42	35	727.4 (545.9-969.2)	35	35	100 (90.0-100)	
		385	32	198.5 (165.1-238.7)	32	32	100 (89.1 -100)	14.2 (11.8-17.1)
		392	32	489.6 (381.7-628.0)	32	32	100 (89.1 -100)	
Flu A/Vietnam/ 1194/2004	190_B	0	34	14.6 (13.8-15.4)				
		42	36	217.6 (187.7-252.2)	34	34	100 (89.7-100)	
		385	33	113.0 (85.3-149.9)	31	27	87.1 (70.2-96.4)	7.6 (5.5-10.3)
		392	34	320.0 (259.8-394.1)	32	31	96.9 (83.8-99.9)	
	090_C	0	32	14.6 (13.7-15.5)				
		42	33	195.2 (156.7-243.1)	32	31	96.9 (83.8-99.9)	
		385	33	88.0 (64.0-121.0)	32	27	84.4 (67.2-94.7)	5.8 (4.2-8.1)
		392	33	256.6 (212.5-309.9)	32	31	96.9 (83.8-99.9)	
	190_C	0	37	14.8 (13.6-16.1)				
		42	37	177.3 (147.8-212.7)	37	36	97.3 (85.8-99.9)	
		385	35	80.7 (58.7-111.1)	35	27	77.1 (59.9-89.6)	5.4 (4.0-7.4)
		392	37	239.2 (202.5-282.7)	37	37	100 (90.5-100)	
	375_C	0	30	14.0 (14.0-14.0)				
		42	31	176.9 (139.0-225.2)	30	29	96.7 (82.8-99.9)	
		385	31	103.6 (80.5-133.2)	30	28	93.3 (77.9-99.2)	7.5 (5.8-9.8)
		392	31	270.4 (237.2-308.3)	30	30	100 (88.4-100)	
	375_D	0	35	15.2 (13.5-17.0)				
		42	35	149.3 (117.6-189.6)	35	32	91.4 (76.9-98.2)	
		385	32	89.0 (67.2-118.0)	32	25	78.1 (60.0-90.7)	6.1 (4.5-8.3)
		392	32	216.5 (179.0-261.8)	32	30	93.8 (79.2-99.2)	

GMT: geometric mean titre; MGI: mean geometric increase; VRR: vaccine response rate
VRR is defined as: for initially seronegative subjects an antibody titre ≥56 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects.
N is the number of subjects with results available (GMT)
N' is the number of subjects with both pre- and postvaccination results available (SCR and MGI)

Table 8 presents the percentages of vaccinees with homologous HI antibody titres above cut-off levels on a logarithmic scale at all timepoints for the different groups and the reverse cumulative distribution curve in Figure 2.

Table 8 Distribution of vaccine homologous and MN antibody titres (Adapted ATP cohort for immunogenicity study Q-PAN H5N1-023)

				<10 1/DIL		>=10 1/DIL		>=100 1/DIL		>=1000 1/DIL	
Antibody	**Group**	**Timing**	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Flu A/Indonesia/5/2005 H5N1 MN	190_B	PRE	36	0	0.0	36	100	0	0.0	0	0.0
		PII(D42)	36	0	0.0	36	100	36	100	21	58.3
		PII(D385)	34	0	0.0	34	100	34	100	2	5.9
		PIII(D392)	34	0	0.0	34	100	34	100	15	44.1
	090_C	PRE	32	0	0.0	32	100	0	0.0	0	0.0
		PII(D42)	32	0	0.0	32	100	32	100	19	59.4
		PII(D385)	33	0	0.0	33	100	32	97.0	0	0.0
		PIII(D392)	33	0	0.0	33	100	33	100	12	36.4
	190_C	PRE	37	0	0.0	37	100	0	0.0	0	0.0
		PII(D42)	37	0	0.0	37	100	37	100	21	56.8
		PII(D385)	37	0	0.0	37	100	35	94.6	0	0.0
		PIII(D392)	37	0	0.0	37	100	37	100	10	27.0
	375_C	PRE	29	0	0.0	29	100	0	0.0	0	0.0
		PII(D42)	31	0	0.0	31	100	31	100	10	32.3
		PII(D385)	31	0	0.0	31	100	31	100	0	0.0
		PIII(D392)	31	0	0.0	31	100	31	100	7	22.6
	375_D	PRE	35	0	0.0	35	100	0	0.0	0	0.0
		PII(D42)	35	0	0.0	35	100	35	100	10	28.6
		PII(D385)	32	0	0.0	32	100	32	100	0	0.0
		PIII(D392)	32	0	0.0	32	100	32	100	3	9.4

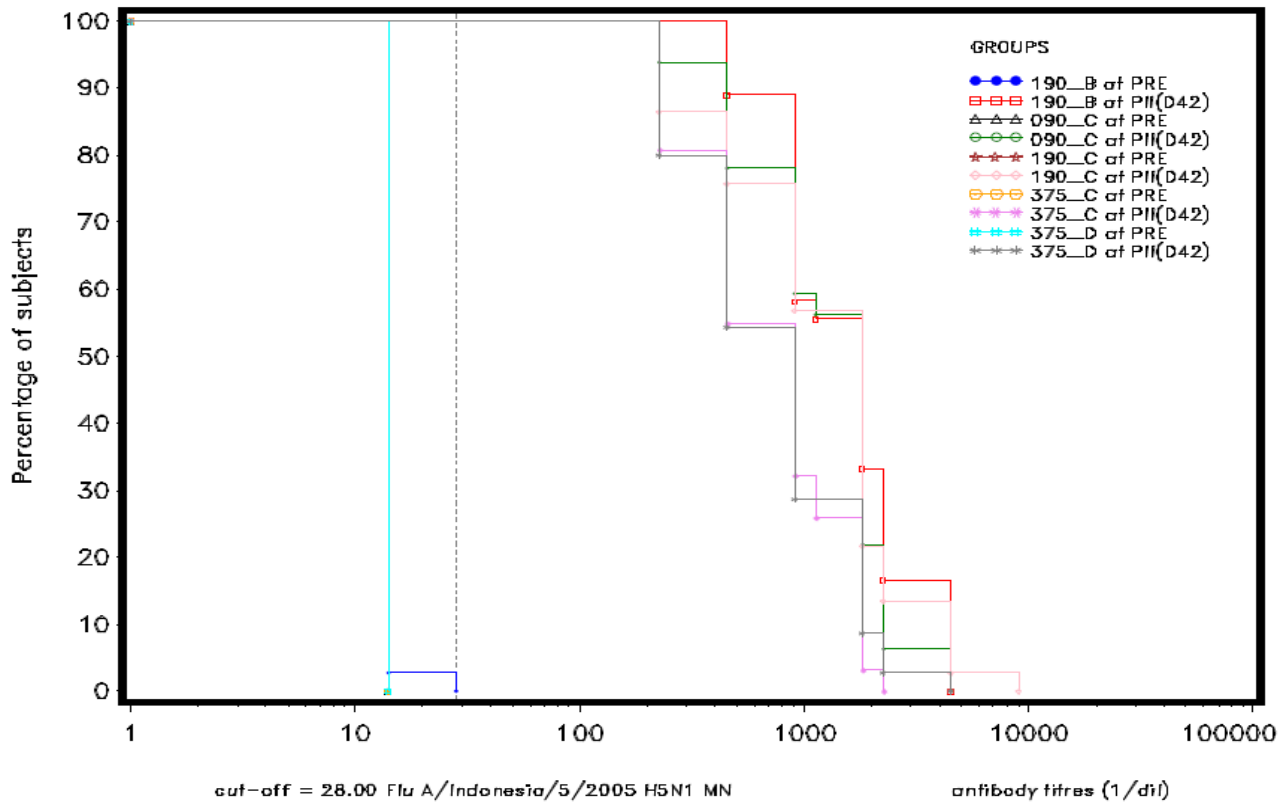


Figure 2 Reverse cumulative distribution curve of Flu A/Indonesia/05/2005 MN antibodies at Day 0 and Day 42 (ATP cohort for immunogenicity at Day 42 study Q-PAN H5N1-023)

Vaccine response rates for vaccine-homologous and -1 heterologous HI antibody (Flu A/Vietnam/1194/2004 H5N1) are presented in Table 9 by serostatus at Day 385.

Table 9 Seroconversion rate for vaccine homologous and heterologous MN antibodies at D392 relative to D385 by serostatus at D385 (Q-PAN H5N1-023)

Antibody	Group	Seronegative at D 385			Seropositive at D 385		
		N	n	VRR % (95%CI)	N	n	VRR % (95%CI)
Flu A/Indonesia/ 5/2005	190_B	0	-	-	34	21	61.8 (43.6-77.8)
	090_C	0	-	-	33	24	72.7 (54.5-86.7)
	190_C	0	-	-	37	14	37.8 (22.5-55.2)
	375_C	0	-	-	31	15	48.4 (30.2-66.9)
	375_D	0	-	-	32	13	40.6 (23.7-59.4)
Flu A/Vietnam/ 1194/2004	190_B	1	1	100 (2.5-100)	32	9	28.1 (13.7-46.7)
	090_C	4	4	100 (39.8-100)	29	6	20.7 (8.0-39.7)
	190_C	4	4	100 (39.8-100)	31	6	19.4 (7.5-37.5)
	375_C	0	-	-	31	7	22.6 (9.6-41.1)
	375_D	1	1	100 (2.5-100)	31	5	16.1 (5.5-33.7)

VRR: vaccine response rate
VRR is defined as: for initially seronegative subjects an antibody titre ≥56 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders

RCDCs and tables presenting percentages of vaccinees with titres above cut-off levels on a logarithmic scale (titres above 1:10, 1:100 and 1:1000) at all timepoints for the different groups were provided. The RCDC curves show that the immune responses are highest in groups 190_B and 090_C. For all groups, the curves show a similar shape, indicating a similar response though reduced in some groups, especially 375_C and 375_D. These data are also reflected in the table containing the percentage of participants with titres above cut-off levels.

The MN antibody results were generally in line with the HI antibody results, indicating a robust immune response.

At Day 42, 21 days after the last vaccination of the primary vaccination series, all formulations induced a substantial vaccine-homologous immune response by MN assay, as VRR was 100% for all formulations. At Day 42, vaccine-homologous GMTs were highest in Group 190_B, followed by 090_C, 190_C, 375_C and lastly 375_D.

The H5N1 vaccination induced both vaccine-homologous and -heterologous MN antibody titres in all groups, which declined over time but remained well above baseline for 1 year. VRR for homologous MN antibodies was 100% 1 year after the primary vaccination and ranged from 77.1% (190_C) to 93.3% (375_C) for heterologous MN antibodies. A booster dose of unadjuvanted vaccine 1 year after the primary vaccination was able to elicit an immune response in all groups, leading to VRR for both homologous and heterologous MN antibodies of >90%.

All participants in all groups were seropositive for homologous MN antibodies at 1 year postvaccination. For heterologous MN antibodies, seronegative participants did occur, however, for both Flu A/duck/Bangladesh/19097/2013 and Flu A/Vietnam/1194/2004 the maximum number of participants in each group being seronegative was 5. Due to the low number of seronegative participants at D385, no conclusion can be drawn in this group, although the fact that all seronegative subjects became seropositive is a good sign. In seropositive participants, VRR for homologous MN antibodies at D392 relative to D385 ranged from 37.8% (375_C) to 72.7 (090_C), while VRR for heterologous MN antibodies was considerably lower, ranging from 16.1% (375_C) to 28.1 (190_B).

In conclusion, as seen with HI antibodies, the highest immune response was seen in the 190_B group receiving the half adult dose. However, a quarter adult dose, 090_C, induced an immune response that was only slightly less immunogenic, as seen for example by GMT 95% CI that overlap. At 21 days post primary vaccination, both doses induced VRR of 100% for homologous antibodies and >80% for heterologous antibodies.

Cellular immune response

CMI parameters at Day 0, 42, 385 and 392 were evaluated:

- Antigen-specific CD4+/CD8+ T Cells identified as CD4/CD8+ T-cells producing two or more markers within CD40L, IL-2, TNF-α, IFN-γ upon in vitro stimulation using A/Indonesia/05/2005 (H5N1) split virus,
- The frequency of the response for CD4+/CD8+T-cells stained with probes for various cytokines and activation marker (IFN- γ, TNF- α, IL-2, CD40L) and elicited by vaccine components measured in a sub-cohort of approximately 20 subjects per group at Days 0, 42, 385 and 392 were described according to the technical specifications provided by R&D (Clinical Data – Information Sheet).

CMI data were analysed based on the total vaccinated sub-cohort (TVC CMI sub-cohort) for the subjects with CMI results available.

A total of 100 subjects were included in the TVC CMI sub-cohort (21 in the 190_B group, 21 in the 090_C group, 20 in the 190_C group, 19 in the 375_D group and 19 in the 375_D group).

A trend for higher CD4+ T-cell responses was observed at Day 42 for the reference group (190_B). For all formulations, CD4+ T cell responses were higher than baseline at all time points, see Table 10.

No vaccine specific CD8+ T cells response was detected in any of the groups, see Table 11.

Table 10 Descriptive statistics on the frequency of influenza-specific CD4 T-cells (per million CD4 Tcells) upon in vitro stimulation using Flu A/Indonesia/05/2005 virus strain at D0, 42, 385 and 392 (TVC CMI sub cohort) (Q-PAN H5N1-023)

Immune marker	Group	Timing	N	Nmiss	GM	Mean	SD	Min	Q1	Median	Q3	Max
CD4 dble_All (Polypositives)	190_B	PRE	20	1	28.56	164.20	232.15	1	1.0	55.5	227.0	769
		PII(D42)	18	3	2350.11	4255.72	4758.93	126	1669.0	2711.0	5165.0	18674
		PII(D385)	20	0	1356.39	2519.55	3769.53	181	632.5	1530.0	2293.5	17198
		PIII(D392)	20	0	1378.61	2853.50	3289.31	15	759.5	1417.0	3955.5	12675
	090_C	PRE	19	2	27.18	111.42	153.40	1	3.0	42.0	185.0	590
		PII(D42)	19	0	1805.76	3214.00	3446.34	288	707.0	1629.0	4301.0	13230
		PII(D385)	18	1	1110.19	1507.39	1118.74	161	560.0	1255.0	2096.0	4044
		PIII(D392)	17	2	992.77	1901.65	2098.05	37	582.0	1129.0	3221.0	8453
	190_C	PRE	17	3	26.89	207.59	520.58	1	1.0	43.0	90.0	2166
		PII(D42)	17	3	1002.79	1891.76	2679.80	192	432.0	960.0	1379.0	9284
		PII(D385)	18	2	1080.81	1949.11	2652.18	151	469.0	1413.0	1834.0	10197
		PIII(D392)	19	1	771.18	1393.63	1740.16	73	448.0	731.0	1461.0	7006
	375_C	PRE	18	1	58.07	340.33	896.95	1	26.0	89.5	217.0	3878
		PII(D42)	16	2	1366.05	1987.31	2042.72	232	748.0	1337.5	2793.0	8597
		PII(D385)	18	0	753.88	979.67	620.54	82	495.0	954.0	1199.0	2255
		PIII(D392)	18	0	591.17	927.50	928.30	85	260.0	722.5	907.0	3336
	375_D	PRE	19	0	39.39	582.63	1969.89	1	1.0	74.0	277.0	8689
		PII(D42)	16	3	1181.79	2182.81	2290.70	74	426.5	1372.5	2911.5	7699
		PII(D385)	17	0	740.36	1352.35	1930.06	130	373.0	596.0	1167.0	7892
		PIII(D392)	17	0	744.95	1156.12	1140.47	143	345.0	832.0	1497.0	3542

N = number of subjects with available results for post and pre timepoints
Nmiss = number of subjects with missing results
GM= Geometric Mean
SD = Standard Deviation
Q1,Q3 = First and third quartiles
Min/Max = Minimum/Maximum
PRE = Pre-vaccination dose 1 at Day 0
PII(D42) = Post-vaccination dose 2 at Day 42
PII(D385) = Pre-vaccination dose 3 at Day 385
PIII(D392) = Post-vaccination dose 3 at Day 392

Table 11 Descriptive statistics on the frequency of influenza-specific CD8 T-cells (per million CD8 Tcells) upon in vitro stimulation using Flu A/Indonesia/05/2005 virus strain at D0, 42, 385 and 392 (TVC CMI sub cohort) (Q-PAN H5N1-023)

Immune marker	Group	Timing	N	Nmiss	GM	Mean	SD	Min	Q1	Median	Q3	Max
CD8 dble_All (Polypositives)	190_B	PRE	20	1	8.06	55.00	91.67	1	1.0	3.5	68.5	321
		PII(D42)	17	4	34.01	280.12	679.90	1	2.0	48.0	186.0	2840
		PII(D385)	20	0	20.41	138.70	271.51	1	1.0	33.5	108.5	1029
		PIII(D392)	19	1	33.13	209.32	375.83	1	1.0	63.0	200.0	1542
	090_C	PRE	19	2	7.35	41.21	80.26	1	1.0	5.0	45.0	336
		PII(D42)	19	0	58.81	213.74	345.58	1	42.0	63.0	238.0	1373
		PII(D385)	18	1	21.92	92.28	109.80	1	1.0	62.5	147.0	426
		PIII(D392)	17	2	18.37	101.88	153.65	1	1.0	33.0	88.0	455
	190_C	PRE	17	3	8.82	74.18	205.98	1	1.0	30.0	40.0	865
		PII(D42)	17	3	24.02	194.76	411.00	1	1.0	45.0	83.0	1412
		PII(D385)	19	1	4.56	52.42	110.11	1	1.0	1.0	107.0	455
		PIII(D392)	19	1	11.28	106.68	225.06	1	1.0	25.0	70.0	906
	375_C	PRE	18	1	27.24	386.28	1261.01	1	1.0	47.0	121.0	5412
		PII(D42)	16	2	62.95	200.25	282.28	1	54.5	125.0	220.5	1172
		PII(D385)	18	0	24.40	121.39	157.59	1	1.0	56.0	194.0	553
		PIII(D392)	18	0	23.48	139.72	202.72	1	1.0	60.5	126.0	653
	375_D	PRE	19	0	5.78	42.89	85.32	1	1.0	1.0	58.0	354
		PII(D42)	15	4	66.39	390.60	711.11	1	10.0	128.0	323.0	2703
		PII(D385)	17	0	7.73	183.82	565.04	1	1.0	1.0	79.0	2347
		PIII(D392)	17	0	14.06	195.12	492.92	1	1.0	26.0	99.0	2016

N = number of subjects with available results for post and pre timepoints
Nmiss = number of subjects with missing results
GM= Geometric Mean
SD = Standard Deviation
Q1,Q3 = First and third quartiles
Min/Max = Minimum/Maximum
PRE = Pre-vaccination dose 1 at Day 0
PII(D42) = Post-vaccination dose 2 at Day 42
PII(D385) = Pre-vaccination dose 3 at Day 385
PIII(D392) = Post-vaccination dose 3 at Day 392

CD4 T-cells increased after in vitro stimulation with A/Indonesia/05/2005 (H5N1) split virus in all groups, while CD8 T-cells did not increase. However, even the increase in CD4 T-cells is minimal as an increase of approximately 2000 cells/million cells was observed, indicating an increase of 0.2%.

As the percentage of vaccinated subjects eliminated from the ATP cohort was more than 5% in at least 1 group, a secondary analysis was performed on the TVC.

The results of the TVC secondary analysis were in line with the results for the ATP cohort, which was reassuring and indicative of a robust response.

Both half adult dose and a quarter adult dose induced a substantial immune response. Numerically the response to half adult dose was higher compared to the quarter dose at all time points measured as well as considering the heterologous response, however, only a slight decrease in immunogenicity was seen at Day 42 of which the clinical relevance is unknown.

Safety

In general, the majority of subjects reported at least 1 solicited AE in both 190_B and 090_C groups. Incidence of solicited AEs, Grade 3 AEs and vaccine-related Grade 3 AEs was highest in group 190_B. The solicited AEs were of short duration (<3 days).

Pain was the most frequently reported solicited local reaction, reported by 16 subjects (42.1%) in group 190_B and 11 subjects (29.7%) in group 090_C. Grade 3 pain was reported by 2 subjects (5.3%) in group 190_B and none in group 090_C. The mean duration of pain was 2.6 days in group 190_B and 1.9 days in group 090_C.

The most frequently reported systemic AEs were drowsiness and fever in group 190_B (reported by 23 subjects [60.5%]) and drowsiness in group 090_C (reported by 16 subjects [43.2%]). Mean duration of drowsiness, irritability and loss of appetite was short <3 days in all groups.

Vaccine-related fever occurred in 22 subjects (57.9%) in group 190_B and 12 subjects (32.4%) in group 090_C. An increased incidence of fever, but not of other systemic solicited AEs, was observed after the second dose in groups 190_B and 090_C. Grade 3 fever (39.0-40.0°C) related to the vaccine occurred in 5 subjects (13.2%) in group 190_B and 2 subjects (5.2%) in group 090_C. The mean duration of the fever was short (<2 days) for all groups.

Each of the solicited systemic AEs occurred at a higher frequency in group 190_B compared to the other groups.

The majority of participants reported at least 1 unsolicited AE; 23 subjects (60.5%) in group 190_B and 20 subjects (54.1%) in group 090_C. Of these the number of subjects reporting a vaccine-related unsolicited AE was 3 (7.9%) in group 190_B and 0 (0.0%) in group 090_C.

All in all, the safety profile of the half adult dose was worse compared to the quarter dose. Incidence of solicited AEs and unsolicited AEs was higher in group 190_B. This worse safety profile is mainly driven by fever; the incidence of all fever and Grade 3 fever was approximately twice as high in the 190_B group compared to the 090_C group.

As conclusion on the dose finding study, all dosing regimens elicited a robust vaccine-homologous immune response at Day 42, as both SCR (evaluating HI antibodies) and VRR (evaluating MN antibodies) were 100% for all formulations.

The dosing regimens of groups 190_B and 090_C elicited the highest immune response of all groups for HI and MN antibodies. Although numerically the response in group 190_B was higher, the increase in immunogenicity was considered small. At Day 42, SCR and VRR to homologous stimulation was 100% in both groups. Heterologous stimulation led to an SCR and VRR of 100% in group 190_B and >91% in group 090_C. For both HI and MN antibodies, the unadjuvanted vaccine 1 year after the primary vaccination was able to elicit a robust vaccine-homologous and -heterologous immune response in both groups, though this response was lower compared to the original response at D42.

In all groups, the majority of subjects reported at least 1 solicited AE in all groups. The incidence of solicited AEs, vaccine-related Grade 3 solicited AEs and unsolicited AEs was highest in group 190_B.

In young children, aged 6 months to 36 months, fever is an AE of concern as especially in children in this age category it can lead to febrile seizures. The likelihood of a febrile seizure is related to the height of temperature during the fever. Febrile seizures have been linked to vaccination in some cases, including Pandemrix.

Vaccine-related fever occurred in 22 subjects (57.9%) in group 190_B, 12 subjects (32.4%) in group 090_C and Grade 3 fever (39.0-40.0°C) related to the vaccine occurred in 5 subjects (13.2%) in group 190_B, 2 subjects (5.2%) in group 090_C. These results indicate an incidence of fever and severe fever that was approximately twice as high in group 190_B compared to group 090_C. A post-hoc analysis based on cross-study comparisons showed that the reported incidence of fever was higher than expected for group 190_B in this study, however, this increase in fever reporting would reasonably also have been expected to occur across all groups including 090_C.

Overall, the immunogenicity data showed that a quarter adult dose was only slightly less immunogenic compared to a half adult dose, whilst there is less reactogenicity when using the quarter adult dose.

This conclusion is in line with previous advice from VWP given in relation to scientific advice (EMEA/H/SA/3998/1/2018/PED/II). In infants and toddler from 6 months to 36 months of age the VWP concluded that a quarter adult dose may be preferable since it seemed sufficiently immunogenic (including in cross-immunogenicity studies) and had a slightly better safety profile than the half adult dose. In addition, the VWP concluded that a further study of the quarter adult dose in this age was not required as the data would be sufficient to conclude on a posology. When deciding this, the VWP took into account the ethical controversies around vaccinating children with H5N1 in lack of an imminent threat.

2.4.2. Main study(ies)

Methods

Study D-PAN H5N1-013 was a phase II, multicentre, non-randomized, open-label, prime-boost study, to evaluate the safety and immunogenicity of the adjuvanted (pre-) pandemic H5N1 influenza candidate vaccine following a heterologous prime-boost schedule (six months apart) in children 6 to 35 months of age.

Study D-PAN H5N1-032 was a phase III, single-centre, randomized, open-label, active-controlled, prime-boost study to evaluate the safety and immunogenicity of a prime-boost schedule of the H5N1 candidate vaccine adjuvanted with $AS03_B$ administered to children aged 3 to 17 years old.

The fact that study D-PAN H5N1-013 is an open-label, single arm study, was considered unfortunate as there is no comparison for reactogenicity. The single arm design was considered acceptable from an immunogenicity perspective.

For study D-PAN H5N1-032, the open-label character of the study was regretted, as it might affect safety reporting. However, it was understood that unnecessary blood draws and vaccinations were not wanted in the young population. Again here, no impact was expected on the immunogenicity outcomes.

Study participants

Both studies enrolled healthy paediatric subjects, as established by medical history and clinical examination before entering the study, for whom the investigator believed that the parents/LAR(s) could and would comply with the requirements of the protocol. Written informed consent was obtained from the parent(s)/LAR(s) of the subject (assent was obtained from the subject when applicable).

Study D-PAN H5N1-013 enrolled healthy (in the investigator's clinical judgment) male and female children 6 and 35 months of age at the time of the first vaccination.

Study D-PAN H5N1-032 enrolled healthy (in the investigator's clinical judgment) male and female children 3 to 17 years of age (inclusive) at the time of the first vaccination. Lactating female subjects and of childbearing potential that lack a history of reliable contraceptive practices (as defined by the protocol) and pregnant women were excluded from the study.

The main exclusion criteria were:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period.
- Planned administration of any vaccine 30 days prior and 21 days after any study vaccine administration.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines such as egg protein or thiomersal.
- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).
- History of any neurological disorders or seizures.
- Acute disease at the time of enrolment.
- Previous vaccination at any time with an H5N1 vaccine.
- Medical history of physician-confirmed infection with a H5N1 virus

Treatments

In **Study D-PAN H5N1-013** subjects received D-PAN H5N1 vaccine, containing A/Indonesia HA antigen and $AS03_B$, on Day 0 and 21 and a heterologous booster vaccination, containing A/turkey/Turkey HA antigen and $AS03_B$, on Day 182. Blood samples for humoral immune response, including neutralization antibodies were collected at Days 0, 42, 182, 192 and 364 for all subjects.

In **Study D-PAN H5N1-032** subjects were randomized to 3:3:2:2 to the following 4 treatment groups:

Group	Day 0	Day 21	Day 182	Day 364
H5N1-H5N1	D-PAN H5N1: 1.9 µg A/Indonesia HA antigen and $AS03_B$	D-PAN H5N1: 1.9 µg A/Indonesia HA antigen and $AS03_B$	D-PAN H5N1: 1.9 µg A/turkey/Turkey HA antigen and $AS03_B$	Havrix or Havrix Junior[1]
H5N1-Havrix	D-PAN H5N1: 1.9 µg A/Indonesia HA antigen and $AS03_B$	D-PAN H5N1: 1.9 µg A/Indonesia HA antigen and $AS03_B$	Havrix or Havrix Junior	Havrix or Havrix Junior
Havrix-H5N1	Havrix or Havrix Junior	-	D-PAN H5N1: 1.9 µg A/turkey/Turkey HA antigen and $AS03_B$	Havrix or Havrix Junior
Havrix-Havrix	Havrix or Havrix Junior	-	Havrix or Havrix Junior	-

1 Second dose was given after at least a 6-month interval outside the study setting

Blood samples for antibody determination were collected at Days 0, 42, 182 for all subjects; at Day 192 for groups H5N1_H5N1 and Havrix_H5N1; and at Day 364 for groups H5N1_H5N1, H5N1_Havrix and Havrix_H5N1.

Recommended posology by the MAH was 2 doses of Adjupanrix containing 1.9 µg HA antigen and $AS03_B$ given at least 3 weeks apart for all children aged 6 months to <18 years.

This is consistent with the treatment during study D-PAN H5N1-013 and the treatment in groups H5N1-H5N1 and H5N1-Havrix in study D-PAN H5N1-032. Havrix is a hepatitis A vaccine and used as a comparator in the study D-PAN H5N1-032. Use of an active comparator is appreciated.

Comparing groups H5N1-H5N1 and H5N1-Havrix allows the assessment of the effect of a heterologous booster dose at 6 months after the primary vaccination. Comparing groups H5N1-H5N1 and Havrix-H5N1 allows the assessment of the effect of the primary vaccination on the heterologous booster dose.

Objectives and Outcomes/endpoints

Study D-PAN H5N1-013

Primary objective was to assess whether a heterologous booster dose of 1.9 µg A/turkey/Turkey/1/2005 (H5N1) HA with $AS03_B$ given 6 months following a 2-dose primary vaccination series with 1.9 µg A/Indonesia/05/2005 (H5N1) HA with $AS03_B$ elicits an antibody response that meets the SCR of >40%, SPR of >70% and MGI of >2.5 based on HI responses to A/turkey/Turkey/1/2005 (H5N1) 10 days following booster vaccination.

Secondary objectives were: 1) to assess of HI and neutralizing antibody responses against A/Indonesia/05/2005 and A/turkey/Turkey/1/2005 strains, on Day 0, Day 42 (for HI only A/Indonesia/05/2005 H5N1 strain) , Day 182, Day 192, and Day 364. On Day 42 only HI antibody responses against the was tested; 2) to describe the humoral immune response in terms of the 3 age strata (6–11 Mo, 12–23 Mo and 24-35 Mo) used for enrolment in this study.

The following immunogenicity endpoints were analysed: H5N1 HI and MN antibody titres against A/Indonesia and A/Turkey virus strains at Days 0, 42*, 182, 192 and 364 (*only A/Indonesia strain for HI). The following derived variables were computed:

- GMT (HI and MN), seropositivity rate (HI and MN) and SPR (HI) of H5N1 antibody titres, at Days 0, 42 (only for A/Indonesia strain), 182, 192 and 364.
- SCR (HI) and mean geometric increase (MGI) (HI) at Days 42 (only for A/Indonesia), 182, 192 and 364.
- Booster Factor (BF) and Booster SCR (HI), and Booster VRR (MN; percentage of subjects with 4-fold increase in post-booster vaccination titre relative to pre-booster [Day 182]) at Days 192 and 364 (only A/Turkey strain).

Study D-PAN H5N1-032

Primary objective was to assess the superiority of the HI antibody response against A/turkey/Turkey/01/2005 (H5N1) 10 days following H5N1 vaccination on Day 182 (1.9 µg A/turkey/Turkey/01/2005 [H5N1] HA antigen adjuvanted with $AS03_B$) in subjects previously primed with two doses of heterologous A/Indonesia/5/2005 (H5N1) vaccine versus non primed subjects. Criterion used: lower limit of the 2-sided 95% confidence interval (CI) for the HI GMT ratio on Day 192 (Group H5N1_H5N1 compared to Group Havrix_H5N1) was greater than 1.0.

Secondary objectives were: 1) to assess the HI antibody response in terms of seropositivity rates, GMTs, SCR (based on Day 0), SPR and MGI (based on Day 0), against A/Indonesia/5/2005 and A/turkey/Turkey/01/2005 (H5N1) strains on Days 0, 42 and 182 (all subjects), on Day 192 (Groups H5N1_H5N1 and Havrix_H5N1) [and on Day 364 (Groups H5N1_H5N1, H5N1_Havrix and Havrix_H5N1)]; 2) to describe the humoral immune response in terms of the age strata used for

enrollment in this study; and 3) to describe the H5N1 neutralizing antibody responses against A/Indonesia/5/2005 and A/turkey/Turkey/01/2005 strains on Days 0, 42, 182 (all subjects), on Day 192 (Groups H5N1_H5N1 and Havrix_H5N1) and on Day 364 (Groups H5N1_H5N1, H5N1_Havrix and Havrix_H5N1).

The primary outcome variable was the humoral immune response in terms of H5N1 HI antibodies against the A/turkey/Turkey/01/2005 (H5N1) strain on Day 192. The following derived variables were computed:

- GMTs of H5N1 HI antibody titres on Day 192.
- GMT ratio on Day 192 of Group H5N1_H5N1 over Group Havrix_H5N1.

The following secondary outcome variables were analysed: H5N1 HI and MN antibody titres against A/Indonesia and A/Turkey virus strains at Days 0, 42, 182 (all subjects), 192 (Groups H5N1_H5N1 and Havrix_H5N1) and on Day 364 (Groups H5N1_H5N1, H5N1_Havrix and Havrix_H5N1). The following derived variables were computed:

- GMTs (HI and MN) and seropositivity rates (HI and MN) of H5N1 antibody titres, at Days 0, 42, 182, 192 and 364.
- SCR (HI) and VRR (MN) on Days 42, 182, 192 and 364.
- SPR on Days 0, 42, 182, 192 and 364.
- MGI (HI) at Days 42, 182, 192 and 364.
- BF and Booster SCR (HI), and Booster VRR (MN) at Days 192 and 364.

The Guideline on Influenza Vaccines (EMA/CHMP/VWP/457259/2014) states: "*The HI titre of 1:40 was previously suggested to represent a reasonable statistical correlate for an efficacy of 50–70% against clinical symptoms of influenza based on challenge studies in healthy adults. Since then, evidence has emerged to indicate that there remains a need to better define correlates of protection against influenza, which potentially may vary according to individual characteristics, populations, specific age group (e.g. paediatric population) and vaccine type.*"

No correlate of protection exists for Influenza. This hampered the interpretation of the clinical relevance of the observed vaccine-induced immunogenicity. Assessment was based on totality of immunogenicity findings based on all relevant parameters. Totality of all immunogenicity results should be sufficiently convincing to ensure CHMP that the candidate vaccine is likely to be efficacious in the event of a pandemic regardless of a statistically significant effect.

The MAH expressed the seroprotection rate (SPR) as the percentage of subjects with a HI titre >1:40. As there is no clear clinical relevance of this cut-off, and as the percentages are closely reflected by the seroconversion rates (SCR), the focus of assessment has been based on the SCR next to GMTs, which were defined as the primary outcome.

Sample size

D-PAN H5N1-013

The target sample size was approximately 120 subjects 6 to 35 months of age (6-11, 12-23 and 24-35 months with a ratio 2:1:1) in order to reach 108 evaluable subjects, assuming that 10% of subjects (drop-out) were non-evaluable.

D-PAN H5N1-032

The study planned to enroll 520 eligible subjects with a randomization ratio of 3:3:2:2 in order to reach 500 evaluable subjects, assuming that 4% of subjects (dropout) would be non-evaluable on Day 192.

The first co-primary objective of this study was to demonstrate the superiority of the HI antibody response against A/turkey/Turkey/01/2005 (H5N1) 10 days following an heterologous H5N1 booster vaccination on Day 182 (1.9 µg A/turkey/Turkey/01/2005 HA antigen adjuvanted with $AS03_B$) in subjects previously primed with two doses of A/Indonesia/5/2005 H5N1 vaccine (Group H5N1_H5N1) versus non primed subjects (Group Havrix_H5N1). Using data from recipients of the D-PAN-H5N1-009 study, a standard deviation of 0.52 was obtained for log10 HI titre specific for an H5N1 antigen on Day 42 based on the 1.9 µg antigen dose with $AS03_B$ in children. A sample of 150 subjects in Group H5N1_H5N1 and 100 subjects in Group Havrix_H5N1 had 99.4% power to detect a two-fold increase in the H5N1 antibody response between the two groups H5N1_H5N1 and Havrix_H5N1, assuming the common deviation is 0.52 (in log unit) and using a one-sided two-group t-test with a 0.025 significance level.

For the second co-primary objective:

- With 300 evaluable subjects in the H5N1 study vaccine groups, there was at least a probability of 91.0% to detect one AE with an occurrence rate of 0.8%.
- With 200 evaluable subjects in the control groups, there was at least a probability of 79.9% to detect one AE with an occurrence rate of 0.8%.

Study D-PAN H5N1-013 was a descriptive study and not designed to test statistical hypothesis. The main driver was to contribute to the overall immunogenicity and safety database.

The main driver for the sample size for study D-PAN H5N1-032 was to demonstrate superiority HI antibody response against A/turkey/Turkey/01/2005 (H5N1) 10 days following an heterologous H5N1 booster vaccination on Day 182 (1.9 µg A/turkey/Turkey/01/2005 HA antigen adjuvanted with $AS03_B$) in subjects previously primed with two doses of A/Indonesia/5/2005 H5N1 vaccine (Group H5N1_H5N1) versus non primed subjects (Group Havrix_H5N1).

Based on the fact that study D-PAN H5N1-009 enrolled healthy participants aged 3-9 years of age, the assumption that immune response was similar between the studies was questioned, as this study also enrolled adolescents. Younger children are known to have a higher immune response to this type of adjuvanted vaccine. However, as there is neither an established threshold value associated with clinical benefit, nor a good knowledge on the impact of inducing a lower-than-average antibody response, interpretation of meeting or not meeting any pre-specified acceptance criteria was considered difficult.

Randomisation and Blinding (masking)

PAN H5N1-013

The study was non-randomized. The treatment allocation at the investigator site was performed using a central randomization system on internet (SBIR). The treatment numbers were allocated by dose. The randomization algorithm used a minimization procedure accounting for centre and age (6 to 11 months, 12 to 23 months and 24 to 35 months). Centre and age minimization factors had equal weight in the minimization algorithm.

The enrolment was to be performed to ensure a distribution with the ratio of 2:1:1 of the three age strata (6 to 11 months, 12 to 23 months and 24 to 35 months).

The study was open label, no blinding was performed.

D-PAN H5N1-032

Subjects were randomly assigned to four study groups in a 3:3:2:2 ratio. Subject numbers were assigned sequentially to subjects consenting to participate in the study, according to the range of subject numbers allocated to each study centre.

The treatment allocation at the investigator site was performed using a central randomization system on internet (SBIR). The treatment numbers were allocated by dose. The randomization algorithm used a minimization procedure accounting for center and age (3 to 9 years old versus 10 to 17 year old). Minimization factors had equal weight in the minimization algorithm

The enrolment was performed to ensure at least 40% of the subjects were included in each of the two age strata in every group (3 to 9 years old versus 10 to 17 years old).

The study was open label, no blinding was performed. Randomization and blinding was considered acceptable.

Study D-PAN H5N1-013 was a phase II descriptive study, adding to the immunogenicity and safety database.

For study D-PAN H5N1-032 randomisation was stratified for age and ensured that in every group at least 40% of subjects were included in each of the two age strata (3-9 years and 10-17 years). Randomisation was skewed to include slightly more participants in the H5N1-H5N1 and H5N1-Havrix groups compared to the Havrix-H5N1 and Havrix-Havrix groups, which was endorsed.

Statistical methods

Analysis populations

The total vaccinated cohort (TVC) included all vaccinated subjects (i.e., subjects who received at least one dose of vaccine in the studies) for whom data were available. The TVC analysis of immunogenicity included vaccinated subjects for whom data concerning immunogenicity endpoint measures were available. The TVC analysis was performed per vaccine actually administered at the first dose.

The according-to-protocol (ATP) cohort for analysis of immunogenicity included all subjects for whom HI assay results were available for antibodies against at least one study vaccine strain 21 days after primary vaccination [Day 42 (priming)], 10 days after booster vaccination [Month 6 (booster)] and 12 months after primary vaccination [Month 12 (persistence)].

Statistical methods

For all studies, the primary analysis was based on the ATP cohort for analysis of immunogenicity. Since the percentage of vaccinated subjects with serological results excluded from the ATP cohort was more than 5%, a second analysis based on the TVC was performed to complement the ATP analysis.

A seronegative subject was a subject whose titre was below the cut-off value. A seropositive subject was a subject whose titre was greater than or equal to the cut off value.

SCR was defined as the percentage of vaccinees that had either a pre-vaccination (Day 0) titre <1:10 and a post-vaccination titre ≥1:40 or a pre-vaccination titre ≥1:10 and at least a four-fold increase in post-vaccination titre.

SPR was defined as the percentage of vaccinees with a serum H5N1 HI antibody titre ≥1:40, that usually was accepted as indicating protection.

MGI was defined as the geometric mean of the within-subject ratios of the post-vaccination reciprocal HI titre to the pre-vaccination (Day 0) reciprocal HI titre.

The GMT calculations are performed by taking the anti-log of the mean of the log titre transformations. Antibody titres below the cut-off of the assay are given an arbitrary value of half the cut-off for the purpose of GMT calculation.

Booster SCR: For seronegative subjects at pre-booster (Day 182), antibody titre ≥1:40 at post-booster timepoint(s). For seropositive subjects at pre-booster (Day 182), antibody titre at post-booster timepoint(s) ≥4-fold the pre-booster antibody titre.

BF was defined as the geometric mean of the within-subject ratios of the post-booster vaccination reciprocal HI titre to the pre-booster (Day 182) reciprocal titre.

In **D-Pan H5N1-013** study:

VRR was defined as the percentage of vaccinees with at least a 4-fold increase in postvaccination titre relative to Day 0 (for MN antibodies).

Booster VRR was defined as the percentage of vaccinees with at least a 4-fold increase in post-booster vaccination titre relative to pre-booster (Day 182) (for MN antibodies).

In **D-Pan H5N1-032** study:

VRR was defined as the percentage of vaccinees that had either a pre-vaccination (Day 0) titre <1:28 and a post-vaccination titre ≥1:56, or a pre-vaccination titre ≥1:28 and at least a 4-fold increase in post-vaccination titre (for MN antibodies).

Booster VRR is defined as the percentage of vaccinees that have either a pre-booster (Day 182) titre <1:28 and a post-booster titre ≥1:56, or a pre-booster (Day 182) titre ≥1:28 and at least a 4-fold increase in post-booster titre (for MN antibodies).

Missing information

For a given subject and a given immunogenicity measurement, missing or non-evaluable measurements were not replaced. Therefore, an analysis excluded subjects with missing or non-evaluable measurements.

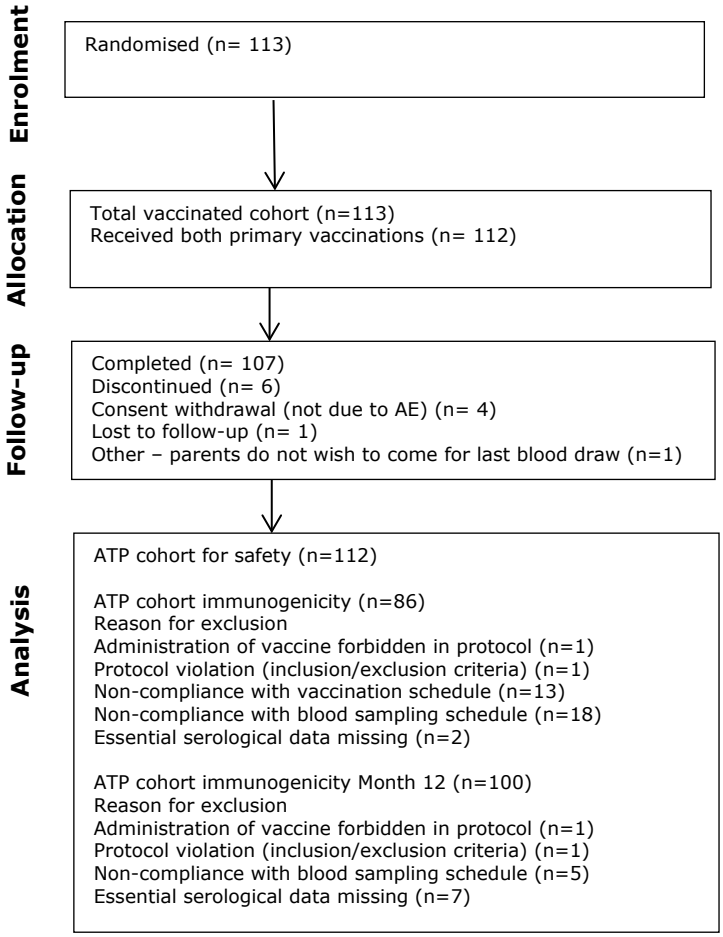
Calculation CI

All CIs were two-sided 95% CI. The exact 95% CIs for a proportion within a group was calculated from Proc StatXact (Clopper, 1934). The 95% CIs for GMT were obtained within each group separately. The 95% CI for the mean of log-transformed titre was first obtained assuming that log-transformed titres were normally distributed with unknown variance. The 95% CI for the GMT was then obtained by exponential-transformation of the 95% CI for the mean of log-transformed titre. The 95% CI for the adjusted GMT was obtained by exponential-transformation of the 95% CI for the group least square mean of the used analysis of covariance (ANCOVA) model.

Results

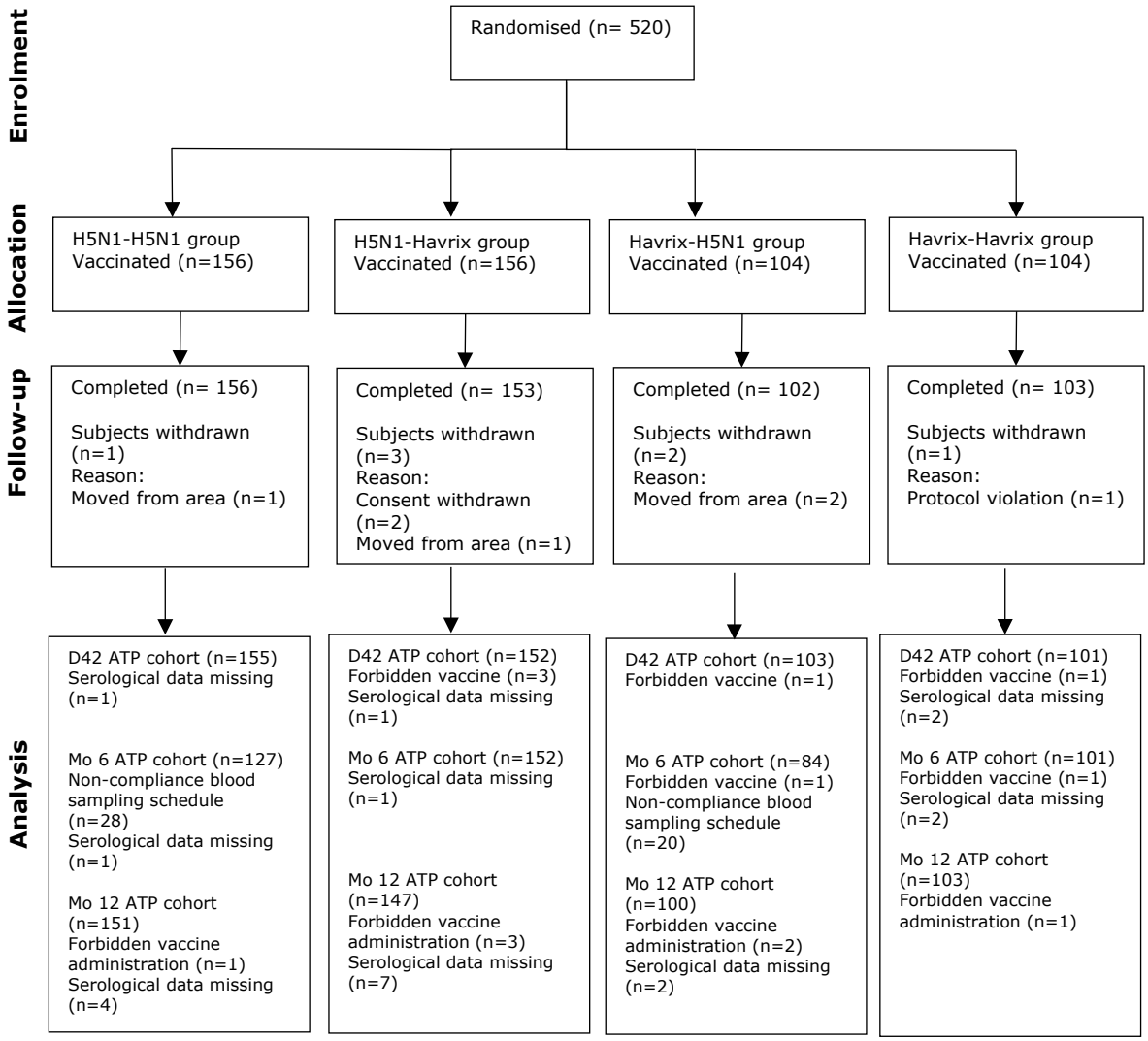
Participant flow

D-PAN H5N1-013



ATP cohorts for the different time points prior to month 12 were not defined. The MAH corrected the number of participants who completed the study reported in the Summary of clinical efficacy based on the Final CSR (dated 28-MAR-2013).

D-PAN H5N1-032



The MAH corrected the number of participants who completed the study reported in the Summary of clinical efficacy based on the Final CSR (dated 08-MAR-2013).

Recruitment

Study D-PAN H5N1-013

The study was conducted at 6 sites in 2 countries; 4 sites in Australia and 2 sites in Singapore.

First subject first visit: 18 April 2011, Last subject last visit: 02 November 2012.

Study D-PAN H5N1-032

The study was conducted at 1 site in the Philippines.

First subject first visit: 28 July 2011, Last subject last visit: 05 October 2012.

Conduct of the study

Study D-PAN H5N1-013

Amendments

There were **3 amendments** to the original study protocol (dd. 07 December 2010). Amendment 1 (24 January 2011) was executed to correct errors in vaccine tables where commas were left out in volumes and to clarify the contents of the vials and vaccine doses. Amendment 2 (16 June 2011) was written to exclude subjects who had had a past medical history of infection with a H5N1 virus or vaccination with a H5N1 vaccine. Amendment 3 (04 November 2011) was written as the age stratification ratio of 2:1:1 for children 6 to 11 months, 12 to 23 months, and 24 to 35 months of age, respectively, was not to be maintained due to recruitment difficulties. The overall subject enrolment goal did not change.

Other changes

Compared to the protocol, an additional ATP cohort at Month 6 for kinetic analysis had been defined. Also the fever definition was adapted following the decision to harmonize the way fever is defined and reported for paediatric clinical trials (definition of fever changed from ≥37.5˚C to ≥38.0˚C).

Protocol deviations

One protocol violation, administration of vaccine(s) forbidden in the protocol, led to exclusion from the ATP safety cohort, see Table 12. In total, 27 participants (23.9%) had protocol deviations that led to exclusion from the ATP cohort for immunogenicity: 18 participants (15.9%) were non-compliant with blood sampling schedule (including wrong and unknown dates), 13 participants (11.5%) were non-compliant with vaccination schedule (including wrong and unknown dates), 2 participants (1.8%) had essential serological data missing, 1 participant (0.9%) had a violation of inclusion/exclusion criteria and as mentioned 1 (0.9%) participant had a forbidden vaccine administered.

Table 12 Summary of subjects excluded from ATP analyses with reasons for exclusion by age stratum (D-PAN H5N1-013)

	All			6<12 M		12<24 M		24<36 M	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total cohort	113			46		34		33	
Total vaccinated cohort	113		100	46		34		33	
Administration of vaccine(s) forbidden in the protocol (code 1040)	1	1		1	1	0	0	0	0
ATP cohort for safety	112		99.1	45		34		33	
Protocol violation (inclusion/exclusion criteria) (code 2010)	0	1		0	1	0	0	0	0
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	13	13		5	5	6	6	2	2
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	11	18		6	10	3	5	2	3
Essential serological data missing (code 2100)	2	2		1	1	1	1	0	0
ATP cohort for immunogenicity	86		76.1	33		24		29	

Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

The ATP cohort at Month 12 is presented in Table 13. One protocol violation, administration of vaccine(s) forbidden in the protocol, led to exclusion from the ATP safety cohort, see Table 13. In total, 13 participants (11.5%) had protocol deviations that led to exclusion from the ATP cohort for

immunogenicity: 5 participants (4.4%) were non-compliant with vaccination schedule (including wrong and unknown dates), 7 participants (6.2%) had essential serological data missing, 1 participant (0.9%) had a violation of inclusion/exclusion criteria and as mentioned 1 (0.9%) participant had a forbidden vaccine administered.

Table 13 Summary of subjects excluded from Month 12 ATP analyses with reasons for exclusion by age stratum (D-PAN H5N1-013)

	Total			6<12 M		12<24 M		24<36 M	
Title	**n**	**s**	**%**	**n**	**s**	**n**	**s**	**n**	**s**
Total cohort	113			46		34		33	
Total Vaccinated cohort	113		100	46		34		33	
Administration of vaccine(s) forbidden in the protocol (code 1040)	1	1		1	1	0	0	0	0
ATP cohort for safety	112		99.1	45		34		33	
Protocol violation (inclusion/exclusion criteria) (code 2010)	0	1		0	1	0	0	0	0
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	5	5		1	1	3	3	1	1
Essential serological data missing (code 2100)	7	7		3	3	4	4	0	0
ATP cohort for immunogenicity (M12)	100		88.5	41		27		32	

Note: Subjects may have more than one elimination code assigned
n = number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number
s = number of subjects with the elimination code assigned
% = percentage of subjects in the considered ATP cohort relative to the Total vaccinated cohort

Study D-PAN H5N1-032

Amendments

There were **no amendments** to the original study protocol (dd. 02 December 2010).

The statistical analysis was performed according to the SAP Amendment 1 dated 21 June 2012. Changes to the conduct of the study are summarized below:

- Compared to the protocol, an additional ATP cohort for analysis of immunogenicity at Month 6 (booster) for kinetics analysis was defined.
- The fever definition was adapted following the decision to harmonize the way fever is defined and reported in paediatric settings.
- A further specification as to how the analyses on concomitant medication were performed was given in Section 5.9.9.
- Although the study was originally planned as a multi-center study, the study was carried out as a single-center study due to logistic issues.
- A post hoc analysis was performed to include data on unsolicited adverse events (Day 0 to Day 42) pooling groups according to their primary schedule and also to support a two dose priming schedule for regulatory submission.

Protocol deviations

Five protocol violation, administration of vaccine(s) forbidden in the protocol, led to exclusion from the ATP safety cohort, see Table 14.

In total, 9 participants (1.7%) had protocol deviations that led to exclusion from the ATP cohort for immunogenicity at Day 42: 4 participants (0.8%) had essential serological data missing, and 5 participants (1.0%) had a forbidden vaccine administered.

In total, 56 participants (10.8%) had protocol deviations that led to exclusion from the ATP cohort for immunogenicity at Month 6: 48 participants (9.2%) were non-compliant with blood sampling schedule (including wrong and unknown dates), 4 participants (0.8%) had essential serological data missing, and 5 participants (1.0%) had a forbidden vaccine administered.

In total, 19 participants (3.7%) had protocol deviations that led to exclusion from the ATP cohort for immunogenicity at Month 12: 13 participants (2.5%) had essential serological data missing, and 7 participants (1.3%) had a forbidden vaccine administered.

Table 14 Summary of subjects excluded from ATP analyses with reasons for exclusion by age stratum (D-PAN H5N1-032)

Title	Total			H5-H5		H5-Hav		Hav-H5		Hav-Hav	
	n	s	%	n	s	n	s	n	s	n	s
Total cohort	520			156		156		104		104	
Total vaccinated cohort	520		100	156		156		104		104	
Administration of vaccines forbidden in the protocol (code 1040)	5	5		0	0	3	3	1	1	1	1
ATP cohort for safety	515		99.0	156		153		103		103	
Essential serological data missing (code 2100)	4	4		1	1	1	1	0	0	2	2
Day 42 ATP cohort for immunogenicity	511		98.3	155		152		103		101	
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	47	48		28	28	0	0	19	20	0	0
Essential serological data missing (code 2100)	4	4		1	1	1	1	0	0	2	2
Month 6 ATP cohort for immunogenicity	464		89.2	127		152		84		101	
Month 12 ATP cohorts											
Administration vaccines forbidden in protocol	7	7		1	1	3	3	2	2	1	1
ATP cohort for safety	513		98.7	155		153		102		103	
Essential serological data missing	12	13		4	4	6	7	2	2	0	0
Month 12 ATP cohort for immunogenicity	501		96.3	151		147		100		103	

The study conduct was overall acceptable for both studies.

The change in fever definition, from ≥37.5˚C to ≥38.0˚C, was endorsed.

For study D-PAN H5N1-013 it was understood that due to recruitment difficulties age stratification ratio of 2:1:1 for children 6-11 months, 12-23 months and 24-35 months of age was not maintained. This could be accepted as overall subject enrolment goal was maintained. From immunogenicity standpoint

children aged 6 months to 2 years of age were considered comparable. As amendment 2 was executed after study enrolment had started, the MAH was asked to determine how many participants entered the study that had a history of either H5N1 disease or vaccination. None of the participants enrolled had a history of either H5N1 disease or H5N1 vaccination.

The MAH comprehensively monitored the protocol deviations during study D-PAN H5N1-013. Important protocol deviations leading to exclusion from ATP cohort were reported by at most 27 participants (23.9%) during the study, most of which were deviations in trial procedures, with non-compliance to blood sampling schedule (15.9%) and vaccination schedule (11.5%). The maximum percentage of clinically important protocol deviations were relatively high, leading to an exclusion rate of 23.9%. However, this could be expected with these young children.

For study D-PAN H5N1-032, important protocol deviations leading to exclusion from ATP cohort at Day 42 were reported by in total 9 participants (1.7%) during the study, which included missing essential serology data and administration of vaccines forbidden in the study protocol. Important protocol deviations leading to exclusion from ATP cohort at Month 6 were reported by in total 56 participants (10.8%) during the study, most of which were non-compliance to blood sampling schedule (9.2%).

Baseline data

D-PAN H5N1-013

Study **D-PAN H5N1-013** included healthy children 6 and 35 months of age at the time of the first vaccination. The baseline demographic data of the study is shown in Table 16.

Table 15 Summary of demographic characteristics by age stratum – Total vaccinated cohort (D-PAN H5N1-013)

		6<12 M N = 46		12<24 M N = 34		24<36 M N = 33		All N = 113	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (months) at vaccination dose: 1	Mean	8.3	-	16.1	-	29.6	-	16.9	-
	SD	1.56	-	3.44	-	3.38	-	9.29	-
	Median	8.0	-	15.0	-	30.0	-	13.0	-
	Minimum	6	-	12	-	24	-	6	-
	Maximum	11	-	23	-	35	-	35	-
Gender	Female	25	54.3	19	55.9	19	57.6	63	55.8
	Male	21	45.7	15	44.1	14	42.4	50	44.2
Geographic Ancestry	African heritage / african american	0	0.0	0	0.0	0	0.0	0	0.0
	American indian or alaskan native	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - central/south asian heritage	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - east asian heritage	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - south east asian heritage	34	73.9	26	76.5	22	66.7	82	72.6
	Native hawaiian or other pacific islander	0	0.0	0	0.0	0	0.0	0	0.0
	White - arabic / north african heritage	0	0.0	0	0.0	0	0.0	0	0.0
	White - caucasian / european heritage	12	26.1	8	23.5	9	27.3	29	25.7
	Other	0	0.0	0	0.0	2	6.1	2	1.8

6<12 M = Subjects 6 months to less than 12 months of age
12<24 M = Subjects 12 months to less than 24 months of age
24<36 M = Subjects 24 months to less than 36 months of age
All= 2 doses (D0, D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9 µg HA + AS03B)
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

The study included slightly more female than male participants.

Off note, in the 24 to <36 months old category geographic ancestry was slightly different compared to the other groups, with a smaller proportion of Asian -south east Asian heritage population and an increased Other population.

D-PAN H5N1-032

Study **D-PAN H5N1-032** included healthy children 3 to 17 years of age (inclusive) at the time of the first vaccination. The baseline demographic data of the study is shown in Table 16. The baseline characteristics of the different ATP cohorts for immunogenicity do not differ substantially from the total vaccinated cohort.

Table 16 Summary of baseline characteristics – Total vaccinated cohort (D-PAN H5N1-032)

		H5_H5 N = 156		H5_Hav N = 156		Hav_H5 N = 104		Hav_Hav N = 104		Total N = 520	
Characteristics	**Parameters or Categories**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**	**Value or n**	**%**
Age (years) at vaccination dose: 1	Mean	9.7	-	9.4	-	9.3	-	9.6	-	9.5	-
	SD	4.26	-	3.88	-	3.87	-	4.23	-	4.06	-
	Median	9.0	-	9.0	-	9.0	-	9.5	-	9.0	-
	Minimum	3	-	3	-	3	-	3	-	3	-
	Maximum	17	-	17	-	17	-	17	-	17	-
Gender	Female	81	51.9	81	51.9	52	50.0	52	50.0	266	51.2
	Male	75	48.1	75	48.1	52	50.0	52	50.0	254	48.8
Geographic Ancestry	African heritage / african american	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	American indian or alaskan native	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - central/south asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - east asian heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - japanese heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Asian - south east asian heritage	156	100	156	100	104	100	104	100	520	100
	Native hawaiian or other pacific islander	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - arabic / north african heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	White - caucasian / european heritage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
	Other	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

H5_H5 = H5N1_H5N1: 2 doses (D0,D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$), 1 dose (D364) of Havrix
H5_Hav = H5N1_Havrix: 2 doses (D0,D21) of H5N1 Indo (1.9 µg HA + $AS03_B$) and 2 doses (D182, D364) of Havrix
Hav_H5 = Havrix_H5N1: 1 dose (D0) of Havrix and 1 dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$), 1 dose (D364) of Havrix
Hav_Hav = Havrix_Havrix: 2 doses (D0, D182) of Havrix
N = total number of subjects
n/% = number / percentage of subjects in a given category
Value = value of the considered parameter
SD = standard deviation

The study included slightly more female than male participants.

As it was a single centre study, all participants were of Asian -south east Asian heritage.

Numbers analysed

See participant flow.

Outcomes and estimation

Study D-PAN H5N1-013

Primary immunogenicity endpoint

The primary immunogenicity objective of assessing whether a heterologous booster dose of 1.9 µg A/turkey/Turkey/1/2005 (H5N1) HA with $AS03_B$ given six months following a two-dose primary vaccination series elicits an antibody response that meets the CHMP criteria was met as the following were fulfilled:

- The point estimate for SCR was equal to 100% for all subjects (100% for 6M<12M, 100% for 12M<24M, 100% for 24M<36M) (CHMP criterion >40%) see Table 22.
- The point estimate for SPR was equal to 100% for all subjects (100% for 6M<12M, 100% for 12M<24M, 100% for 24M<36M) (CHMP criterion >70%).
- The point estimate for MGI was equal to 357.7 for all subjects (424.1 for 6M<12M, 317.6 for 12M<24M, 321.2 for 24M<36M) (CHMP criterion >2.5) see Table 22.

Table 17 Summary of vaccine heterologous HI antibody parameters (GMT, SCR and MGI) – ATP cohort for immunogenicity (D-PAN H5N1-013)

Antibody	Group	Day	N	GMT (95% CI)	N'	SCR n	SCR % (95% CI)	MGI (95% CI)
Flu A/ turkey/Turkey /01/2005	6 to <12 mo	0	33	5.8 (5.2-6.5)				
		182	33	95.7 (75.5-121.1)	33	31	93.9 (79.8-99.3)	16.5 (12.8-21.4)
		192	33	2454.6 (1935.7-3112.6)	33	33	100 (89.4-100)	424.1 (327.3-549.4)
	12 to <24 mo	0	24	5.8 (4.8-6.9)				
		182	21	84.1 (65.5-108.1)	21	20	95.2 (76.2-99.9)	14.8 (10.8-20.1)
		192	21	1810.2 (1207.1-2714.7)	21	21	100 (83.9-100)	317.6 (208.4-484.0)
	24 to <36 mo	0	29	5.5 (4.7-6.4)				
		182	29	86.1 (73.8-100.4)	29	28	96.9 (82.2-99.9)	15.6 (12.5-19.5)
		192	29	1767.4 (1403.0-2226.3)	29	29	100 (88.1-100)	321.2 (248.4-415.5)
	All	0	86	5.7 (5.2-6.2)				
		182	83	89.3 (79.1-100.7)	83	79	95.2 (88.1-98.7)	15.8 (13.6-18.2)
		192	83	2026.2 (1731.3-2371.3)	83	83	100 (95.7-100)	357.7 (302.4-423.2)

GMT: geometric mean titre; MGI: mean geometric increase; SCR: seroconversion rate
SCR is defined as: for initially seronegative subjects an antibody titre ≥40 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects.
N is the number of subjects with results available (GMT)
N' is the number of subjects with both pre- and postvaccination results available (SCR and MGI)

The primary immunogenicity objective of the study of assessing the immune response after a heterologous booster 6 months after the primary vaccination was met, as the point estimate for SCR was over 40%, 100% in all age stratums, the point estimate for SPR was >70% and the point estimate for MGI was >2.5 (>317 in all age stratums).

Ten days after a booster with 1.9µg A/turkey HA +AS03$_B$, a substantial immune response as measured by A/turkey HI parameters was seen, as reflected by a SCR of 100% and a MGI of >317.This indicates that in children primed with A/Indonesia, a booster with A/turkey 6 months after the primary vaccination, were able to elicit a substantial immune response to the booster. In a real world setting during a pandemic, this would mean that up to 6 months after the primary vaccination the children would be able to elicit a robust immune response to an antigenically drifted strain.

Secondary immunogenicity objectives

The results for GMTs for HI antibodies against the A/Indonesia/05/2005 H5N1 virus strain on Day 0, Day 42, Day 182 and Day 192 are detailed in Table 18. The results for GMTs for HI antibodies against the A/Indonesia/05/2005 H5N1 virus strain on Day 0, and Day 364 are detailed in Table 19.

Table 18 Summary of vaccine homologous HI antibody parameters (GMT, SCR and MGI) – ATP cohort for immunogenicity (D-PAN H5N1-013)

Antibody	Group	Day	N	GMT (95% CI)	N'	SCR n	SCR % (95% CI)	MGI (95% CI)
Flu A/ Indonesia/ 5/2005	6 to <12 mo	0	33	5.0 (5.0–5.0)				
		42	32	945.2 (745.8-1197.9)	32	32	100 (89.1-100)	189.0 (149.2-239.6)
		182	33	160.0 (125.4-204.2)	33	32	97.0 (84.2-99.9)	32.0 (25.1-40.8)
		192	33	2163.9 (1772.7-2641.4)	33	33	100 (89.4-100)	432.8 (354.5-528.3)
	12 to <24 mo	0	24	5.0 (5.0-5.0)				
		42	24	1336.7 (990.3-1804.2)	24	24	100 (85.8-100)	267.3 (198.1-360.8)
		182	21	147.3 (113.2-191.7)	21	21	100 (83.9-100)	29.5 (22.6-38.3)
		192	21	1534.7 (1108.1-2125.5)	21	21	100 (83.9-100)	306.9 (221.6-425.1)
	24 to <36 mo	0	29	5.0 (5.0-5.0)				
		42	29	1044.7 (832.6-1310.9)	29	29	100 (88.1-100)	208.9 (166.5-262.2)
		182	29	133.7 (113.1-158.1)	29	29	100 (88.1-100)	26.7 (22.6-31.6)
		192	29	1606.2 (1254.3-2056.9)	29	29	100 (88.1-100)	321.2 (187.1-248.7)
	All	0	86	5.0 (5.0-5.0)				
		42	85	1078.6 (935.3-1243.7)	85	85	100 (95.8-100)	215.7 (187.1-248.7)
		182	83	147.2 (129.6-167.1)	83	82	98.8 (93.5-100)	29.4 (25.9-33.4)

Antibody	Group	Day	N	GMT (95% CI)	N'	SCR n	SCR % (95% CI)	MGI (95% CI)
		192	83	17887.6 (1552.4-2058.3)	83	83	100 (95.7-100)	357.5 (310.5-411.7)

GMT: geometric mean titre; MGI: mean geometric increase; SCR: seroconversion rate
SCR is defined as: for initially seronegative subjects an antibody titre ≥40 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects.
N is the number of subjects with results available (GMT)
N' is the number of subjects with both pre- and postvaccination results available (SCR and MGI)

Table 19 Summary of vaccine homologous and heterologous HI antibody parameters (GMT, SCR and MGI) – Month 12 ATP cohort for immunogenicity (D-PAN H5N1-013)

Antibody	Group	Day	N	GMT (95% CI)	N'	SCR n	SCR % (95% CI)	MGI (95% CI)
Flu A/ Indonesia/ 5/2005	6 to <12 mo	0	41	5.0 (5.0-5.0)				
		364	41	1465.4 (1168.2-1838.1)	41	41	100 (91.4-100)	293.1 (233.6)
	12 to <24 mo	0	27	5.0 (5.0-5.0)				
		364	27	1055.8 (769.2-1449.1)	27	27	100 (87.2-100)	211.2 (153.8-289.8)
	24 to <36 mo	0	32	5.0 (5.0-5.0)				
		364	32	668.4 (505.2-884.2)	32	32	100 (89.1-100)	133.7 (101.0-176.8)
	All	0	100	5.0 (5.0-5.0)				
		364	100	1043.3 (886.1-1228.4)	100	100	100 (96.4-100)	208.7 (177.2-245.7)
Flu A/ turkey/Turkey/01/2005	6 to <12 mo	0	41	6.0 (5.3-6.7)				
		364	41	1810.1 (1466.6-2234.0)	41	41	100 (91.4-100)	19.9 (15.2-26.1)
	12 to <24 mo	0	27	5.5 (4.8-6.4)				
		364	27	1263.8 (929.1-1719.0)	26	26	100 (86.8-100)	16.4 (12.6-21.4)
	24 to <36 mo	0	32	5.6 (4.8-6.5)				
		364	32	803.4 (609.7-1058.8)	32	28	87.5 (71.0-96.5)	9.5 (7.2-12.5)
	All	0	100	5.7 (5.3-6.2)				
		364	100	1266.8 (1080.6-1485.0)	99	95	96.0 (90.0-98.9)	14.9 (12.6-17.6)

GMT: geometric mean titre; MGI: mean geometric increase; SCR: seroconversion rate
SCR is defined as: for initially seronegative subjects an antibody titre ≥40 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects.
N is the number of subjects with results available (GMT)
N' is the number of subjects with both pre- and postvaccination results available (SCR and MGI)

The primary vaccination induced a robust increase in homologous HI antibodies, as in all age stratums a SCR of 100% was seen at D42. GMTs remained well above baseline for at least 6 months, as on D182 in all age stratums a SCR of ≥97% was observed. Ten days after a booster with 1.9µg A/turkey HA +AS03$_B$, a substantial booster response in A/Indonesia HI parameters was seen, in that GMTs increased to 17887.6 (1552.4-2058.3), SCR was 100% and MGI was 357.5 (310.5-411.7) in the entire population. This indicates that an antigenically drifted strain (A/turkey) was able to elicit an anamnestic response for A/Indonesia antibodies that was higher compared to the primary response (as seen as GMTs at D42) at 6 months after the primary vaccination. Substantial cross-reactivity is seen in the immune response.

Six months after a heterologous booster dose (D364), primary vaccine homologous GMTs declined, however, in all age stratums a SCR of 100% was seen. These results indicate that vaccine homologous HI antibody response was induced by the primary vaccination. The HI antibodies declined over time, but persisted for at least 6 months. A booster is able to increase GMTs above levels reached in the primary vaccination and antibodies persisted for at least 6 months after a booster.

Six months after a boost with A/turkey, A/turkey HI antibody GMTs were still present well above baseline line levels, with a SCR of > 87% in all age stratums. These results show that a booster given 6 months after a primary vaccination is able to elicit HI antibodies that persist for at least 6 months after boost.

Table 20 Summary of vaccine homologous and heterologous MN antibody parameters (GMT, VRR and MGI) – Month 6 ATP cohort for immunogenicity (D-PAN H5N1-013)

Antibody	Group	Day	N	GMT (95% CI)	N'	VRR	
						n	% (95% CI)
Flu A/ Indonesia/ 5/2005	6 to <12 mo	0	29	14.0 (14.0-14.0)			
		42	24	1785.9 (1168.6-2729.5)	22	22	100 (84.6-100)
		182	32	526.6 (397.1-698.2)	28	28	100 (87.7-100)
		192	33	12667.0 (10522.9-15248.1)	29	29	100 (88.1-100)
	12 to <24 mo	0	22	14.0 (14.0-14.0)			
		42	21	2080.4 (1422.8-3041.7)	19	19	100 (82.4-100)
		182	21	483.3 (333.1-701.3)	19	19	100 (82.4-100)
		192	21	11031.5 (8157.8-14917.5)	19	19	100 (82.4-100)
	24 to <36 mo	0	24	14.4 (13.6-15.3)			
		42	25	1755.2 (1191.3-2586.1)	21	21	100 (83.9-100)
		182	28	353.4 (273.7-456.2)	23	22	95.7 (78.1-99.9)
		192	29	9883.1 (7631.9-12798.4)	24	24	100 (85.8-100)
	All	0	75	14.1 (13.9-14.4)			
		42	70	1858.0 (1491.3-2315.0)	62	62	100 (94.2-100)
		182	81	448.7 (379.0-531.2)	70	69	98.6 (92.3-100)
		192	83	11215.7 (9797.4-12839.2)	72	72	100 (95.0-100)
Flu A/ turkey/Turkey/01/ 2005	6 to <12 mo	0	29	14.0 (14.0-14.0)			
		182	32	137.5 (108.3-174.7)	28	22	78.6 (59.0-91.7)
		192	33	7391.0 (5117.8-10674.0)	29	29	100 (88.1-100)
	12 to <24 mo	0	22	14.0 (14.0-14.0)			
		182	21	124.9 (104.3-149.5)	19	17	89.5 (66.9-98.7)
		192	21	5464.2 (3426.9-8712.7)	19	19	100 (82.4-100)
	24 to <36 mo	0	24	14.0 (14.0-14.0)			
		182	28	113.2 (96.2-133.2)	23	19	82.6 (61.2-95.0)
		192	29	3349.4 (2249.8-4986.4)	24	24	100 (85.8-100)
	All	0	75	14.0 (14.0-14.0)			
		182	81	125.4 (111.6-140.8)	70	58	82.9 (72.0-90.8)
		192	83	5192.9 (4101.3-6575.1)	72	72	100 (95.0-100)

GMT: geometric mean titre; MGI: mean geometric increase; SCR: seroconversion rate
SCR is defined as: for initially seronegative subjects an antibody titre ≥40 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects.
N is the number of subjects with results available (GMT)
N' is the number of subjects with both pre- and postvaccination results available (SCR and MGI)

Neutralizing antibodies are functional antibodies. The primary vaccination induced a robust increase in homologous MN antibodies, as in all age stratums a VRR of 100% was seen at D42. GMTs remained well above baseline for at least 6 months, as on D182 in all age stratums a VRR of >95% was observed. Ten days after a heterologous boost, a significant increase in MN antibodies was observed which led to a VRR of 100% in all age stratums and GMTs were higher compared to the GMTs at D42. Six months after a heterologous booster dose (D364), primary vaccine homologous GMTs declined, however, in all age stratums a VRR of 100% was seen. These results indicate that vaccine homologous MN antibody response was induced by the primary vaccination. The MN antibodies decline over time, but persist for at least 6 months. A booster is able to increase GMTs above levels reached in the primary vaccination and antibodies persist for at least 6 months after a booster.

Six months after a primary vaccination with A/Indonesia, A/turkey MN antibody GMTs were still present well above baseline line levels, with a VRR of > 78% in all age stratums. Ten days after a boost with A/turkey, a robust increase in GMTs was seen in all age stratums, leading to a VRR of 100%. VRR was 100% in all age stratums at D364. These results indicate that vaccine heterologous MN antibody response was induced by the primary vaccination, which persisted for at least 6 months as prevaccination titers were lower compared to D182. A booster is able to increase GMTs leading to a VRR of 100%. This VRR persisted for at least 6 months after boost.

Study D-PAN H5N1-032

Primary immunogenicity endpoint

The primary immunogenicity objective was to assess the superiority of the HI antibody response against A/turkey/Turkey/01/2005 (H5N1) 10 days following H5N1 vaccination on Day 182 (1.9 µg A/turkey/Turkey/01/2005 (H5N1) HA antigen adjuvanted with $AS03_B$) in subjects previously primed with two doses of heterologous A/Indonesia/5/2005 (H5N1) vaccine (Group H5N1_H5N1) versus non primed subjects (Group Havrix_H5N1).

The primary immunogenicity objective was met as the lower limit of the two-sided 95% confidence interval for the HI GMT ratio on Day 192 (Group H5N1_H5N1 compared to Group Havrix_H5N1) was 7.30, which is greater than 1.0, see Table 21.

Table 21 Adjusted GMT ratios of HI antibodies post vaccination between group H5N1_H5N1 and group Havrix_H5N1 for A/turkey/Turkey/01/2005 strain on Day 192 (Month 6 ATP cohort) (D-PAN H5N1-032)

				Adjusted GMT ratio (H5_H5 / Hav_H5)		
H5_H5		Hav_H5			95% CI	
N	Adjusted GMT	N	Adjusted GMT	Value	LL	UL
127	510.4	84	43.1	11.84	7.30	19.20

H5_H5 = H5N1_H5N1: 2 doses (D0,D21) of H5N1 Indo and 1 booster dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$), 1 dose (D364) of Havrix
Hav_H5 = Havrix_H5N1: 1 dose (D0) of Havrix and 1 dose (D182) of H5N1 Turkey (1.9 µg HA + $AS03_B$), 1 dose (D364) of Havrix
Adjusted GMT = geometric mean antibody titer adjusted for baseline titer (baseline = Day 182)
N = Number of subjects with both pre- and post-vaccination results available
95% CI = 95% confidence interval for the adjusted GMT ratio (Ancova model: adjustment for baseline titer (baseline = Day 182) - pooled variance ; LL = lower limit, UL = upper limit

At D182 the H5N1/Turkey HI GMT was higher in the H5_H5 group (39.6 [35.8-43.8]) compared to the Hav_H5 group (6.0 [5.5-6.5]). At D192, 10 days after booster vaccination with H5N1/Turkey, H5N1/Turkey HI GMT was 737.6 (646.8-841.1) in the H5_H5 group vs 24.7 (19.7-31.0) in the Hav_H5 group. Both groups showed an increase in HI GMT after the booster vaccination with H5N1/Turkey, however, the response was significantly higher in the H5_H5 group, indicating the presence of an anamnestic immune response to an antigenically drifted strain after primary vaccination with H5N1/Indonesia.

Secondary immunogenicity objectives

The results for GMTs, SCR and MGI for HI antibodies against the A/Indonesia/05/2005 H5N1 and A/turkey/Turkey/01/2005 virus strains on Day 0, Day 42, and Day 182 for all groups and Day 192 for H5_H5 and Hav_H5 groups are detailed in Table 22.

Table 22 Summary of vaccine homologous and heterologous HI antibody parameters (GMT, SCR and MGI) – ATP cohort for immunogenicity (D-PAN H5N1-032)

Antibody	Group	Day	N	GMT (95% CI)	N'	SCR		MGI*
						n	% (95% CI)	(95% CI)
Flu A/ Indonesia/ 5/2005	H5-H5	0	155	5.7 (5.4-6.0)				
		42	155	553.5 (490.9-624.1)	155	154	99.4 (96.5-100)	96.9 (84.9-110.4)
		182	155	52.2 (47.7-57.1)	155	122	78.7 (71.4-84.9)	9.1 (8.3-10.1)
		192	127	674.1 (595.0-763.8)	127	127	100 (97.1-100)	117.7 (103.0-134.5)
	H5-Hav	0	152	5.5 (5.2-5.8)				
		42	152	595.0 (522.1-678.2)	152	151	99.3 (96.4-100)	108.4 (94.2-124.7)
		182	152	54.1 (49.5-59.1)	152	121	79.6 (72.3-85.7)	9.8 (9.0-10.8)
		192						

Antibody	Group	Day	N	GMT (95% CI)	N'	SCR		MGI* (95% CI)
						n	% (95% CI)	
	Hav-H5	0	103	5.4 (5.1-5.8)				
		42	103	5.6 (5.2-6.0)	103	1	1.0 (0.0-5.3)	1.0 (1.0-1.1)
		182	103	5.1 (5.0-5.2)	103	0	0.0 (0.0-3.5)	0.9 (0.9-1.0)
		192	84	7.6 (6.7-8.5)	84	3	3.6 (0.7-10.1)	1.4 (1.2-1.6)
	Hav-Hav	0	101	5.8 (5.3-6.3)				
		42	101	6.2 (5.6-7.0)	101	1	1.0 (0.0-5.4)	1.1 (0.9-1.2)
		182	101	5.6 (5.3-6.0)	101	0	0.0 (0.0-3.6)	1.0 (0.9-1.1)
		192						
Flu A/ turkey/Turkey /01/2005	H5-H5	0	155	7.0 (6.3-7.7)				
		42	155	193.0 (172.1-216.5)	155	153	98.7 (95.4-99.8)	27.7 (24.0-31.9)
		182	127	39.6 (35.8-43.8)	155	75	48.4 (40.3-56.5)	5.6 (5.0-6.3)
		192	127	737.6 (646.8-841.1)	127	127	100 (97.1-100)	
	H5-Hav	0	155	6.4 (5.9-7.0)				
		42	155	212.6 (188.1-240.3)	152	149	98.0 (94.3-99.6)	33.1 (28.6-38.3)
		182	152	42.5 (38.9-46.4)	152	101	66.4 (58.3-73.9)	6.6 (6.0-7.4)
		192						
	Hav-H5	0	103	6.1 (5.6-6.8)				
		42	103	6.9 (6.1-7.9)	103	4	3.9 (1.1-9.6)	1.1 (1.0-1.3)
		182	84	6.0 (5.5-6.5)	103	1	1.0 (0.0-5.3)	1.0 (0.9-1.1)
		192	84	24.7 (19.7-31.0)	84	27	32.1 (22.4-43.2)	
	Hav-Hav	0	101	7.2 (6.3-8.2)				
		42	101	8.5 (7.2-10.0)	101	4	4.0 (1.1-9.8)	1.2 (1.1-1.3)
		182	101	7.0 (6.1-8.0)	101	2	2.0 (0.2-7.0)	1.0 (0.9-1.1)
		192						

GMT: geometric mean titre; MGI: mean geometric increase; SCR: seroconversion rate
SCR is defined as: for initially seronegative subjects an antibody titre ≥40 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects.
N is the number of subjects with results available (GMT)
N' is the number of subjects with both pre- and postvaccination results available (SCR and MGI)
*MGI is the mean GMT increase compared to Day 0.

Pre-vaccination homologous HI GMT was comparably low (<6.0) between the groups, indicating that a H5N1 naïve population was selected. At D42, 21 days after primary vaccination with 1.9 µg A/Indonesia HA + $AS03_B$, a significant increase in homologous HI GMT was observed in both H5_H5 and H5_Hav groups leading to an >99% SCR (99.4% and 99.3% respectively) and >96 MGI (96.9 and 108.4 respectively). Groups Hav_H5 and Hav_Hav received Havrix or Havrix junior at D0 and as expected did not show an increase in A/Indonesia HI GMT at D42. These results indicate that the primary vaccination with H5N1 vaccine was able to elicit a robust immune response leading to an SCR of nearly 100% at 21 days after vaccination.

Homologous HI GMTs declined over time; they were lower at D182 as compared to D42 in groups H5_H5 and H5_Hav. However, they remained well above baseline as SCR was >78% at D182 for both groups (78.7% and 79.6% respectively) and MGI was >9 (9.1 and 9.8 respectively).

Ten days after a booster with 1.9 µg A/turkey HA +$AS03_B$, group H5_H5 showed a substantial booster response in A/Indonesia HI parameters, in that GMTs increased to 674.1, SCR was 100% and MGI was 117.7. As shown above, an antigenically drifted strain (A/turkey) was able to elicit an anamnestic response for A/Indonesia antibodies that was higher compared to the primary response at 6 months after the primary vaccination. In group without primary vaccination series, Hav_H5, 10 days after the heterologous booster dose A/Indonesia GMTs, SCR and MGI increased only slightly.

Pre-vaccination heterologous HI GMT was comparably low (<7.5) between the groups, indicating that a H5N1 naïve population was selected. At D42, 21 days after primary vaccination with 1.9µg A/Indonesia HA +$AS03_B$, a significant increase in A/turkey HI GMT was observed in both H5_H5 and H5_Hav groups leading to an >97% SCR (98.7% and 98.0% respectively) and >27 MGI (27.7 and 33.1 respectively). The increase in heterologous HI GMT was lower compared to homologous HI GMT, which is expected. Groups Hav_H5 and Hav_Hav received Havrix or Havrix junior at D0 and as expected did not show an increase in A/turkey HI GMT at D42. These results indicate that the primary vaccination with H5N1

vaccine was able to elicit a robust heterologous immune response leading to an SCR of over 95% at 21 days after vaccination.

Heterologous HI GMTs declined over time; they were lower at D182 as compared to D42 in groups H5_H5 and H5_Hav. However, they remained well above baseline. At D182 groups H5_H5 and H5_Hav groups had higher mean A/turkey HI GMTs (39.6 and 42.5 respectively) compared to Hav_H5 and Hav_Hav groups (6.0 and 7.0 respectively). Ten days after a booster with 1.9µg A/turkey HA +AS03$_B$, the H5_H5 group showed a substantial booster response in A/turkey HI parameters, as GMTs increased to 737.6 and SCR was 100%. This indicates that a heterologous boost with A/turkey induces a substantial immune response within 10 days in individuals primed with A/Indonesia, leading to an SCR of 100%. In the Hav_H5 group, an immune response was seen as A/turkey HI GMTs increased to 24.7 from 6.0 prevaccination, leading to an 32.1% SCR. These results indicate that priming substantially increases the immune response to a heterologous boost.

The results for GMTs, SCR and MGI for HI antibodies against the A/Indonesia/05/2005 H5N1 virus strain and the A/turkey/Turkey/01/2005 H5N1 virus strain on Day 0 and Day 364 for the Month 12 ATP cohort are detailed in Table 23.

Table 23 Summary of vaccine homologous HI antibody parameters (GMT, SCR and MGI) – Month 12 ATP cohort for immunogenicity (D-PAN H5N1-032)

Antibody	Group	Day	N	GMT	N'	SCR		MGI
				(95% CI)		n	% (95% CI)	(95% CI)
Flu A/ Indonesia/ 5/2005	H5-H5	0	151	5.7 (5.4-6.0)				
		364	151	205.5 (183.3-230.4)	151	151	100 (97.6-100)	36.2 (32.0-40.9)
	H5-Hav	0	147	5.5 (5.2-5.7)				
		364	147	40.4 (36.8-44.5)	147	100	68.0 (59.8-75.5)	7.4 (6.7-8.2)
	Hav-H5	0	100	5.5 (5.1-5.8)				
		364	100	8.5 (7.6-9.4)	100	1	1.0 (0.0-5.4)	1.6 (1.4-1.7)

GMT: geometric mean titre; MGI: mean geometric increase; SCR: seroconversion rate
SCR is defined as: for initially seronegative subjects an antibody titre ≥40 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects.
N is the number of subjects with results available (GMT)
N' is the number of subjects with both pre- and postvaccination results available (SCR and MGI)

The results for GMTs, SCR and MGI for HI antibodies against the A/turkey/Turkey/01/2005 H5N1 virus strain on Day 182 and Day 364 for the Month 12 ATP cohort are detailed in Table 23

Table 24 Summary of vaccine heterologous HI antibody parameters (GMT, SCR and MGI) – Month 12 ATP cohort for immunogenicity (D-PAN H5N1-032)

Antibody	Group	Day	N	GMT	N'	SCR		MGI
				(95% CI)		n	% (95% CI)	(95% CI)
Flu A/ turkey/Turkey/01/2005	H5-H5	182	151	38.5 (35.1-42.2)				
		364	151	215.1 (190.3-243.3)	151	105	69.5 (61.5-76.8)	31.4 (26.9-36.7)
	H5-Hav	182	147	43.0 (39.4-47.0)				
		364	147	35.4 (32.2-39.0)				5.6 (5.0-6.3)
	Hav-H5	182	100	6.1 (5.6-6.6)				
		364	100	18.4 (16.3-20.9)	100	18	18.0 (11.0-26.9)	3.0 (2.6-3.4)

GMT: geometric mean titre; MGI: mean geometric increase; SCR: seroconversion rate
SCR is defined as: for initially seronegative subjects an antibody titre ≥40 1/DIL at postvaccination an antibody titre ≥4-fold the prevaccination titre in initially seropositive subjects.
N is the number of subjects with results available (GMT)
N' is the number of subjects with both pre- and postvaccination results available (SCR and MGI)

At D364, 6 months after booster vaccination with A/turkey, A/Indonesia HI parameters were substantially increased compared to prevaccination, with a GMT of 205.5 compared to 5.7 and an SCR of 100% in the H5_H5 group. In the H5_Hav group, 1 year after primary vaccination, A/Indonesia HI

parameters were lower compared to the group that received the booster with A/turkey (H5_H5), however, still higher compared to the prevaccination baseline, as SCR was 68.0% and MGI 7.4. These results indicate that the heterologous booster is able to induce an anamnestic immune response to an antigenically different strain that persists for at least 6 months in primed individuals.

In the group that was unprimed and only received a single dose of A/turkey containing vaccine (Hav_H5), A/Indonesia HI parameters at 6 months after the dose were comparable to prevaccination parameters. This indicates that a primary vaccination is required before a single dose can induce lasting cross-reactive immune response.

At D364, A/turkey HI parameters were substantially increased compared to D182 (prebooster), with a GMT of 215.1 compared to 38.5 and an SCR of 69.5% in the H5_H5 group. In the H5_Hav group, at D364 A/turkey HI parameters slightly lower compared to D182, 35.4 vs 43.0. This indicates that the immune response declines over time. These results indicate that in primed individuals a heterologous booster is able to induce an immune response that declines over time, from 100% 10 days after boost to 69.5% 6 months later.

In unprimed individuals, a single dose of A/turkey, leads to an increase in GMTs that is still seen 6 months after the dose: with an GMT of 18.4 (16.3-20.9) at D364 compared to 6.1 (5.6-6.6) at D182, leading to an SCR of 18.0% and MGI of 3.0. A single dose of vaccine is able to induce a response that persists for 6 months, however, the response is substantially higher in individuals primed with a primary vaccination.

The results for GMTs and VRR for MN antibodies against the A/Indonesia/05/2005 H5N1 virus strain and the A/turkey/Turkey/01/2005 H5N1 virus strain on Day 0, 42, 182, 192 and Day 364 are detailed in Table 25.

Table 25 Summary of vaccine homologous and heterologous MN antibody parameters (GMT and VRR) – ATP cohort for immunogenicity (D-PAN H5N1-032)

Antibody	**Group**	**Day**	**N**	**GMT**	**N'**	**VRR**	
				(95% CI)		**n**	**% (95% CI)**
Flu A/ Indonesia/ 5/2005	H5-H5	0	154	16.6 (15.4-17.8)			
		42	155	724.3 (646.0-812.1)	154	152	98.7 (95.4-99.8)
		182	156	132.6 (124.7-141.0)	154	132	85.7 (79.2-90.8)
		192	154	2088.0 (1834.1-2377.0)	152	152	100 (97.6-100)
		364	153	518.7 (450.4-597.5)	152	148	97.4 (93.4-99.3)
	H5-Hav	0	154	16.0 (15.0-16.9)			
		42	155	815.5 (724.1-918.4)	153	151	98.7 (95.4-99.8)
		182	155	140.5 (132.2-149.3)	153	122	79.7 (72.5-85.8)
		364	152	131.4 (122.7-140.8)	150	129	86.0 (79.4-91.1)
	Hav-H5	0	102	15.2 (14.3-16.2)			
		42	103	15.6 (14.5-16.7)	102	0	0.0 (0.0-3.6)
		182	104	14.9 (14.2-26.7)	102	0	0.0 (0.0-3.6)
		192	103	38.2 (33.4-43.6)	101	5	5.0 (1.6-11.2)
		364	102	30.1 (26.6-34.0)	100	8	8.0 (3.5-15.2)
	Hav-Hav	0	100	16.0 (14.9-17.2)			
		42	101	16.9 (15.1-19.1)	99	2	2.0 (0.2-7.1)
		182	103	14.7 (14.0-15.5)	99	0	0.0 (0.0-3.7)
Flu A/ turkey/Turkey /01/2005	H5-H5	0	154	16.5 (15.4-17.7)			
		42	155	155.1 (141.6-169.8)			
		182	156	85.4 (80.0-91.2)			
		192	155	1406.0 (1222.2-1617.5)	155	146	94.2 (89.3-97.3)
		364	153	408.6 (354.4-471.2)	153	87	56.9 (48.6-64.8)
	H5-Hav	0	154	15.8 (14.9-16.8)			
		42	155	164.6 (149.9-180.8)			
		182	155	84.9 (79.2-91.0)			
		364	150	98.9 (91.7-106.8)			
	Hav-H5	0	102	15.5 (14.4-16.7)			
		42	103	16.4 (14.8-18.1)			
		182	104	15.8 (14.7-17.0)			

Antibody	Group	Day	N	GMT	N'	VRR	
				(95% CI)		n	% (95% CI)
		192	104	67.2 (57.2-79.0)	104	39	37.5 (28.2-47.5)
		364	100	66.9 (59.4-75.2)	100	37	37.0 (27.6-47.2)
	Hav-Hav	0	101	17.3 (15.7-19.0)			
		42	101	17.6 (15.9-19.4)			
		182	102	15.4 (14.5-16.5)			

MN is a functional assay, measuring virus neutralizing antibodies. The results of this analysis are in line with the results for the HI analysis.

At D42, 21 days after the primary vaccination series, a significant increase in homologous MN GMT was observed in both H5_H5 and H5_Hav groups leading to an >98% VRR (98.7% and 98.7% respectively). Groups Hav_H5 and Hav_Hav did not show an increase in A/Indonesia MN GMT at D42. As with HI antibodies, MN GMTs declined over time; they were lower at D182 as compared to D42 in groups H5_H5 and H5_Hav. However, they remained well above baseline as VRR was >79% at D182 for both groups (85.7% and 79.7% respectively).

Ten days after a heterologous booster with 1.9µg A/turkey HA +AS03$_B$, group H5_H5 showed a substantial booster response in A/Indonesia MN parameters, in that GMTs increased to 2088.0 and VRR was 100%. As shown above, an antigenically drifted strain (A/turkey) was able to elicit an anamnestic response for A/Indonesia antibodies that was higher compared to the primary response at 6 months after the primary vaccination. In the group without primary vaccination series, Hav_H5, 10 days after the heterologous booster dose A/Indonesia GMTs and VRR increased only slightly (38.2 and 5.0% respectively).

Results for heterologous antibodies are in line with the homologous MN antibodies. After primary vaccination, a substantial increase in MN GMT for A/turkey are observed in both groups receiving the primary vaccination, leading to an MGI of approximately 10 fold. Ten days after a heterologous booster, VRR increased to 94.2% in the H5_H5 group, compared to 37.5% in the Hav_H5 group. This response decreased over time in the H5_H5 group, with VRR being 56.9% 6 months after the booster dose.

Ancillary analyses

Study D-PAN H5N1-013

GMTs were comparable across both sexes and age sub-groups, see Table 26 . The GMT for the A/Indonesia strain peaked at Day 42 and remained well above baseline through Day 182 for both sexes across all age sub-groups. After the booster dose of A/Turkey at Day 182, GMT peaked at Day 192. GMTs consistently remained well above baseline through Day 364 for both sexes across all age sub-groups. There was a significant increase in GMT for the A/Turkey strain at Day 192. GMT remained well above baseline through Day 364 for both sexes across all age sub-groups.

Table 26 GMTs of HI antibodies against A/Indonesia/05/2005 H5N1 and A/turkey/Turkey/01/2005 H5N1 virus strains at Day 0, Day 42, D182 and D192 by sex and age strata (ATP cohort for immunogenicity study D-PAN H5N1-013)

				Females			Males			
					95% CI				95% CI	
Antibody	Group	Timing	N	GMT	LL	UL	N	GMT	LL	UL
A/Indonesia/05/2005.HA Ab	6<12 M	PRE	17	5.0	5.0	5.0	16	5.0	5.0	5.0
		PII(D42)	**16**	945.1	670.7	1331.9	16	945.2	653.8	1366.4
		PII(D182)	17	180.8	129.6	252.2	16	140.6	95.5	206.8
		PIII(D192)	17	2045.6	1512.8	2766.2	16	2297.1	1715.8	3075.2
	12<24 M	PRE	11	5.0	5.0	5.0	13	5.0	5.0	5.0

				Females			Males			
					95% CI				95% CI	
Antibody	**Group**	**Timing**	**N**	**GMT**	**LL**	**UL**	**N**	**GMT**	**LL**	**UL**
		PII(D42)	11	1498.3	983.3	2283.2	13	1213.6	754.9	1951.0
		PII(D182)	10	159.9	114.9	222.5	11	136.7	86.5	216.0
		PIII(D192)	10	1575.7	866.3	2866.0	11	1498.3	983.3	2283.1
	24<36 M	PRE	17	5.0	5.0	5.0	12	5.0	5.0	5.0
		PII(D42)	17	1022.9	772.1	1355.2	12	1076.4	696.5	1663.5
		PII(D182)	17	135.9	108.2	170.6	12	130.7	97.9	174.4
		PIII(D192)	17	1634.7	1244.3	2147.6	12	1566.8	933.3	2630.4
A/turkey/Turkey/01/2005.HA Ab	6<12 M	PRE	17	5.8	4.9	6.8	16	5.8	4.9	6.9
		PII(D182)	17	102.2	71.3	146.6	16	89.2	63.4	125.5
		PIII(D192)	17	2265.2	1560.9	3287.3	16	2673.3	1922.8	3716.6
	12<24 M	PRE	11	5.5	4.5	6.8	13	6.0	4.5	8.1
		PII(D182)	10	88.8	60.3	130.9	11	80.1	54.3	118.2
		PIII(D192)	10	1873.9	963.0	3646.6	11	1754.2	960.6	3203.2
	24<36 M	PRE	17	5.7	4.4	7.3	12	5.3	4.7	6.0
		PII(D182)	17	90.5	71.1	115.4	12	80.1	66.5	96.5
		PIII(D192)	17	1737.8	1321.6	2285.0	12	1810.1	1142.7	2867.3

Study D-PAN H5N1-032

The results for GMTs of HI antibodies against the A/Indonesia strain at Day 0, Day 42, Day 182 were comparable by sex and age sub-groups (3-9 years and 10-17 years) in the H5_H5 and H5_HAV study groups, see Table 27. Boosting with A/Turkey on Day 182 elicited strong GMTs of HI antibodies against A/Turkey on Day 192 in the H5_H5 group with comparable data by sex and age strata.

Table 27 GMTs of HI antibodies against H5N1 A/Indonesia/05/2005 strain at Day 0, Day 42 and D182 by sex and age strata (Day 42 ATP cohort for immunogenicity)

				Females				Males			
						95% CI				95% CI	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**GMT**	**LL**	**UL**	**N**	**GMT**	**LL**	**UL**
Flu A/Ind/05/05 (H5N1).HA Ab	H5_H5	F_3-9 YOA	PRE	43	5.8	5.1	6.6	36	5.5	4.9	6.1
			PII(D42)	43	650.5	539.3	784.8	36	697.9	525.6	926.8
			PII(D182)	43	59.4	51.0	69.2	36	55.5	45.0	68.4
		F_10-17 YOA	PRE	37	5.9	5.1	6.7	39	5.7	5.2	6.3
			PII(D42)	37	572.1	471.8	693.7	39	362.4	277.4	473.5
			PII(D182)	37	53.5	45.7	62.7	39	41.8	34.0	51.4
	H5_Hav	F_3-9 YOA	PRE	42	5.4	4.9	5.9	34	5.2	4.9	5.5
			PII(D42)	42	624.5	441.9	882.6	34	776.9	636.0	948.9
			PII(D182)	42	59.5	51.1	69.3	34	62.0	51.0	75.5
		F_10-17 YOA	PRE	38	5.8	5.1	6.7	38	5.5	5.1	6.0
			PII(D42)	38	563.3	460.1	689.7	38	469.3	367.7	599.0
			PII(D182)	38	52.6	43.4	63.9	38	44.1	37.0	52.7
	Hav_H5	F_3-9 YOA	PRE	27	5.3	4.9	5.7	25	5.2	4.8	5.7
			PI(D42)	27	5.3	4.9	5.7	25	5.1	4.9	5.4
			PI(D182)	27	5.1	4.9	5.4	25	5.1	4.9	5.4
		F_10-17 YOA	PRE	25	5.6	4.7	6.7	26	5.7	4.8	6.8
			PI(D42)	25	6.3	5.0	8.1	26	5.7	4.6	7.0
			PI(D182)	25	5.0	5.0	5.0	26	5.0	5.0	5.0

				Females				Males			
						95% CI				95% CI	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**GMT**	**LL**	**UL**	**N**	**GMT**	**LL**	**UL**
	Hav_Hav	F_3-9 YOA	PRE	23	5.4	4.8	6.0	27	5.5	4.5	6.8
			PI(D42)	23	6.6	5.3	8.3	27	6.2	4.4	8.7
			PI(D182)	23	5.8	4.8	7.0	27	5.3	4.9	5.8
		F_10-17 YOA	PRE	28	6.4	5.3	7.7	23	5.9	4.9	7.1
			PI(D42)	28	6.6	5.5	8.0	23	5.5	4.9	6.1
			PI(D182)	28	5.9	5.0	6.9	23	5.5	4.9	6.1

Study Q-PAN H5N1-023

The antibody geometric mean titres (GMTs) were comparable across all age sub-groups for both sexes, see Table 28. High GMTs were observed at Day 42 (both sexes across all age sub-groups) for homologous and heterologous strains. The vaccine-homologous and heterologous HI antibody titres declined for all formulations at Day 385 (both sexes across all age sub-groups). Day 392 elicited strong immune response with GMTs raising well above Day 385 (both sexes across all age sub-groups).

Table 28 Summary of vaccine homologous HI GMT titers at Day 0, Day 42, Day 385 and Day 392 by sex and age strata (Adapted ATP cohort for immunogenicity study Q-PAN H5N1-023)

				Female				Male			
						95%CI				95%CI	
Antibody	**Group**	**Sub-group**	**Timing**	**N**	**GMT**	**LL**	**UL**	**N**	**GMT**	**LL**	**UL**
Flu A/Indonesia/5/2005 H5N1 HI	190_B	6<12 M	PRE	2	5.0	5.0	5.0	3	5.0	5.0	5.0
			PII(D42)	2	905.1	11.1	73989.4	3	2560.0	457.6	14323.2
			PII(D385)	2	56.6	0.7	4624.3	3	226.3	23.2	2210.2
			PIII(D392)	2	226.0	226.0	226.0	3	1436.7	164.6	12539.1
		12<24 M	PRE	10	5.0	5.0	5.0	6	5.0	5.0	5.0
			PII(D42)	10	1194.3	637.8	2236.0	6	854.4	500.4	1459.0
			PII(D385)	10	139.3	82.4	235.5	5	65.2	40.0	106.2
			PIII(D392)	10	618.3	379.5	1007.4	5	211.1	63.9	697.0
		24<36 M	PRE	4	5.0	5.0	5.0	11	5.3	4.6	6.1
			PII(D42)	4	830.0	244.4	2819.0	11	1128.5	795.6	1600.6
			PII(D385)	4	67.1	25.6	175.6	10	85.7	59.5	123.6
			PIII(D392)	4	380.5	132.4	1094.0	10	502.2	270.4	932.7
	090_C	6<12 M	PRE	2	5.0	5.0	5.0	3	5.0	5.0	5.0
			PII(D42)	2	452.5	0.0	2.4722E8	3	718.4	437.1	1180.7
			PII(D385)	2	28.3	0.0	15451410	3	63.3	10.4	384.6
			PIII(D392)	2	160.7	0.0	84177806	3	452.5	80.8	2535.2
		12<24 M	PRE	6	5.0	5.0	5.0	5	5.0	5.0	5.0
			PII(D42)	6	1280.0	765.3	2140.8	5	685.9	284.0	1656.8
			PII(D385)	6	126.9	94.3	170.9	6	63.4	36.5	109.9
			PIII(D392)	6	678.3	334.9	1373.5	6	359.3	207.7	621.6
		24<36 M	PRE	5	5.7	3.9	8.4	12	5.0	5.0	5.0
			PII(D42)	5	519.8	184.4	1465.3	12	1107.9	710.0	1728.7
			PII(D385)	5	52.9	32.8	85.3	11	49.9	27.8	89.3
			PIII(D392)	5	319.9	122.1	838.0	11	425.0	277.3	651.4
	190_C	6<12 M	PRE	2	5.0	5.0	5.0	4	5.0	5.0	5.0
			PII(D42)	2	1522.1	168.5	13752.7	4	2347.5	637.8	8639.5
			PII(D385)	2	320.0	320.0	320.0	4	146.7	30.1	715.1
			PIII(D392)	2	761.1	84.2	6876.3	4	761.3	90.0	6441.8
		12<24 M	PRE	6	5.0	5.0	5.0	9	5.6	4.3	7.3
			PII(D42)	6	1015.9	754.9	1367.2	9	871.0	398.6	1903.2

				Female				Male			
						95%CI				95%CI	
Antibody	Group	Sub-group	Timing	N	GMT	LL	UL	N	GMT	LL	UL
			PII(D385)	6	106.8	74.7	152.7	9	68.5	34.2	137.2
			PIII(D392)	6	452.7	327.0	626.7	9	274.3	148.7	505.9
		24<36 M	PRE	7	5.0	5.0	5.0	9	5.0	5.0	5.0
			PII(D42)	7	742.5	372.8	1478.6	9	615.8	255.9	1481.8
			PII(D385)	7	56.5	18.9	169.1	9	37.0	19.3	71.1
			PIII(D392)	7	237.8	107.4	526.5	9	172.8	103.5	288.4
	375_C	6<12 M	PRE	3	5.0	5.0	5.0	1	5.0	-	-
			PII(D42)	3	905.1	92.8	8828.4	1	1280.0	-	-
			PII(D385)	3	403.4	245.1	664.2	1	160.0	-	-
			PIII(D392)	3	718.6	193.1	2674.0	1	905.0	-	-
		12<24 M	PRE	7	5.0	5.0	5.0	7	5.0	5.0	5.0
			PII(D42)	7	1103.3	733.8	1658.9	7	551.7	308.6	986.4
			PII(D385)	7	84.0	41.6	169.7	7	62.6	42.0	93.5
			PIII(D392)	7	320.0	164.2	623.7	7	195.0	85.5	444.9
		24<36 M	PRE	10	5.0	5.0	5.0	3	5.0	5.0	5.0
			PII(D42)	10	452.6	255.3	802.3	3	452.5	101.9	2010.0
			PII(D385)	10	56.5	37.7	84.8	3	56.4	12.5	254.1
			PIII(D392)	10	226.3	146.1	350.4	3	320.0	134.9	758.9
	375_D	6<12 M	PRE	2	5.0	5.0	5.0	2	5.0	5.0	5.0
			PII(D42)	2	538.4	59.9	4837.5	2	1076.3	119.0	9737.8
			PII(D385)	2	67.2	0.1	49310.1	2	320.0	3.9	26526.2
			PIII(D392)	2	226.3	2.8	18497.3	2	452.5	5.5	36994.7
		12<24 M	PRE	10	5.4	4.6	6.3				
			PII(D42)	10	576.9	356.1	934.7	11	5.0	5.0	5.0
			PII(D385)	10	50.8	32.2	80.3	11	640.0	401.8	1019.6
			PIII(D392)	10	183.7	124.2	271.8	9	71.3	41.9	121.4
		24<36 M	PRE	6	5.0	5.0	5.0	4	11.8	2.4	57.6
			PII(D42)	6	427.3	147.4	1238.9	4	452.5	117.2	1746.9
			PII(D385)	5	28.2	18.4	43.4	4	61.6	23.9	159.0
			PIII(D392)	5	139.4	68.1	285.2	4	174.8	44.2	690.6

No trends were observed with respect to immunogenicity and gender. It appears that younger subjects had higher immune responses. However, as numbers are small in the different subgroups, no strong conclusions could be drawn.

Summary of main studies

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

Table 29 Summary of Immunogenicity for trial Q-PAN H5N1-023

Title: A phase II observer-blind, multicenter, dose-ranging study of children 6 to less than 36 months of age who are to be primed with a 2-dose series of GSK Biologicals' AS03-adjuvanted A/Indonesia/05/2005 (H5N1) vaccine		
Study identifier	eTrack study number and Abbreviated Title: 116938 (FLU Q-PAN H5N1=AS03-023) EudraCT Number: 2015-003458-42	
Design	Phase II, randomised, controlled, observer-blind, dose-ranging study	
	Duration of main phase:	415 days (Primary Epoch: Day 0 to Day 385; The Booster Epoch: Day 385 – Day 415).
	Duration of Run-in phase:	not applicable

	Duration of Extension phase:		not applicable
Hypothesis	Exploratory: descriptive		
Treatments groups	190_B		Priming dose: 1.9 µg HA + $AS03_B$ Primary vaccination: 2 doses (Day 0, 21) of AS03-adjuvanted HA (A/Indonesia strain) Booster vaccination: 1 dose (Day 385) of unadjuvanted 3.75 µg HA Q-Pan H5N1 vaccine (A/Indonesia strain) According to protocol (ATP) cohort for immunogenicity: Day 42: 36 subjects Day 385: 34 subjects Day 392: 34 subjects Total vaccinated cohort (TVC): 38 subjects
	090_C		Priming dose: 0.9 µg HA + $AS03_C$ Primary vaccination: 2 doses (Day 0, 21) of AS03-adjuvanted HA (A/Indonesia strain) Booster vaccination: 1 dose (Day 385) of unadjuvanted 3.75 µg HA Q-Pan H5N1 vaccine (A/Indonesia strain) ATP cohort for immunogenicity: Day 42: 33 subjects Day 385: 33 subjects Day 392: 33 subjects TVC: 37 subjects
Notes	The dose-ranging study included more treatment groups: 190_C, 375_C and 375_D. Group 190_B and 090_C were considered to provide the main evidence in this study and therefore will be described in this summary.		
Endpoints and definitions	Primary endpoints	Immunogenicity	• Immunogenicity-fever-index for HI during primary vaccination • Immunogenicity-fever-index for MN during primary vaccination • Mean geometric increase (MGI) HI at Day 392 relative to Day 385 (effect of booster) • MGI MN at Day 392 relative to Day 385 (effect of booster)
	Secondary endpoints	Immunogenicity	• HI immune response to the vaccine-homologous virus 21 days after second dose • Persistence of immune response by HI and MN assay • Vaccine homologous and heterologous HI GMTs on D0, 42, 385 and 392 • Vaccine homologous and heterologous MN GMTs on D0, 42, 385 and 392
Database lock	25 May 2018		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary analysis was based on the ATP cohort for analysis of immunogenicity. <u>Time points:</u> Day 0 (before vaccination 1), Day 42 (after vaccination 2), Day 385 (before vaccination 3) and Day 392 (after vaccination 3).		
Results	Treatment group	190_B	090_C
	Number of subjects	34	33
	HI fever-immunogenicity index (GMT ratio)	0.92	0.70
	MN fever-immunogenicity index	0.92	0.72
	Homologous MGI HI: GMT ratio (95%CI)	4.9 (3.8-6.3)	6.6 (4.9 – 9.0)
	Heterologous (Vietnam) MGI HI: GMT ratio (95%CI)	5.0 (3.7 – 6.8)	6.3 (4.5 – 8.7)

	Homologous MGI MN: GMT ratio (95%CI)	4.3 (3.3 – 5.7)	4.8 (3.4 – 6.6)
	Heterologous (Vietnam) MGI MN: GMT ratio (95%CI)	2.9 (2.2 – 3.8)	2.9 (2.1 – 4.1)
Notes	The usefulness of this immunogenicity-fever-index for both the HI as well as the MN antibodies is limited. The totality of all immunogenicity and safety results was evaluated to determine which dose is considered appropriate for children and was based on the immunogenicity aspects mentioned in the Guideline on Influenza Vaccines.		
Analysis description	**Secondary analysis**		
	The secondary analysis was based on the ATP cohort for analysis of immunogenicity. Time points: Day 0 (before vaccination 1), Day 42 (after vaccination 2), Day 385 (before vaccination 3) and Day 392 (after vaccination 3).		
Results	Treatment group	**190_B**	**090_C**
	Number of subjects	36	33
	Homologous (Flu/Indonesia) Seroconversion rate (SCR)		
	Day 42 (21 D after primary vaccination)	100 (90.3-100)	100 (89.4-100)
	Day 385 (1 yr after primary vaccination)	97.1 (84.7-99.9)	78.8 (61.1-91.0)
	Day 392 (post boost)	100 (89.7-100)	100 (89.4-100)
	Homologous (Flu/Indonesia) Vaccine Response Rate (VRR) (MN)		
	Day 42 (21 D after primary vaccination)	100 (90.3-100)	100 (88.8-100)
	Day 385 (1 yr after primary vaccination)	100 (89.7-100)	100 (89.1-100)
	Day 392 (post boost)	100 (89.7-100)	100 (89.1-100)
	Heterologous (Flu/Vietnam) SCR (HI)		
	Day 42 (21 D after primary vaccination)	100 (88.4-100)	91.7 (73.0-99.0)
	Day 392 (post boost)	96.7 (82.8-99.9)	100 (88.1-100)
	Heterologous (Flu/Vietnam) VRR (MN)		
	Day 42 (21 D after primary vaccination)	100 (89.7-100)	96.9 (83.8-99.9)
	Day 392 (post boost)	96.9 (83.8-99.9)	96.9 (83.8-99.9)
Notes	As there is no correlate of protection, the clinical relevance of the achieved immune response is unknown. A summary of vaccine homologous and heterologous HI antibody parameters, geometric mean titre (GMT), seroconversion rate (SCR) and MGI for homologous and a selected heterologous antibody (Flu A/Vietnam/1194/2004 H5N1) are presented in Table 4. A summary of vaccine homologous and heterologous MN antibody parameters, GMT, vaccine response rate (VRR) and MGI, for homologous and 1 heterologous antibody (Flu A/Vietnam/1194/2004 H5N1) are presented in Table 7.		

Table 30 Summary of Immunogenicity for trial D-PAN H5N1-013

Title: A phase II, non-randomized, open-label study to evaluate the safety and immunogenicity of the adjuvanted (pre-) pandemic H5N1 influenza candidate vaccine following a heterologous prime-boost schedule (six months apart) in children aged 6 to 35 months		
Study identifier	eTrack study number and abbreviated title: 109825 (H5N1-013)	
Design	Non-randomized, single-arm, open-label, multi-center, multi-country.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months not applicable not applicable
Hypothesis	Exploratory: descriptive	

Treatments groups	H5N1		**Primary vaccination**: 2 doses (Day 0, 21) of 1.9 µg HA (A/Indonesia strain) + $AS03_B$ **Booster vaccination**: 1 dose (Day 182) of 1.9 µg HA (A/Turkey strain) + $AS03_B$ According to protocol (ATP) cohort for immunogenicity: Day 42: 86 subjects Day 182: 83 subjects Day 192: 83 subjects Day 364: 100 subjects Total vaccinated cohort (TVC): 113 subjects.
Endpoints and definitions	Primary endpoint	Immunogenicity	• To assess whether a heterologous booster dose of 1.9 µg A/turkey/Turkey/1/2005 (H5N1) HA with $AS03_B$ given 6 months following a 2-dose primary vaccination series with 1.9 µg A/Indonesia/05/2005 (H5N1) HA with $AS03_B$ elicits an antibody response that meets the SCR of >40%, SPR of >70% and MGI of >2.5 based on HI responses to A/turkey/Turkey/1/2005 (H5N1) ten days following booster vaccination.
	Secondary endpoint	Immunogenicity	• To assess the HI response against A/Indonesia/05/2005 and A/turkey/Turkey/1/2005 strains in terms of seropositivity rates, geometric mean titers (GMTs), SCRs, SPRs and MGIs on Day 0, Day 42*, Day 182, Day 192, and Day 364. *Only for the A/Indonesia/05/2005 H5N1 virus strain • To describe the humoral immune responses in terms of the three age strata used for enrollment in this study • To describe the H5N1 neutralizing antibody responses against A/Indonesia/05/2005 and A/turkey/Turkey/1/2005 strains on Day 0, Day 42, Day 182, Day 192, and Day 364.
Database lock	24-January-2013 (Day 364)		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	The primary analysis was based on the ATP cohort for analysis of immunogenicity. Time points: Days 0, 42, 182, 192 and 364.	
Descriptive statistics and estimate variability	Treatment group	H5N1
	Number of subjects	Day 42: 86 Day 192: 100
	SCR (%) (95%CI)	100 % (95.7-100)
	MGI (95% CI)	357.7 (302.4-423.2)
Notes	No correlate of protection exists for Influenza. This hampers the interpretation of the clinical relevance of the observed vaccine-induced immunogenicity.	
Analysis description	**Secondary analysis**	
Analysis population and time point description	The primary analysis was based on the ATP cohort for analysis of immunogenicity. Time points: Days 0, 42, 182, 192 and 364.	
Descriptive statistics and estimate variability		
	Homologous (Flu/Indonesia) Seroconversion rate (SCR) measuring HI antibodies	
	Day 42 (21 D after primary vaccination)	100% (95.8-100)
	Day 182 (6 mo after primary vaccination)	98.8% (93.5-100)
	Day 192 (post boost)	100% (95.7-100)
	Homologous (Flu/Indonesia) Vaccine response rate (VRR) measuring MN antibodies	
	Day 42 (21 D after primary vaccination)	100% (84.6-100)
	Day 182 (6 mo after primary vaccination)	100% (87.7-100)

	Day 192 (post boost)	100% (88.1-100)
	Heterologous (Flu/Indonesia) Seroconversion rate (SCR) measuring HI antibodies	
	Day 182 (6 mo after primary vaccination)	95.2% (88.1-100)
	Day 192 (post boost)	100% (95.7-100)
	Heterologous (Flu/Indonesia) Vaccine response rate (VRR) measuring MN antibodies	
	Day 182 (6 mo after primary vaccination)	82.9% (72.0 -100)
	Day 192 (post boost)	100% (95.0-100)
Notes	N/A	

Table 31 Summary of Immunogenicity for trial D-PAN H5N1-032

Title: : A phase III, randomized, open, active-controlled study to evaluate the safety and immunogenicity of a prime-boost schedule of the H5N1 candidate vaccine adjuvanted with AS03$_B$ administered to children aged 3 to 17 years.		
Study identifier	eTrack study number and Abbreviated Title: 115115 (FLU D-PAN H5N1=AS03-032)	
Design	Phase III, four parallel groups, randomized, open, active controlled, single-center	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 months not applicable not applicable
Hypothesis	Exploratory: descriptive; Superiority.	
Treatments groups	H5_H5	Priming H5N1 A/Indonesia + booster dose H5N1 A/Turkey on Day 182 (+Day 364 Havrix) According to protocol (ATP) cohort for immunogenicity: Day 42: 155 subjects Month 6: 127 subjects Month 12: 151 subjects Total vaccinated cohort (TVC): 156 subjects
	H5_Hav	Priming H5N1 A/Indonesia + Havrix on Day 182 (+Day 364 Havrix) ATP cohort for immunogenicity Day 42: 152 Month 6: 152 Month 12: 147 TVC N:156 subjects
	Hav_H5	Day 0 Havrix + Day 182 H5N1 A/Turkey (+Day 364 Havrix) ATP cohort for immunogenicity Day 42: 103 Month 6: 84 Month 12: 100 TVC: 104 subjects
	Hav_Hav	Day 0, 182 Havrix ATP cohort for immunogenicity Day 42: 101 Month 6: 101 Month 12: 103 TVC: 104 subjects

Endpoints and definitions	Primary endpoint	Immunogenicity	Superiority of HI antibody response against A/turkey 10 days following H5N1 vaccination on Day 182 (1.9µg A/turkey HA antigen + $AS03_B$) in group H5_H5 (primed subjects) vs Hav_H5 (unprimed subjects)			
	Secondary endpoint	Immunogenicity	Assess HI antibody response in terms of GMT, SCR and MGI against A/Indonesia and A/turkey			
	Tertiary endpoint	Immunogenicity	Assess MN antibody response in terms of GMT, SCR and MGI			
Database lock	23-January-2013 (Day 364)					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	The primary analysis was based on the ATP cohort for analysis of immunogenicity. Time points: Days 0, 42, 182, 192 and 364.					
Descriptive statistics and estimate variability	Treatment group	H5_H5	Hav_H5			
	Number of subjects	155	103			
	Day 192 HI GMT	737.6 (646.8-841.1)	24.7 (19.7-31.0)			
Effect estimate per comparison	Primary endpoint	Comparison groups	H5_H5/Hav_H5			
		GMT ratio	11.84			
		95% CI	LL: 7.30; UL:19.20			
		ANCOVA Model	LL of 95% CI >1.0			
Notes	N/A					
Analysis description	**Secondary analysis:**					
Analysis population and time point description	The primary analysis was based on the ATP cohort for analysis of immunogenicity. Time points: Days 0, 42, 182, 192 and 364.					
Results	Treatment group	H5_H5	H5_Hav	Hav_H5	Hav_Hav	
	Homologous (Flu/Indonesia) Seroconversion rate (SCR)					
	Day 42 (21 D after primary vaccination)	99.4 (96.5-100)	99.3 (96.4-100)	1.0 (0.0-5.3)	1.0 (0.0-5.4)	
	Day 182 (6 mo after primary vaccination)	78.7 (71.4-84.9)	79.6 (72.3-85.7)	0.0 (0.0-3.5)	0.0 (0.0-3.6)	
	Day 192 (post boost)	100 (97.1-100)		3.6 (0.7-10.1)		
	Homologous (Flu/Indonesia) Vaccine Response Rate (VRR) (MN)					
	Day 42 (21 D after primary vaccination)	98.7 (95.4-99.8)	98.7 (95.4-99.8)	0.0 (0.0-3.6)	2.0 (0.2-7.1)	
	Day 182 (6 mo after primary vaccination)	85.7 (79.2-90.8)	79.7 (72.5-85.8)	0.0 (0.0-3.6)	0.0 (0.0-3.7)	
	Day 192 (post boost)	100 (97.6-100)		5.0 (1.6-11.2)		
	Heterologous (Flu/Vietnam) SCR (HI)					
	Day 42 (21 D after primary vaccination)	98.7 (95.4-99.8)	98.0 (94.3-99.6)	3.9 (1.1-9.6)	4.0 (1.1-9.8)	
	Day 182 (6 mo after primary vaccination)	48.4 (40.3-56.5)	66.4 (58.3-73.9)	1.0 (0.0-5.3)	2.0 (0.2-7.0)	
	Day 192 (post boost)	100 (97.1-100)		32.1 (22.4-43.2)		
	Heterologous (Flu/Vietnam) VRR (MN)					
	Day 192 (post boost)	94.2 (89.3-97.3)		37.5 (28.2-47.5)		
	Day 364 (post boost)	56.9 (48.6-64.8)		37.0 (27.6-47.2)		
Notes	N/A					

Analysis performed across trials (pooled analyses and meta-analysis)

No analysis across trials was performed.

Clinical studies in special populations

Healthy children were included in all studies. No special populations were investigated.

Supportive study

Study Design: Study Q-PAN H5N1-021 was a Phase 2/3, randomized, controlled, observer-blind, multi-centre trial to evaluate the safety and immunogenicity of a two-dose primary vaccination series of monovalent A/Indonesia/5/2005 (H5N1) vaccine antigen adjuvanted with AS03 in children aged 6 months to <18 years of age.

Treatment: Participants in Study Q-PAN H5N1-021 were randomized in a 8:3 ratio to receive a two doses of either Q-Pan H5N1 adjuvanted with $AS03_B$ vaccine or placebo on days 0 and 21 in Year 1. Each Year 1 placebo recipient who remained eligible and elected to receive the Q-Pan H5N1 vaccine after data lock for Study Day 385 was to be asked to participate in Study Year 2 for an additional 385 days, in which participants received two doses of Q-Pan H5N1 adjuvanted with $AS03_B$ vaccine on days 0 and 21.

Study Participants: The study population will consist of healthy males or females ≥6 months and <18 years of age at the time of first vaccination in study year 1, without prior administration of any H5N1 vaccine. In total 838 subjects were enrolled.

In the Q-Pan group, 607 participants were randomized and vaccinated with Q-Pan H5N1. In total, 565 (93.1%) completed and 42 (6.9%) discontinued from the study. In the year 1 placebo group, 231 participants were randomized and treated with placebo. In total, 217 (93.9%) completed and 14 (6.1%) discontinued from the study. In year 2, 155 subjects were vaccinated, 152 (98.1%) completed and 3 (1.9%) discontinued the study.

Demographic characteristics, including age, gender, race, and ethnicity, were presented descriptively. Demographic characteristics were generally comparable for vaccinated participants across intervention groups, although slightly more males were included in the Q-PAN group compared to the Placebo group. No inferential statistics were planned.

Objectives: The primary objective of the study, evaluated in Year 1, was to assess whether 2 doses of H5N1 antigen in association with AS03 elicited an immune response, measured by postimmunisation vaccine-homologous virus HI titres, that met or exceeded the Center for Biologics Evaluation and Research (CBER)/CHMP young adult targets for proportion of subjects attaining post-immunisation reciprocal HI titres ≥40 (SPR) against A/Indonesia virus.

The secondary objectives of the study were 1) describe at different time points the immunogenicity of the vaccine regimen in the 3 age strata in terms of HI titers specific for the vaccine-homologous virus using the following parameters: seropositivity rate, geometric mean titer (GMT), SCR, SPR, and mean geometric increase (MGI) in terms of point estimates and 95% confidence interval (CI), 2) to further describe the immunogenicity of the vaccine regimen in the 3 age strata in terms of microneutralization (MN) titers specific for the vaccine homologous virus and for one or more drift-variant viruses.

Results:

Primary Endpoints

The primary objective was met. At Day 42, the lower 98.3% CI was greater than 70% for the vaccine-homologous immune response in terms of HI SPR in the 3 age strata, see Table 32.

Table 32 SPR for HI antibodies against the H5N1 A/Indonesia virus strain at Day 42 by age stratum

				SPR			
						98.3% CI	
Strain	**Group**	**Sub-group**	**N**	**n**	**%**	**LL**	**UL**
Flu A/Indonesia/5/2005 H5N1 HI	Q-Pan	6M-<36M	175	175	**100**	97.3	100
		3Y-<9Y	185	184	**99.5**	96.4	100
		9Y-<18Y	203	201	**99.0**	95.8	99.9
	Placebo	6M-<36M	64	0	**0.0**	0.0	7.2
		3Y-<9Y	71	0	**0.0**	0.0	6.5
		9Y-<18Y	76	1	**1.3**	0.0	8.6

Q-Pan = QPAN H5N1 1.9 µg + $AS03_B$; Placebo = Phosphate buffered saline; 6M-<36M = Children 6 to < 36 months old; 3Y-<9Y = Children 3 to < 9 years old; 9Y-<18Y = Children 9 to < 18 years old; N = Number of subjects with available results; n/% = Number/percentage of seroprotected subjects (HI titer ≥ 40 1/DIL); 98.3% CI = 98.3% confidence interval, LL = Lower Limit, UL = Upper Limit; SPR = Seroprotection rate

The clinical relevance of meeting the primary immunogenicity endpoints is not known.

Secondary Endpoint

A summary of vaccine homologous HI antibody parameters, SPR, GMT, SCR and MGI are presented in Table 33. A summary of vaccine homologous and heterologous neutralizing antibody parameters, GMT and VRR are presented in Table 34.

Table 33 A/Indonesia/05/2005 HI antibody parameters at Day 0, 21, 42, 182 and 385 – adapted ATP (Q-PAN H5N1-021)

			N	SPR*				GMT			N'	SCR				MGI		
						95%CI			95%CI					95%CI			95%CI	
Group	**Sub-group**	**Timing**		**n**	**%**	**LL**	**UL**	**Value**	**LL**	**UL**		**n'**	**%**	**LL**	**UL**	**Value**	**LL**	**UL**
Q-Pan	6M-<36M	PRE	182	1	**0.5**	0.0	3.0	**5.3**	5.1	5.5	.	.	.	.	.			
		PI(D21)	179	105	**58.7**	51.1	66.0	**38.7**	33.9	44.2	179	103	**57.5**	49.9	64.9	**7.3**	6.4	8.4
		PII(D42)	175	175	**100.0**	97.3	100.0	**777.1**	705.6	855.9	175	175	**100**	97.9	100.0	**148.5**	134.5	164.1
		PII(D182)	84	80	**95.2**	88.3	98.7	**90.6**	78.1	105.0	84	80	**95.2**	88.3	98.7	**17.8**	15.3	20.8
		PII(D385)	63	54	**85.7**	74.6	93.3	**65.6**	55.9	76.9	63	53	**84.1**	72.7	92.1	**12.1**	10.3	14.2
	3Y-<9Y	PRE	184	2	**1.1**	0.1	3.9	**5.6**	5.3	5.9	.	.	.	.	.			
		PI(D21)	184	110	**59.8**	52.3	66.9	**44.6**	39.2	50.9	183	107	**58.5**	51.0	65.7	**8.0**	7.0	9.1
		PII(D42)	185	184	**99.5**	96.4	100.0	**543.8**	484.9	609.8	184	183	**99.5**	97.0	100.0	**96.9**	85.3	110.1
		PII(D182)	89	75	**84.3**	75.0	91.1	**57.4**	50.8	64.9	89	75	**84.3**	75.0	91.1	**11.0**	9.7	12.4
		PII(D385)	85	47	**55.3**	44.1	66.1	**32.8**	28.1	38.4	84	45	**53.6**	42.4	64.5	**5.5**	4.7	6.6
	9Y-<18Y	PRE	204	1	**0.5**	0.0	2.7	**5.7**	5.4	6.1	.	.	.	.	.			
		PI(D21)	204	108	**52.9**	45.8	59.9	**35.3**	31.7	39.5	204	105	**51.5**	44.4	58.5	**6.2**	5.5	6.9
		PII(D42)	203	201	**99.0**	95.8	99.9	**416.2**	371.5	466.2	203	201	**99.0**	96.5	99.9	**72.4**	63.9	82.0
		PII(D182)	87	63	**72.4**	61.8	81.5	**50.2**	43.3	58.2	87	61	**70.1**	59.4	79.5	**8.8**	7.5	10.4
		PII(D385)	95	27	**28.4**	19.6	38.6	**21.6**	18.6	25.1	95	23	**24.2**	16.0	34.1	**3.6**	3.1	4.3
	6M-<18Y	PRE	570	4	**0.7**	0.2	1.8	**5.5**	5.4	5.7	.	.	.	.	.			
		PI(D21)	567	323	**57.0**	52.8	61.1	**39.3**	36.5	42.2	566	315	**55.7**	51.5	59.8	**7.1**	6.6	7.6
		PII(D42)	563	560	**99.5**	98.5	99.9	**551.8**	516.4	589.6	562	559	**99.5**	98.4	99.9	**99.6**	92.6	107.1
		PII(D182)	260	218	**83.8**	78.8	88.1	**63.6**	58.4	69.3	260	216	**83.1**	78.0	87.4	**11.9**	10.9	13.1
		PII(D385)	243	128	**52.7**	46.2	59.1	**33.4**	30.1	37.0	242	121	**50.0**	43.5	56.5	**5.8**	5.1	6.4
Placebo	6M-<36M	PRE	67	0	**0.0**	0.0	5.4	**5.3**	5.0	5.7	.	.	.	.	.			
		PI(D21)	67	0	**0.0**	0.0	5.4	**5.2**	5.0	5.4	67	0	**0.0**	0.0	5.4	**1.0**	0.9	1.0
		PII(D42)	64	0	**0.0**	0.0	7.2	**5.1**	4.9	5.3	64	0	**0.0**	0.0	5.6	**1.0**	0.9	1.0
		PII(D182)	29	0	**0.0**	0.0	11.9	**5.0**	5.0	5.0	29	0	**0.0**	0.0	11.9	**1.0**	0.9	1.0
		PII(D385)	26	0	**0.0**	0.0	13.2	**5.1**	4.9	5.4	26	0	**0.0**	0.0	13.2	**1.0**	0.9	1.1
	3Y-<9Y	PRE	71	0	**0.0**	0.0	5.1	**5.6**	5.1	6.0	.	.	.	.	.			
		PI(D21)	70	1	**1.4**	0.0	7.7	**5.4**	5.0	5.7	70	0	**0.0**	0.0	5.1	**1.0**	0.9	1.0
		PII(D42)	71	0	**0.0**	0.0	6.5	**5.4**	5.0	5.7	71	0	**0.0**	0.0	5.1	**1.0**	0.9	1.0
		PII(D182)	34	0	**0.0**	0.0	10.3	**5.4**	4.9	6.0	34	0	**0.0**	0.0	10.3	**1.1**	1.0	1.2
		PII(D385)	34	0	**0.0**	0.0	10.3	**5.4**	4.9	5.8	34	0	**0.0**	0.0	10.3	**0.9**	0.8	1.0
Placebo	9Y-<18Y	PRE	76	0	**0.0**	0.0	4.7	**5.4**	5.1	5.8	.	.	.	.	.			
		PI(D21)	76	0	**0.0**	0.0	4.7	**5.4**	5.1	5.7	76	0	**0.0**	0.0	4.7	**1.0**	0.9	1.1
		PII(D42)	76	1	**1.3**	0.0	8.6	**5.8**	5.3	6.3	76	1	**1.3**	0.0	7.1	**1.1**	1.0	1.2
		PII(D182)	31	0	**0.0**	0.0	11.2	**5.4**	4.9	5.9	31	0	**0.0**	0.0	11.2	**1.0**	0.9	1.2
		PII(D385)	36	0	**0.0**	0.0	9.7	**5.3**	4.8	5.9	36	0	**0.0**	0.0	9.7	**1.0**	0.8	1.1
	6M-<18Y	PRE	214	0	**0.0**	0.0	1.7	**5.4**	5.2	5.7	.	.	.	.	.			
		PI(D21)	213	1	**0.5**	0.0	2.6	**5.3**	5.1	5.5	213	0	**0.0**	0.0	1.7	**1.0**	0.9	1.0
		PII(D42)	211	1	**0.5**	0.0	2.6	**5.4**	5.2	5.6	211	1	**0.5**	0.0	2.6	**1.0**	1.0	1.0
		PII(D182)	94	0	**0.0**	0.0	3.8	**5.3**	5.1	5.5	94	0	**0.0**	0.0	3.8	**1.0**	1.0	1.1
		PII(D385)	96	0	**0.0**	0.0	3.8	**5.3**	5.0	5.6	96	0	**0.0**	0.0	3.8	**0.9**	0.9	1.0

Q-Pan = QPAN H5N1 1.9 µg + $AS03_B$; Placebo = Phosphate buffered saline;
6M-<36M = Children 6 to < 36 months old; 3Y-<9Y = Children 3 to < 9 years old; 9Y-<18Y = Children 9 to < 18 years old;
N=Number of subjects with results available (for GMT and SPR computation); n/% = number/percentage of seroprotected subjects;
N'= Number of subjects with both pre and post results available (for SCR and MGI computation); n'/% = number/percentage of seroconverted subjects; GMT = geometric mean antibody titer calculated on all subjects;
SPR = Seroprotection rate (HI titer ≥ 40 1/DIL);

Table 34 Vaccine homologous (A/Indonesia) and drift variant (A/Vietnam) neutralizing antibody parameters at Day 0, 21,42, 182 and 385 by age stratum - Adapted ATP cohort (Q-PAN H5N1-021)

Antibody	Group	Day	N	GMT	N'	VRR	
				(95% CI)		n	% (95% CI)
Flu A/ Indonesia/ 5/2005	Q-PAN 6 mo - <18 yr	0	113	15.07 (14.43-15.75)			
		21	112	46.470 (41.49-51.88)	112	62	55.4 (45.7-64.8)
		42	111	585.33 (476.83-718.53)	115	114	99.1 (95.3-100)
		182	105	142.54 (124.16-163.64)			
		385	95	109.08 (95.86-124.13)			
	Placebo 6 mo - <18 yr	0	28	14.71 (13.71-15.78)			
		21	28	15.09 (13.48-16.89)	28	1	3.6 (0.1-18.3)
		42	27	14.36 (13.63-15.14)	27	0	0.0 (0.0-12.8)
		182	29	15.80 (13.68-18.24)			
		385	28	15.46 (14.05-17.01)			
Flu A/ Vietnam/ 1194/2004	Q-PAN 6 mo - <18 yr	0	112	19.59 (17.85-21.50)			
		21	112	34.37 (30.94-38.17)	111	22	19.8 (12.9-28.5)
		42	111	68.07 (62.73-73.86)	114	74	64.9 (55.4-73.6)
		182	105	50.58 (44.48-57.52)			
		385	95	47.06 (41.39-53.50)			
	Placebo 6 mo - <18 yr	0	28	17.96 (15.17-21.25)			
		21	28	20.36 (16.42-25.25)	28	0	0.0 (0.0-12.3)
		42	27	22.31 (17.11-28.10)	27	1	3.7 (0.1-19.0)
		182	29	20.08 (16.11-25.03)			
		385	28	20.86 (16.09-27.04)			

In the Q-PAN group vaccine-homologous HI titers reached a peak at Day 42, 21 days after the primary vaccination series, leading to an SCR of 99.5% (98.4-100) and MGI of 99.6 (92.6-107.1). After the peak the HI antibodies declined over time, however remained well above baseline until at least 1 year after the primary vaccination series, as seen by an SCR of 50.0% (43.5-56.5) and MGI of 5.8 (5.1-6.4). The response HI antibody response was highest in the youngest age category. In the Placebo group no significant increase in HI titers were observed.

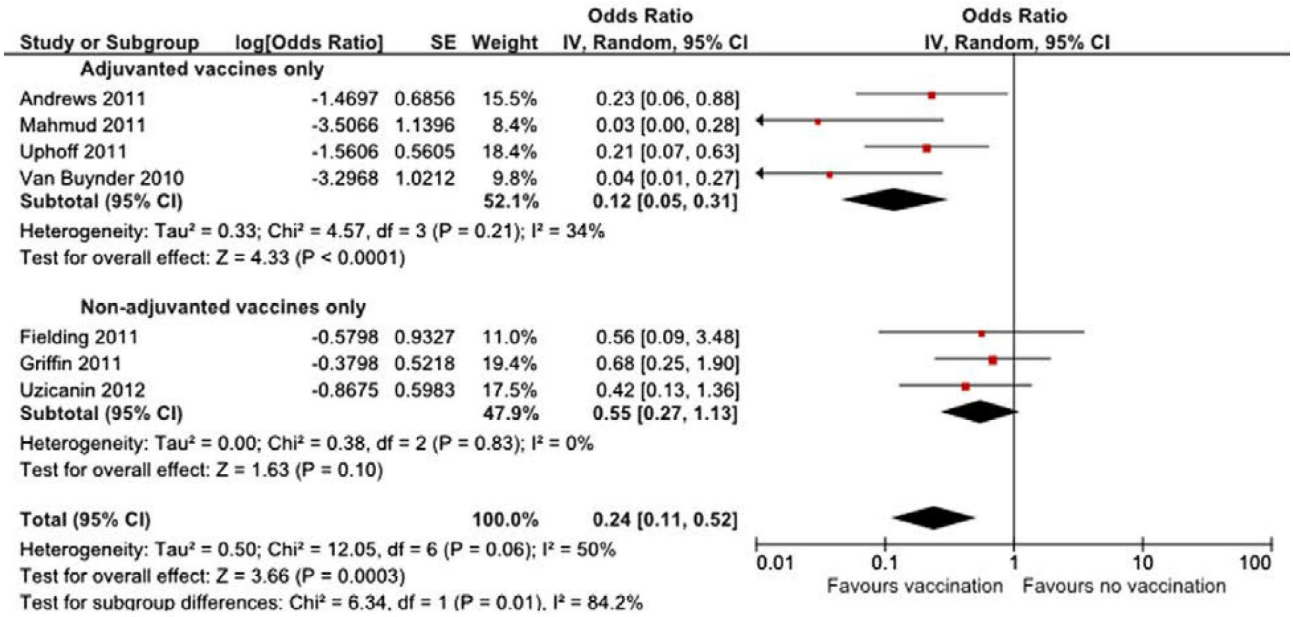
The vaccine-homologous MN antibody titers developed identically compared to the HI titers, in that a peak was reached at Day 42 after which a decline in titer starts. Vaccine-homologous titers remain well above baseline for at least 1 year after primary vaccination in all age categories (MGI of >5). For the vaccine-homologous MN response, the response was again highest in the youngest age category.

The response for vaccine-heterologous MN antibody titers develop similarly compared to the vaccine-homologous MN titers, though to a considerably lesser extent. The peak GMT in the entire population was 68.07 (62.73-73.86) compared to 585.33 (476.83-718.53). Again after the peak titers decline, but remain above baseline for at least 1 year. However, no effect of age could be observed.

Supportive evidence from an H1N1-based vaccine

In a meta-analysis, data were analysed from 38 studies including a total of 7 643 738 adults (⩾18 years of age and ⩾50 years of age) vaccinated with inactivated adjuvanted or unadjuvanted monovalent pandemic H1N1 vaccine or placebo or not vaccinated (Lansbury, 2017). This meta-analysis included data from effectiveness studies of the AS03 adjuvanted Q Pan H1N1 vaccine Arepanrix and the D-Pan H1N1 AS03 adjuvanted vaccine Pandemrix.

Vaccine effectiveness against laboratory-confirmed influenza 14 days after vaccination compared with non-vaccinated subjects of all ages revealed a pooled VE point estimate of 80% for adjuvanted H1N1 vaccines (95% CI 59–90%; p<0.00001) compared with non-vaccinated individuals. In children (<18 years of age), vaccine effectiveness was 88% (95% CI 69–95%; p<0.0001) for adjuvanted H1N1 vaccines and 45% (95% CI 13–73; p=0.83) for unadjuvanted H1N1 vaccines (Figure 3).



*VE (%) = (1 – OR)*100. CI, confidence interval; †Planned comparisons between AS03 and MF59 were not possible as almost all studies included used AS03; VE, vaccine effectiveness; Weight - the inverse of the variance of the effect estimate

Figure 3 Forest plot of studies of laboratory-confirmed influenza A(H1N1) pdm09 illness, adjusted ORs, vaccinated versus non-vaccinated persons in children under 18 years (Lansbury et al. Vaccine 2017)

Adjuvanted H1N1 vaccines were significantly more effective at preventing hospitalisation for influenza in children within 14 days of vaccination (85%, 95% CI 67–94; p<0.00001) than in adults (p=0.04).

Several studies have evaluated the effectiveness of Pandemrix and Arepanrix at the national or regional level in different countries using different methodologies (Table 1).

Table 35 Summary of Studies Conducted in Countries Using Pandemrix and Arepanrix

Population	Stratification (eg age)	VE (95% CI)	Country / Method
Studies in countries using PANDEMRIX			
General population	14–59 years	**96.8%** (95.2–97.9)	Germany / Screening method[1]
	60+ years	83.3% (71.0–90.5)	
	<14 years	87% (78–92)	Germany / Case series method[2]
	>14 years	74% (64–82)	
	Adjusted: age, HC setting, chronic conditions, period	89% (36–100)	Navarre, Spain / Case-control[3]
	All ages (6 months–64 years)	**87–95%**	Sweden / Prospective cohort[4]
	All (crude)	88% (66–95)	England and Scotland / Case-control[5]
Risk group all ages	All	62% (33–78)	England / Test-negative case-control[6]
	<10 years	77% (11–94)	
	10–24 years	**100%** (80–100)	
	25–49 years	22% (-153–76)	
	50+ years	41% (-71–80)	
Risk groups	All	**95.0%** (76.0–100.0)	Scotland / Retrospective cohort[7]
Hospitalisations	VE for all pandemic vaccines used	**90%** (48–100)	Castellón, Spain / Test-negative case-control[8]
Studies in Canada of AREPANRIX			
General population, children	6–119 months	**100%** (79.5–100)	New Brunswick Canada / Community-based case-control[9]
General population	≥6 months	**95.3%** (80.3–98.9)	Canada, Nationwide[10]

Prospective efficacy study of an AS03-adjuvanted H1N1 vaccine

In a Phase III observer blind study conducted during 2010–2011 in 17 centres in Australia, Brazil, Colombia, Costa Rica, Mexico, the Philippines, Singapore and Thailand, 6 145 children (6 months to10 years of age) were randomised to receive a single dose of AS03-adjuvanted Q-Pan H1N1 vaccine (A/California; Day 0) followed by placebo on Day 21, two doses of AS03-adjuvanted Q-Pan H1N1 vaccine (Day 0, 21) or two doses of unadjuvanted H1N1 vaccine.

The primary objective was to evaluate the efficacy of 2 doses of H1N1-AS03 relative to that of 2 doses of nonadjuvanted vaccine beginning 14 days after dose 1 and continuing until study conclusion on day 385. Noninferiority in terms of relative vaccine efficacy (VE) was concluded if the lower limit of the 95% confidence interval (CI) for relative VE against real-time PCR–confirmed A(H1N1)pdm09 infection (Ad2 vs NAd2) was >-33%. Superiority was concluded if the lower limit of the 95% CI for relative VE was >0.

The relative efficacy of two doses of AS03-adjuvanted Q-Pan H1N1 vaccine compared with two doses of unadjuvanted H1N1 vaccine for the prevention of real-time polymerase chain reaction (PCR)-confirmed pandemic H1N1 infection from days 14 to 385 after vaccination was 76.8% (95% CI 18.5–93.4), which met predefined non-inferiority and superiority criteria for the adjuvanted vaccine. The efficacy of two doses of AS03-adjuvanted Q-Pan H1N1 vaccine was also non-inferior to that of two doses of unadjuvanted vaccine for the prevention of culture-confirmed influenza in all subjects (days 14–385; relative efficacy 74.9% 95% CI -18.2–94.7) and the prevention of real time PCR–confirmed pandemic H1N1 infection in children 3 to 9 years of age (relative efficacy 77.5% 95% CI -4.0–95.2) .

The CHMP criteria were met in all treatment groups on Day 42, including in the subgroups 6–35 months of age and 3–10 years of age (Nolan et al. Journal of Infectious Disease 2014).

The meta-analysis by Lansbury showed that vaccine effectiveness of adjuvanted H1N1 influenza vaccines was 88% in children during the 2009-2010 pandemic. Adjuvanted H1N1 influenza vaccines were observed to be more effective compared to unadjuvanted H1N1 influenza vaccines during the pandemic. This provides confirmation that use of adjuvanted influenza vaccines during a pandemic is appropriate. Table 35 indicates that efficacy of Pandemrix and Arepanrix vary with location and age, however, vaccine efficacy in children was found to be ≥62%.

The study by Nolan et al. (Journal of Infectious Disease 2014) investigated VE of 1 or 2 doses of AS03-adjuvanted Q-Pan H1N1 vaccine (A/California) compared to 2 doses of nonadjuvanted influenza A(H1N1) vaccine (A/California) in children aged 6 months to <10 years. This randomized, observer-blind, controlled study was conducted during 2010–2011. In total, 5803 children were included in ATP time-to-event efficacy analysis (days 14–385), of which 23 had real-time PCR-confirmed A(H1N1)pdm09 infection. The efficacy of the adjuvanted versus the unadjuvanted vaccine for prevention of PCR-confirmed A(H1N1)pdm09 infection from days 14 to 385 was 76.8% (95% CI, 18.5%–93.4%).

These data further confirm that it is reasonable to expect that an AS03-adjuvanted H5N1 vaccine would provide protection against the influenza strain contained in the vaccine during a pandemic.

2.4.3. Discussion on clinical efficacy

Adjupanrix is a split virion, inactivated, AS03-adjuvanted H5N1 pandemic influenza vaccine. It is currently intended for prophylaxis of influenza in the case of an officially declared pandemic. The MAH proposed to extend the indication to include use in children from 6 months to <18 years. Since this MA

is not effective (no indication) before the authorisation of the 'pandemic variation', it was proposed at the time of the MAA to allow the submission of different scenarios in the MA dossier (core pandemic dossier) of the 'mock-up' vaccine and select the relevant scenario at the time of the submission of the 'pandemic variation'. Vaccines registered through the 'mock-up' vaccine procedure prior the authorisation of a 'pandemic' variation are not indicated in a prepandemic setting (the indication has been restricted to the use during a pandemic phase). The guideline on submission and procedural requirement for influenza vaccines (EMA/56793/2014) states: "When a pandemic situation is duly recognised by the WHO or the Union, the MAH should submit a variation application ('pandemic strain update') as per Article 21 of Regulation (EC) No 1234/2008 to include the declared pandemic strain in the pandemic vaccine ('pandemic strain update'). This variation will be reviewed under an accelerated timeframe." Therefore, the indication 4.1 should not be amended. In addition, ethical considerations limit investigations that can be done in very young infants using a mock-up vaccine that will never be used and is thus not of use for them.

Nonetheless, the application remained of interest as the procedure has been used to determine the posology for children aged 6 months to <18 years in the SmPC of Adjupanrix. Of note, as a mock up vaccine, Adjupanrix will not be deployed as is, but in an officially declared pandemic, the pandemic strain will be included in the vaccine. Pandemrix, a H1N1 $AS03_B$ adjuvanted vaccine is a pandemic vaccine prepared using this platform.

The overall objective of the clinical development program was to evaluate the safety and immunogenicity of Adjupanrix administered as a 2-dose regimen in children aged 6 months to <18 years of age. No efficacy or effectiveness data is available, which is acceptable as H5N1 does not circulate. During the 2009/2010 pandemic caused by A(H1N1)pdm09, Pandemrix was effectively used, which shows that the GSK platform works. The MAH provided a summary of effectiveness information obtained using Pandemrix in children during the 2009/2010 pandemic, as well as data from a prospective efficacy study conducted in 2010/2011. The H1N1 adjuvanted vaccine was shown to be effective in children during the pandemic (VE ≥62%). During the study by Nolan et al, it was shown that an AS03-adjuvanted H1N1 vaccine had superior efficacy compared to an unadjuvanted vaccine. While it is acknowledged that data for an H1N1-based vaccine is not directly applicable for the H5N1 construct, it is reassuring. It further confirms that it is reasonable to expect that an AS03-adjuvanted H5N1 vaccine would provide protection against the influenza strain contained in the vaccine during a pandemic.

This application is based on immunogenicity data from 4 studies: 1 dose ranging study in children aged 6 months to <36 months (study Q-PAN H5N1-023), a phase II single arm study in children aged 6 months to 35 months (study D-PAN H5N1-013), a phase III randomized active-controlled study in children aged 3 to 17 years (study D-PAN H5N1-032) and a supportive phase II/III placebo-controlled study in children aged 6 months to <18 years (study Q-PAN H5N1-021). No correlate of protection exists for Influenza. This hampers the interpretation of the clinical relevance of the observed vaccine-induced immunogenicity. Totality of all immunogenicity results should be sufficiently convincing to ensure CHMP of vaccine efficacy regardless of a statistically significant effect.

Design and conduct of clinical studies

With the approval of D-Pan H5N1 products by the European Commission, GSK committed to conduct several paediatric studies using half the adult dose (containing 1.9 µg H5N1 HA antigen adjuvanted with $AS03_B$ [containing 5.93 mg of tocopherol]) as part of the initially agreed D-Pan H5N1 PIP (PIP-EMEA-000160-PIP01-M01). In response to concerns raised by the Paediatric Committee (PDCO) during the review rounds for the PIP on the lack of traditional dose-ranging studies (EMA/PDCO summary report EMA/737469/2010), a dose-ranging study was added to the PIP, Study Q-PAN H5N1-023. The dose-

ranging study Q-PAN H5N1-023 in children aged 6 months to <36 months was conducted concurrently with study D-PAN H5N1-013 in children aged 6 months to 35 months using a half adult dose.

Design

Study Q-PAN H5N1-023 was a randomised, observer blind dose-ranging study, which is acceptable for a dose-ranging study. Both study D-PAN H5N1-013 and D-PAN H5N1-032 are open-label studies, which is regretted from a safety perspective as it might affect reporting of AEs, however it is not expected to influence immunogenicity results.

Treatment

In all studies, primary vaccination included 2 vaccination doses containing A/Indonesia vaccine according to a 0, 21 day schedule. During studies D-PAN H5N1-013 and D-PAN H5N1-032, the primary vaccination vaccine contained half adult dose, consisting of 1.9 µg A/Indonesia HA antigen adjuvanted with $AS03_B$. Treatment during study Q-PAN H5N1-023 included half adult dose (190_B), quarter adult dose (090-C), half adult dose with less adjuvant (190_C), full adult dose with less adjuvant (375_C) and full adult dose (375_D).

Study D-PAN H5N1-013 and D-PAN H5N1-032 investigated the effect of a heterologous booster 6 months after the start of the primary vaccination. The boost contained 1.9 µg A/turkey HA antigen adjuvanted with $AS03_B$. Using a heterologous strain would mimic the response to an antigenically drifted strain. In the case of an influenza pandemic it is expected that the strain will adapt over time, consistent with SARS-CoV-2. Using a heterologous strain will measure cross-reactivity and determine whether an antigenically drifted strain would be able to elicit an anamnestic response.

During study Q-PAN H5N1-023, a year after the primary vaccination, all participants were given an unadjuvanted vaccine containing 3.75 µg A/Indonesia HA antigen. This mimics the situation that children encounter the pandemic causing strain 1 year after primary vaccination. An unadjuvanted vaccine was chosen to reduce reactogenicity. This set up is acceptable.

Population

The population enrolled in the clinical studies consisted of healthy children. This is considered acceptable as this would represent the majority of the population to be vaccinated during a pandemic setting. The studies were conducted in Asia and Australia, with only study Q-PAN H5N1-021 being also conducted in the US and Canada. Considering the fact that the vaccine as it was prepared for the studies will not be used as such, but will be adapted based on the strain causing a pandemic, the studies were used to determine that the platform works and is immunogenic enough to induce a robust immune response. Therefore, the population is acceptable.

Objectives

During study Q-PAN H5N1-023 the primary objective was to assess the performance of the different dosing regimens using an immunogenicity-fever index. The usefulness of this immunogenicity-fever-index for both the HI as well as the MN antibodies is limited, as already mentioned during the scientific advice. The assessment of the totality of evidence will be based on the immunogenicity aspects mentioned in the Guideline on Influenza Vaccines.

During study D-PAN H5N1-013 the primary objective was to assess whether a heterologous booster dose (containing 1.9 µg A/turkey/Turkey/1/2005 HA with $AS03_B$) given 6 months following a 2-dose primary vaccination series with 1.9 µg A/Indonesia/05/2005 HA with $AS03_B$ elicits an antibody response that meets the SCR of >40%, SPR of >70% and MGI of >2.5 based on HI responses to A/turkey/Turkey/1/2005 10 days following booster vaccination. As there is no correlate of protection,

the clinical impact of meeting any pre-defined immunogenicity criteria is unknown. SPR, which assumes a correlate of protection, is not considered a clinically relevant measure and will not be presented.

During study D-PAN H5N1-032 the primary objective was to assess superiority of the A/turkey HI antibody response 10 days following boost with A/turkey on Day 182 (containing 1.9 µg A/turkey/Turkey/01/2005 HA antigen adjuvanted with $AS03_B$) in subjects previously primed with two doses of heterologous A/Indonesia vaccine versus non primed subjects. Criterion used: lower limit of the 2-sided 95% confidence interval (CI) for the HI GMT ratio on Day 192 (Group H5N1_H5N1 compared to Group Havrix_H5N1) was greater than 1.0. In general, the primary endpoint can be agreed as it will allow for comparison of the anamnestic response between primed and unprimed individuals. However, again as there is no correlate of protection the immune response should be convincing regardless of meeting any pre-defined statistical criteria

For all studies, the following secondary outcomes were reported for HI and MN antibody responses at different time points: GMT, SCR/VRR, SPR and MGI. As stated above, the focus is on GMTs where presented as primary endpoint by the MAH and on the SCR/VRR.

Efficacy data and additional analyses

Children aged 3 years to 17 years

In both studies in the age category 3 years to <18 years, study D-PAN H5N1-032 and Q-PAN H5N1-021, the primary vaccination with a vaccine containing A/Indonesia + $AS03_B$ induced a robust increase in homologous HI antibodies, leading to an SCR of nearly 100% (≥99%) at 21 days after vaccination. HI antibodies declined over time, however GMTs remained well above baseline for at least 6 months in study D-PAN H5N1-032 and 12 months in study Q-PAN H5N1-021, with an MGI of ≥9.1 and ≥3.6, respectively. A similar response was seen in vaccine-homologous MN antibodies, leading to a VRR of >97%. MN antibodies also decline over time, but remain well above baseline for at least 6 months in study D-PAN H5N1-013 and 12 months in study Q-PAN H5N1-021.

Vaccine-heterologous HI antibodies, only studied in study D-PAN H5N1-032, also increased substantially after the primary vaccination with A/Indonesia, leading to an SCR of ≥98.0% at Day 42 (21 days after the primary vaccination). Again, titers decline over time, but remain well above baseline with an MGI of ≥5.6. A similar response was seen in vaccine-heterologous MN antibodies, with a substantial peak in GMTs seen at Day 42, which decline over time.

During study D-PAN H5N1-032 it was shown that 10 days after a booster with a vaccine containing the H5N1/Turkey strain, H5N1/turkey HI GMTs increased in both primed and unprimed individuals, however, the increase was significantly higher in the primed group, indicating the presence of an anamnestic immune response to an antigenically drifted strain after primary vaccination with H5N1/Indonesia. SCR of A/turkey HI in primed individuals was 100% 10 days after the boost, while in unprimed individuals this was 32.1%. These results indicate that priming substantially increases the immune response to a heterologous boost.

In addition to the A/turkey HI parameters, 10 days after the booster primed individuals showed a substantial response in A/Indonesia HI parameters, in that GMTs increased to 674.1, SCR was 100% and MGI was 117.7. This indicates that, an antigenically drifted strain (A/turkey) was able to elicit an anamnestic response for A/Indonesia antibodies that was higher compared to the primary response at 6 months after the primary vaccination. In unprimed individuals, 10 days after the heterologous booster dose A/Indonesia GMTs, SCR and MGI increased only slightly. This response persisted for at least 6 months, as at D364, 6 months after booster vaccination with A/turkey, A/Indonesia HI parameters were substantially increased compared to prevaccination, with a GMT of 205.5 compared to 5.7 and an SCR

of 100%. In unprimed individual, which only received a single dose of A/turkey containing vaccine, A/Indonesia HI parameters at 6 months after the dose were comparable to prevaccination parameters. This indicates that a primary vaccination is required before a single dose can induce lasting cross-reactive immune response.

Overall, vaccination with half adult dose was able to induce a robust immune response. This is in line with the conclusions reached during review of the data by the VWP in connection to the scientific advice (EMEA/H/SA/3998/1/2018/PED/II.), as it was found that the data could support use of half the adult dose down to 3 years of age.

Children aged 6 months to 36 months

The most relevant study for this age group is the dose finding study Q-PAN H5N1-023, which compared immunogenicity of half adult dose (190_B), quarter adult dose (090-C), half adult dose with less adjuvant (190_C), full adult dose with less adjuvant (375_C) and full adult dose (375_D) in a single study.

All dosing regimens elicited a robust vaccine-homologous immune response at Day 42, 21 days after the primary vaccination series, as both SCR (evaluating HI antibodies) and VRR (evaluating MN antibodies) were 100% for all formulations. In addition, SCR and VRR for a heterologous HI antigen (A/Vietnam) was >80% in all groups, indicating that 21 days after a primary vaccination series using all doses, a substantial immune response was generated to an antigenically drifted strain. An immune response to an H5N8 strain could also be detected, leading to SCR of 56.7% in group 190_B, 37.5% in group 090_C, 29.4% in group 190_C, 20.0% in group 375_C and 26.7% in group 375_D.

The primary vaccination induced both vaccine-homologous and -heterologous HI and MN antibody titres in all groups, which declined over time but remained above baseline for 1 year. A booster dose of unadjuvanted vaccine 1 year after the primary vaccination was able to elicit an immune response in all groups, however this response measured 7 days after the booster was lower compared to the initial immune response seen at Day 42.

The dosing regimens of groups 190_B and 090_C elicited the highest immune response of all groups for HI and MN antibodies. Although numerically the response in group 190_B was higher, the increase in immunogenicity was considered small. At Day 42, SCR and VRR to homologous stimulation was 100% in both groups. Heterologous stimulation led to an SCR and VRR of 100% in group 190_B and >91% in group 090_C. For both HI and MN antibodies, the unadjuvanted vaccine 1 year after the primary vaccination was able to elicit a robust vaccine-homologous and -heterologous immune response in both groups, though this response was lower compared to the original response at Day 42. Vaccination during a pandemic setting is deployed first and foremost to induce a vaccine-homologous immune response quickly, to reduce spread of the virus and mortality/illness in the naïve population.

Study D-PAN H5N1-013 and Q-PAN H5N1-021 both investigated the immunogenicity of half adult dose (1.9 µg A/Indonesia HA antigen + $AS03_B$). Study Q-PAN H5N1-021 enrolled children aged 6 months to <18 years and evaluated immunogenicity in the following age categories: 6 months to <36 months, 3 years to <9 years and 9 years to <18 years. Similar results were observed compared to study Q-PAN H5N1-023 as the primary vaccination induced a robust increase in homologous HI antibodies, as an SCR of 100% was seen at D42. HI antibodies declined over time, however GMTs remained well above baseline for at least 6 months in study D-PAN H5N1-013 and 12 months in study Q-PAN H5N1-021. A similar response was seen in vaccine-homologous MN antibodies, leading to a VRR of 100% at Day 42. MN antibodies also decline over time, but remained well above baseline for at least 6 months in study D-PAN H5N1-013 and 12 months in study Q-PAN H5N1-021.

Study Q-PAN H5N1-021 showed that the response for vaccine-heterologous MN antibody titers develop similarly compared to the vaccine-homologous MN titers, though to a considerably lesser extent. The

peak GMT in the 6 months to 36 months age category was 68.18 (58.05-80.07) compared to 855.62 (597.88-1224.47).

Study D-PAN H5N1-013 showed that 6 months after primary vaccination with A/Indonesia, vaccine-heterolgous (A/turkey) HI and MN antibodies were well above baseline levels, indicating that the primary vaccination was able to elicit an antibody response to an antigenically drifted strain, leading to an SCR of >95% and VRR of >82% at 6 months after the primary vaccination. Ten days after a heterologous booster, a substantial immune response as measured by A/turkey and A/Indonesia HI parameters was seen, as reflected by a SCR of 100% (both A/turkey and A/Indonesia) and a MGI of >357.7 (302.4-423.2) and 357.5 (310.5-411.7) respectively. This indicates that an antigenically drifted strain (A/turkey) was able to elicit an anamnestic response for A/Indonesia antibodies that was higher compared to the primary response (as seen as GMTs at D42) at 6 months after the primary vaccination. In addition, primed individuals are able to quickly mount a substantial immune response to an antigenically drifted strain. Substantial cross-reactivity is seen in the immune response. In a real world setting during a pandemic, this would mean that up to 6 months after the primary vaccination vaccinated individuals would be able to elicit a robust immune response to an antigenically drifted influenza strain.

As study Q-PAN H5N1-021 enrolled children aged 6 months to <18 years and evaluated immunogenicity in the following age categories: 6 months to <36 months, 3 years to <9 years and 9 years to <18 years, a direct comparison of immune response in the different age categories could be made. It was observed that the vaccine-homologous HI and MN antibody response was highest in the youngest age category, as GMTs were highest. This indicates that immunogenicity of the adjuvanted vaccine declined with age and was highest in the age category of 6 months to 36 months.

Overall, the immunogenicity data showed that a quarter adult dose was only slightly less immunogenic compared to a half adult dose in children aged 6 months to 36 months. The vaccine-homologous HI response was comparable shortly after vaccination as at Day 42 an SCR of 100% was seen for both groups, however numerically, GMTs were slightly lower in the 090_C group compared to the 190_B group (858.8 [659.2-1118.8] vs 1118.6 [884.4-1414.9] respectively). Over time a slightly higher reduction in vaccine-homologous antibody titers was observed in the 090_C group compared to the 190_B group, as 1 year after primary vaccination SCR was 97.1% (84.7-99.9) in the 190_B group and 78.8% (61.1-91.0) in the 090_C group. In addition, vaccine-heterologous responses were also slightly lower. The clinical relevance of this slight decrease is unknown. The slightly lower immune response might be compensated by the fact that the immune response in this age category is higher. This is in line with the conclusions reached during review of the data by the VWP in connection to the scientific advice (EMEA/H/SA/3998/1/2018/PED/II.), as it was found that a quarter dose might be sufficiently immunogenic in the age category of 6 months to 36 months.

2.4.4. Conclusions on the clinical efficacy

Overall, the results indicate that Adjupanrix was very immunogenic across all ages from 6 months to 17 years, especially shortly after vaccination as measured 21 days after primary vaccination. This is the most relevant period in a pandemic situation. A trend towards a higher immune response is seen in the age group 6 months to 36 months compared to 3 years to 17 years.

The data support use of half the adult dose down to 3 years of age. In children aged 6 months to 36 months a quarter adult dose was deemed sufficiently immunogenic, especially in light of the increased immunogenicity in subjects of this age category as compared to children 3 years and older and the reduction in reactogenicity.

2.5. Clinical safety

Introduction

The discussion of clinical safety is based on available safety data from 4 clinical studies. The safety results from the 4 studies were not pooled due to the heterogeneity of the paediatric studies (e.g., studies were not uniformly blinded and included different age groups [6 months to <36 months and 3 to <18 years of age] requiring different safety assessments).

Study **Q-PAN H5N1-023** enrolled children **6 months to less than 36 months** old at time of first study vaccination and was conducted with H5N1/Indonesia (Q-Pan) vaccine (5 different adjuvanted formulations for the primary 2-dose vaccination, and an unadjuvanted formulation [A/Indonesia, 3.75 µg HA] for the booster dose). Safety was assessed in terms of solicited and unsolicited AEs recorded during their respective follow-up periods and in terms of MAEs, adverse events of special interest (AESIs), pIMDs and SAEs during the entire study period.

Study **D-PAN H5N1-013** enrolled children **6 months to less than 36 months** old at time of first study vaccination and was conducted with H5N1/Indonesia (D-Pan) vaccine, and with a heterologous booster dose of H5N1/Turkey. Safety and reactogenicity was assessed in terms of solicited and unsolicited adverse events (AEs) recorded during their respective follow-up periods, and in terms of medically-attended AEs (MAEs), potential immune-mediated diseases (pIMDs), and serious adverse events (SAEs) from the first vaccination up to study end.

Study **D-PAN H5N1-032** enrolled children **3 to 17 years of age** (inclusive) at the time of the first vaccination and was conducted with H5N1/Indonesia (D-Pan) and with a heterologous booster dose of H5N1/Turkey. Safety was assessed in terms of solicited and unsolicited AEs recorded during their follow-up solicited periods, and in terms of MAEs, pIMDs and SAEs during the entire study.

Study **Q-PAN H5N1-021** enrolled children **≥6 months and <18 years** of age at the time of first vaccination in study year 1 and was conducted with H5N1/Indonesia (Q-Pan) vaccine (during both study years). Safety and reactogenicity was assessed in terms of solicited and unsolicited AEs recorded during their respective follow-up periods, and in terms of MAEs, pIMDs and SAEs from the first vaccination until study end. Clinical laboratory abnormalities were also evaluated up to Day 182 for half of the subjects, and up to Day 385 for the remaining subjects.

Due to the fact that study set-up was different, different formulations of the vaccine were used (D-PAN vs Q-PAN) and the studies included children from different age categories, it was agreed not to pool the studies.

The main safety evidence for the quarter dose, to be used in children 6 months to 36 months of age at time of first vaccination, comes from study Q-PAN H5N1. However, as only 37 children were included in the group receiving the quarter dose, additional safety data is retrieved using the additional dosages investigated during the dose-ranging study, study D-PAN H5N1-013 and the subjects 6 months to <36 months included in study Q-PAN H5N1-021. Both latter studies used half adult dose, containing 1.9 µg HA+AS03$_B$.

The main safety evidence for children 3-17 years of age comes from study D-PAN H5N1-032, which is supported by data collected in individuals 3-17 years of age included in study Q-PAN H5N1-021.

Safety evaluation methods

The methods used for safety evaluation were consistent across the submitted studies.

Solicited local and systemic AEs (reactogenicity)

Diary cards were provided to the subjects/subjects' parent(s)/LAR(s) to record solicited (local and systemic) and unsolicited symptoms. Collection and verification of completed diary cards was performed during discussion with the subject/subject's parent(s)/LAR(s) at the next planned site visit.

In all studies, solicited local (pain, redness and swelling) and systemic (drowsiness, fever, irritability/fussiness, loss of appetite, diarrhoea and vomiting) AEs occurring within 7 days post-each vaccination were collected. In addition, in studies D-PAN H5N1-032 and Q-PAN H5N1-021, fatigue, fever, gastrointestinal symptoms (nausea, vomiting, diarrhoea and/or abdominal pain), headache, arthralgia and myalgia were collected in subjects ≥ 6 years of age. In addition, in study Q-PAN H5N1-021, solicited systemic AEs also included shivering (chills) and increased sweating (for children ≥6 years old).

Unsolicited AEs

Occurrence of unsolicited AEs was collected during the 21-day (Days 0–20) follow-up period after each vaccination and overall (Days 0–84 in studies D-PAN H5N1-013 and 032; Days 0–42 in study Q-PAN H5N1-023; and Days 0–42 and U0–U42 [Days 0–42 after unblinding in Year 2, in subjects that received Placebo during Year 1] in study Q-PAN H5N1-021). In addition, in study Q-PAN H5N1-023, the occurrence of unsolicited AEs was followed up for 30 days after the administration of the unadjuvanted booster dose.

SAEs and AESIs

In all studies, the SAEs were collected and recorded during the entire study period.

In study Q-PAN H5N1-023, AEs of special interest (AESI) were also collected throughout the entire study period. These were identified using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) or Standardized MedDRA Queries (SMQs) as recommended in the Committee for Medicinal Products for Human Use (CHMP) Risk Management Plan for Pandemic Vaccines (CHMP, 2009). AESIs included the events listed below; the MedDRA PT or SMQ used to identify reports of these events is provided in parentheses:

- Anaphylaxis (narrow SMQs "Anaphylactic reaction" and "Angioedema")
- Bell's palsy (MedDRA PT "VIIth nerve palsy")
- Convulsion (narrow SMQ "Convulsions")
- Demyelination (narrow SMQ "Demyelination")
- Encephalitis (narrow SMQ "Non-infectious encephalitis")
- Guillain-Barré syndrome (narrow SMQ "Guillain-Barré syndrome")
- Neuritis (MedDRA PT "Neuritis")
- Vasculitis (narrow SMQ "Vasculitis")

Intensity grading

In all studies, the investigator assessed the maximum intensity that occurred over the duration of the event for all solicited local and systemic AEs based on a 4-point intensity scale (from grade 0 to grade 3).

Causal relationship

The investigator was obligated to assess the relationship between the investigational product and the occurrence of each AE/SAE, based on clinical judgement. Alternative plausible causes, based on natural history of the underlying diseases, concomitant therapy, other risk factors and the temporal relationship of the event to the investigational product were to be considered and investigated.

In studies D-PAN H5N1-013 and D-PAN H5N1-032, in case of concomitant administration of multiple vaccines, it could not be possible to determine the causal relationship of systemic AEs to the individual vaccines administered. The investigator should, therefore, have assessed whether the AE could be related to vaccination rather than to the individual vaccines.

All solicited local (injection site) reactions were considered related to vaccination.

Safety evaluation populations

In all studies, the Total Vaccinated Cohort (TVC) included all vaccinated subjects with at least one documented vaccine administration. In study Q-PAN H5N1-023, the TVC for booster safety analysis included all the subjects who received the booster dose. In study Q-PAN H5N1-021, the TVC included all subjects who received at least one study vaccination during the relevant portion of the study.

In studies D-PAN H5N1-013, D-PAN H5N1-032 and Q-PAN H5N1-021 the According-to-protocol (ATP) cohort for analysis of safety included all vaccinated and eligible subjects who met all inclusion criteria and no exclusion criteria for the study, who received at least one dose of study vaccine, for whom administration site of study vaccine/comparator was known, and subjects who had not received a vaccine not specified or forbidden in the protocol. Since the percentage of enrolled subjects excluded from the TVC for analysis of safety (in study D-PAN H5N1-013)/ATP cohort for analysis of safety (in studies D-PAN H5N1-032 and Q-PAN H5N1-021) was less than 5% in any treatment group/year, no second analysis on the ATP cohort was carried out.

In general, methods to assess the reactogenicity and safety of Adjupanrix were considered appropriate. Reactogenicity as measured by local injection-site reactions and systemic reactions was followed for 14 days, which was considered appropriate (see Guideline on clinical evaluation of vaccines). Unsolicited AEs were collected during at least 21 days after vaccination in all studies and SAEs were collected throughout the study period. Subjects were followed for a sufficient period of time in clinical studies to collect relevant adverse events.

In children aged 6 months to 36 months, the measurement of the solicited local AE of pain is considered to be very subjective, as it depends on touch of parent/legal guardian, which makes interpretation of results concerning this solicited AE difficult.

Patient exposure

Patient exposure is presented in Table 36.

Table 36 Number of subjects who received study vaccine doses in all studies – Total vaccinated cohort (study D-PAN H5N1-013, D-PAN H5N1-032, Q-PAN H5N1-023, Q-PAN H5N1-021)

H5N1 A/Indonesia					
Study (age)	**Group**	**Formulation**	**Number of subjects**	**Number of doses**	**Total number of doses**
D-PAN H5N1-013 (6 – <36 months)	H5N1	D-PAN H5N1 1.9 µ HA+AS03$_B$	1	1	225
			112	2	
D-PAN H5N1-032 (3–17 years)	H5N1-H5N1		0	1	624
			156	2	
	H5N1-*Havrix*		2	1	
			156	2	
Q-PAN H5N1-023 (6– <36 months)	190_B	Q-PAN H5N1 1.9 µ HA+AS03$_B$	1	1	75
			37	2	
	090_C	Q-PAN H5N1 0.9 µ HA+AS03$_C$	1	1	73
			36	2	
	190_C	Q-PAN H5N1 1.9 µ HA+AS03$_C$	0	1	76
			38	2	
	375_C	Q-PAN H5N1 3.75 µ HA+AS03$_C$	2	1	72
			35	2	
	375_D	Q-PAN H5N1 3.75 µ HA+AS03$_D$	0	1	70
			35	2	
	190_B	Q-PAN H5N1 3.75 µg HA	36	1	176
	090_C		34	1	
	190_C		38	1	
	375_C		35	1	
	375_D		33	1	
Q-PAN H5N1-021 (6 months – <18 years)	Q-Pan (Year 1)	Q-PAN H5N1 1.9 µ HA+AS03$_B$	14	1	1509
			593	2	
	Placebo (Year 2)		1	1	
			154	2	
H5N1 A/Turkey					
Study	**Group**	**Formulation**	**Number of subjects**	**Number of doses**	**Total number of doses**
D-PAN H5N1-013 (6 – <36 months)	H5N1	D-PAN H5N1 1.9 µg HA+AS03$_B$	108	1	108
D-PAN H5N1-032 (3–17 years)	*Havrix*-H5N1		104	1	104

In study Q-PAN H5N1-023, in the TVC, the mean age (± SD) at the time of first vaccination was 21.4 (± 8.2) months. There was an unequal distribution of males and females across groups; fewer females were observed in the 190_B, 090_C and 190_C groups. Overall, most subjects were of Asian heritage (56.2% Asian/East Asian and 43.2% Asian/South East Asian).

In study D-PAN H5N1-013, in the TVC, the mean age (± standard deviation [SD]) at the time of first vaccination was 16.9 (± 9.29) months. Most of the subjects were of Asian/South-East Asian heritage (72.6%). The study group included a higher proportion of females (55.8%).

In study D-PAN H5N1-032, in the TVC, the mean age (± SD) at the time of first vaccination was 9.5 (± 4.06) years. The study groups were balanced in terms of gender distribution and all participants were of Asian/South-East Asian heritage.

In study Q-PAN H5N1-021, in the TVC for year 1, the mean age (± SD) at the time of first vaccination was 84.9 (± 61.37) months. The study groups were balanced in terms of gender distribution and most of the subjects were of Caucasian/European heritage (45%). In the TVC for year 2 (consisting of a subset of Placebo recipients in Year 1), the mean age (± SD) at the time of first vaccination was 84.5 (± 59.78) months.

The number of participants aged 6 months to <36 months, exposed to at least 1 dose of 0.9 µg HA antigen + $AS03_C$ is relatively small, 37 subjects. Safety information in this age group is bolstered using safety data from participants in the same age group, exposed to at least 1 dose of 1.9 µg HA antigen + $AS03_B$, which included 38 subjects in study Q-PAN H5N1-023, 113 subjects in study D-PAN H5N1-013 and 249 subjects in study Q-PAN H5N1-021.

The number of participants aged 3 to <18 years, exposed to 2 doses of 1.9 µg HA antigen + $AS03_B$, during the pivotal study is 312. This data is bolstered by 512 participants in study Q-PAN H5N1-021 aged 3 to <18 years exposed to at least 1 dose of 1.9 µg HA antigen + $AS03_B$.

Adverse events

Children aged 6 months to 36 months

Study Q-PAN H5N1-023

During the 7-day post-vaccination periods, at least one symptom (solicited and unsolicited) was reported for 92.1% of the subjects in the 190_B group, 70.3% in the 090_C group, 81.6% in the 190_C group, 86.5% in the 375_C group and 80.0% in the 375_D group.

At least one solicited systemic AE was reported for 89.5%, 62.2%, 71.1%, 64.9% and 68.6% of subjects in group 190_B, 090_C, 190_C, 375_C and 375_D respectively. At least one local AE was reported for 42.1%, 29.7%, 34.2%, 45.9% and 37.1% of subjects in group 190_B, 090_C, 190_C, 375_C and 375_D respectively.

At least one Grade 3 solicited AE was reported for 23.7% of subjects (12.0% overall/dose) in the 190_B group, 13.5% of subjects (8.2% overall/dose) in the 090_C group, 10.5% of subjects (5.3% overall/dose) in the 190_C group, 13.5% of subjects (8.3% overall/dose) in the 375_C group and 5.7% of subjects (2.9% overall/dose) in the 375_D group.

At least one vaccine-related Grade 3 solicited AE was reported for 18.4% of subjects in the 190_B group, 10.8% of subjects in the 090_C group, 10.5% of subjects in the 190_C group, 10.8% of subjects in the 375_C group and 5.7% of subjects in the 375_D group.

Study D-PAN H5N1-013

During the 7-day post-vaccination periods, at least one symptom (solicited and unsolicited) was reported for 94.6% of the subjects. Overall, for 91.1% of subjects at least one systemic symptom was reported and for 62.5% at least one local symptom was reported.

Study Q-PAN H5N1-021

During the 7-day post-vaccination periods, at least one symptom (solicited and unsolicited) was reported for 74.9% of the subjects in the Q-PAN group and 68.0% in the Placebo group. At least one solicited AE was reported for 71.9% of subjects (58.4% overall/dose) in the Q-PAN group compared to 58.7% of subjects (44.2% overall/dose) in the Placebo group. Overall, for 60.8% of subjects in the Q-PAN group at least one systemic symptom was reported and for 48.2% at least one local symptom was reported. In the Placebo group at least one systemic symptom was reported for 50.7% of subjects and 29.3% reported at least one local symptom.

In total, 12.1% of subjects experienced a Grade 3 solicited AE in the Q-PAN group vs 9.3% in the Placebo group. Vaccine related grade 3 solicited AEs were experienced by 8.5% of subjects in the Q-PAN group vs 6.7% of subjects in the Placebo group.

In the age group 6 months to <36 months, the majority of subjects, ranging from 70.3% to 94.6%, receiving any dose of the primary vaccination with H5N1 vaccine, experienced at least 1 AE (solicited or unsolicited).

Of the subjects receiving a quarter adult dose, 70.3% experienced at least 1 AE. A solicited systemic AE was reported by 62.2% of subjects and a local AE by 29.7% of subjects. A grade 3 solicited AE was reported by 13.5% of subjects, of which 10.8% were considered related to the vaccine.

Of the subjects receiving a half adult dose (190_B), 74.9% to 94.6% experienced at least 1 AE. A solicited systemic AE was reported by 60.8%-89.5% of subjects and a local AE by 42.1%-48.2% of subjects. A grade 3 solicited AE was reported by 12.1%-23.7% of subjects of which, 8.5%-18.4% were considered related to the vaccine.

Children aged 3 years to 17 years

Study D-PAN H5N1-032

During the 7-day post-vaccination period at least one solicited AE was reported by 84.6%, 88.5%, 76.0% and 58.7% of subjects in Groups H5_H5, H5_Hav, Hav_H5 and Hav_Hav, respectively. Overall, 61.5%, 67.3%, 45.2% and 34.6 % of these subjects, respectively, reported at least one systemic symptom and 82.7%, 82.7%, 70.2% and 51.0% of the subjects, respectively, reported at least one local symptom.

At least one Grade 3 solicited AE was reported for 9.0% of subjects (3.2% overall/dose) in the H5_H5 group, 8.3% of subjects (2.8% overall/dose) in the H5_Hav group, 3.8% of subjects (1.9% overall/dose) in the Hav_H5 group, and 3.8% of subjects (1.9% overall/dose) in the Hav_Hav group.

At least one vaccine-related Grade 3 AE was reported for 8.3% of subjects in the H5_H5 group, 7.1% of subjects in the H5_Hav group, 2.9% of subjects in the Hav_H5 group, and 2.9% of subjects in the Hav_Hav group.

Study Q-PAN H5N1-021

During year 1, at least one solicited AE was reported for 78.8% of subjects (63.8% overall/dose) in the 3 year to <9 year Q-PAN group and 84.3% of subjects (72.6% overall/dose) in the 9 year to <18 year Q-PAN group compared to 60.5% of subjects (39.3% overall/dose) in the 3 year to <9 year and 47.5% of subjects (34.8% overall/dose) in 9 year to <18 year Placebo group.

Grade 3 solicited AEs were reported for 11.1% of subjects (6.9% overall/dose) in the 3 year to <9 year Q-PAN group and 8.6% of subjects (4.5% overall/dose) in the 9 year to <18 year Q-PAN group compared to 1.3% of subjects (0.7% overall/dose) in the 3 year to <9 year and 7.5% of subjects (3.8% overall/dose) in 9 year to <18 year Placebo group.

In the age group 3 years to 17 years, the majority of subjects, ranging from 78.8% to 88.5%, receiving the primary vaccination with H5N1 vaccine experienced at least 1 solicited AE. Grade 3 solicited AEs, were reported by <12% of subjects (<6.9% overall/dose) in both studies.

In the active comparator/placebo control groups in these studies, a substantial number of subjects experienced at least 1 solicited AE, ranging from 47.5% to 76.0%. Grade 3 solicited AEs were reported by 1.3% to 7.1% of subjects.

Local solicited adverse events in children aged 6 months to 36 months

Study Q-PAN H5N1-023

The most frequently reported solicited local AE in any group during the 7-day post-vaccination period was injection site pain. Overall by dose, the incidence of injection site pain was reported after 29.3%, 26.0%, 27.6%, 29.2% and 34.3% of doses in groups 190_B, 090_C, 190_C, 375_C and 375_D. The overall per subject incidence of pain ranged from 29.7% (090_C group) to 43.2% (375_C group).

Grade 3 injection site pain was reported for ≤ 5.3% of subjects during the 7-day post-vaccination period after vaccination.

No subjects in any dose group reported redness and only 1 subject in the 375_C group reported swelling during the 7-day post-vaccination period after Dose 1.

Study D-PAN H5N1-013

In study D-PAN H5N1-013 after the 2 primary doses of D-PAN vaccine (A/Indonesia, 1.9 µg HA+AS03$_B$), pain was the most frequently reported solicited local AE, reported after 30.9% of doses in 45.5% of subjects. Redness and swelling were reported after 4.5% and 3.6% of doses, respectively, in 8.9% and 5.4% of subjects, respectively. Grade 3 pain was reported after 1.8% of doses in 3.6% of subjects; no grade 3 redness or swelling was reported.

After the booster dose, pain was the most frequently reported solicited local AE, reported after 49.1% of doses. Redness and swelling were reported after 16.7% and 10.2% of doses, respectively. Grade 3 pain was reported after 6.5% of doses; no grade 3 redness or swelling was reported.

Study Q-PAN H5N1-021

Year 1:

Pain was the most frequently reported solicited local AE, reported after 37.2% of doses in 47.4% of subjects the Q-Pan group and after 22.1% of doses in 30.1% of subjects in the Placebo group. Redness and swelling were reported after 2.9% and 2.3% of doses in 5.6% and 4.6% of subjects, respectively in the Q-Pan group; no redness and swelling were reported in the Placebo group.

Grade 3 pain was reported after 1.6% of doses in 2.6% of subjects from the Q-Pan group and 1.4% of doses in 2.7% of subjects in the Placebo group, in subjects 6 to <36 months of age.

Year 2:

Pain was the most frequently reported solicited local AE, reported after 45.0% of doses in 58.0% of subjects in the 6 to <36 months age stratum, with Grade 3 pain being reported after 3.0% of doses in 6.0% of subjects. Redness and swelling were reported after 1.0% and 4.0% of doses in 2.0% and 4.0% of subjects respectively.

As stated above, in the age group 6 months to 36 months, injection site pain was the most frequently reported solicited local AE in all doses and all groups.

Using the quarter dose in study Q-PAN H5N1-023 (group 090_C), injection pain was reported after 26.0% of the doses and in 29.7% of subjects. No grade 3 injection pain was reported. No redness or swelling were reported.

Using the half adult dose, injection pain was reported after >29% of doses and in >42% of subjects. Grade 3 injection pain was reported after >1.6% of doses in >2.6% of subjects. In study Q-PAN H5N1-021, it was observed that Grade 3 injection site pain occurred at comparable frequencies in the Q-PAN and placebo group: Grade 3 pain was reported after 1.6% of doses in 2.6% of subjects from the Q-Pan group and 1.4% of doses in 2.7% of subjects in the Placebo group, in subjects 6 to <36 months of age

A trend of increase incidence of local reactions (injection site pain and erythema) from dose 1 to dose 2 to dose 3 was observed.

Local solicited adverse events in children aged 3 years to 17 years

Study D-PAN H5N1-032

Overall, injection site pain was the most frequently reported solicited local symptom. The incidence of injection site pain was 81.4%, 82.7% 70.2% and 51.0% overall, respectively for subjects in Groups H5_H5, H5_Hav, Hav_H5 and Hav_Hav. In Group H5_H5, local pain was reported for 67.9%, 59.6% and 67.3% of subjects, respectively, following dose 1, dose 2 and dose 3. Grade 3 injection site pain was reported for 3.2%, 1.9%, 1.0% and 1.0% of subjects in Groups H5_H5, H5_Hav, Hav_H5 and Hav_Hav, respectively.

Overall swelling was reported for 9.6%, 8.3%, 1.9% and 1.0% of all subjects in Groups H5_H5, H5_Hav, Hav_H5 and Hav_Hav, respectively and redness for 2.6% , 1.3%, 1.0% and 1.0% of all subjects in Groups H5_H5, H5_Hav, Hav_H5 and Hav_Hav, respectively. No Grade 3 swelling or redness was reported.

After the D-PAN H5N1 booster dose (A/Turkey, 1.9 µg HA+AS03$_B$), pain was the most frequently reported solicited local AE, reported after 66.7%-67.5% of booster doses in subjects who received 2 doses of D-PAN vaccine during primary vaccination (H5_H5 group). After Havrix administration as booster (Dose 2), pain was reported after 25.0%-29.1% of doses in subjects who received 1 dose of Havrix as primary vaccination (Hav_Hav group).

Study Q-PAN H5N1-021

Year 1 children 3 years to <9 years:

Pain was the most frequently reported solicited local AE, reported after 56.8% of doses in 71.1% of subjects the Q-Pan group and after 26.0% of doses in 38.2% of subjects in the Placebo group. Redness and swelling were reported after 3.6% and 5.1% of doses in 5.6% and 7.1% of subjects, respectively in the Q-Pan group; no redness and only 1 case of swelling was reported (0.7% of doses in 1.3% of subjects) in the Placebo group.

Grade 3 pain was reported after 1.6% of doses in 2.6% of subjects from the Q-Pan group and 1.4% of doses in 2.7% of subjects in the Placebo group, in subjects 3 years to <9 years of age.

Year 2 children 3 years to <9 years:

Pain was the most frequently reported solicited local AE, reported after 70.5% of doses in 85.4% of subjects in the 3 year to <9 year age stratum, with Grade 3 pain being reported after 2.1% of doses in 4.2% of subjects. Redness and swelling were reported after 1.1% and 2.1% of doses in 2.1% and 2.1% of subjects respectively.

Year 1 children 9 years to <18 years:

Pain was the most frequently reported solicited local AE, reported after 68.5% of doses in 81.9% of subjects the Q-Pan group and after 16.6% of doses in 22.5% of subjects in the Placebo group. Redness and swelling were reported after 1.9% and 5.7% of doses in 3.3% and 8.6% of subjects, respectively in the Q-Pan group; no redness and swelling were reported in the Placebo group.

Grade 3 pain was reported after 2.4% of doses in 4.8% of subjects from the Q-Pan group and 1.3% of doses in 2.5% of subjects in the Placebo group, in subjects 9 years to <18 years of age.

Year 2 children 9 years to <18 years:

Pain was the most frequently reported solicited local AE, reported after 60.4% of doses in 73.2% of subjects in the 9 year to <18 year age stratum, with Grade 3 pain being reported after 0.6% of doses in 5.4% of subjects. Redness and swelling were reported after 3.6% and 1.8% of doses in 7.1% and 3.6% of subjects respectively.

In the age group 3 years to 17 years, injection site pain was the most frequently reported solicited local AE in all age stratums. The percentage of subjects reporting injection site pain ranged from 70.5% to 82.7%. Grade 3 pain was reported by 1.9%-5.4% of subjects. The majority of subjects experiencing injection site pain experienced mild to moderate pain.

Both redness and swelling occurred much less frequently. Redness was reported by 1.3% to 5.6% of subjects, while 2.1% to 9.6% of subjects reported swelling. No grade 3 redness or swelling were reported in both studies.

Systemic solicited adverse events in children age 6 months to 36 months

Study Q-PAN H5N1-023

Overall by dose and subject, the most frequently reported solicited systemic AE during the 7-day post-vaccination period after primary vaccination differed depending on the group, see Table 37.

Table 37 Most frequently report solicited systemic AE overall by dose and subject (Q-PAN H5N1-023)

Group	Overall/dose	Overall/subject
190_B group	drowsiness and irritability (40.0%)	drowsiness and fever (60.5%)
090_C group	drowsiness (30.1%)	drowsiness (43.2%)
190_C group	irritability (30.3%)	irritability (44.7%)
375_C group	irritability (34.7%)	irritability (54.1%)
375_D group	irritability (40.0%)	irritability (54.3%)

Overall by dose, the incidence of fever ranged from 15.8% (190_C group) to 38.7% (190_B group). Overall per subject, fever was reported for 60.5% of subjects in 190_B group, 40.5% of subjects in 090_C group, 31.6% of subjects in the 190_C group, 32.4% of subjects in 375_C group and 28.6% of subject in 375_D group.

The most frequently reported grade 3 solicited systemic AEs in each group were fever (≥39.0°C) (reported after 9.3%, 6.9% and 1.4% of doses in groups 190_B, 375_C and 375_D), drowsiness (reported after 5.5% of doses in group 090_C), irritability/fussiness (reported after 3.9% of doses in group 190_C). Grade 4 fever was reported only in group 190_C for 1 (1.3%) subject.

The most frequently reported solicited systemic AE considered by the investigator as related to vaccination was irritability/fussiness in all groups, reported after 36.0%, 24.7%, 25.0%, 25.0%, 35.7% of doses in groups 190_B, 090_C, 190_C, 375_C, 375_D, respectively.

There was a trend for an increase in the incidence of fever in 190_B group, 090_C group and 190_C group after Dose 2 in comparison to Dose 1.

There was a trend for a higher incidence of solicited systemic AEs in the 1.9 µg HA with $AS03_B$ group than in the other 4 groups.

Study D-PAN H5N1-013

In study D-PAN H5N1-013 after the 2 primary doses of D-PAN vaccine (A/Indonesia, 1.9 µg HA+$AS03_B$), the most frequently reported solicited systemic AE was irritability/fussiness, reported after 38.1% of doses in 51.8% of subjects.

Fever ≥38.0°C was reported after 20.2% of doses (in 33.0% of subjects). Fever (≥39.0°C) was the most frequently reported solicited systemic AE of grade 3 (reported after 3.6% of doses). Grade 4 fever (>40.0°C) was not reported after primary vaccination.

The most frequently reported solicited systemic AE considered by the investigator as related to vaccination was irritability/fussiness, reported after 33.6% of doses, followed by fever, reported after 21.1% of doses.

The most frequently reported grade 3 solicited systemic AEs considered by the investigator as related to vaccination were irritability/fussiness and fever (≥39.0°C), each reported after 3.1% of doses.

After the adjuvanted booster dose, irritability/fussiness was the most frequently reported solicited systemic AE after 50% of doses. Fever ≥38.0˚C was reported after 44.4% of doses. Fever (≥39.0˚C) was the most frequently reported grade 3 solicited systemic AE, reported after 10.2% of doses. Grade 4 fever (>40°C) was reported after 2 (1.9%) of doses. The most frequently reported solicited systemic AE considered by the investigator as related to vaccination was all fever (reported after 48.1% of doses), followed by irritability/fussiness (reported after 47.2% of doses).

Study Q-PAN H5N1-021

Year 1:

After the 2 primary doses of D-PAN vaccine (A/Indonesia, 1.9 µg HA+AS03$_B$), the most frequently reported solicited systemic AE was irritability/fussiness in both the Q-PAN and Placebo group, reported after 35.4% of doses in 50.5% of subjects in the Q-PAN group and 29.0% of doses in 39.7% of subjects in the Placebo group.

Fever ≥38.0°C was reported after 12.5% of doses in 22.4% of subjects in the Q-PAN group compared to after 8.3% of doses in 16.4% of subjects in the Placebo group. Fever (≥39.0°C) was the most frequently reported solicited systemic AE of grade 3, reported by 4.6% of subjects in the Q-PAN group and 5.5%of subjects in the Placebo group. Grade 4 fever (>40.0°C) was not reported after primary vaccination in the Q-PAN group, while it was reported for 2.7% of subjects in the Placebo group.

The most frequently reported solicited systemic AE considered by the investigator as related to vaccination in the Q-PAN group was irritability/fussiness, reported after 29.4% of doses, followed by drowsiness, reported after 18.8% of doses. In the Placebo group the most frequently solicited systemic AE considered related to the vaccination was irritability/fussiness, reported after 24.8% of doses, followed by loss of appetite after 17.2% of doses.

The most frequently reported grade 3 solicited systemic AEs considered by the investigator as related to vaccination were irritability/fussiness reported after 2.3% of doses, followed by drowsiness after 2.1% of doses in the Q-PAN group. In the Placebo group this was irritability/fussiness, loss of appetite and fever, reported after 2.1% of doses in all cases.

Year 2:

The most frequently reported solicited systemic AE was irritability/fussiness, reported after 31.0% of doses in 44.0% of subjects in the Q-PAN group.

Fever ≥38.0°C was reported after 5.0% of doses. Fever (≥39.0°C) was the most frequently reported solicited systemic AE of grade 3 (reported after 2.0% of doses). Grade 4 fever (>40.0°C) was not reported after primary vaccination.

The most frequently reported solicited systemic AE considered by the investigator as related to vaccination was irritability/fussiness, reported after 23.0% of doses, followed by drowsiness, reported after 21.0% of doses.

The most frequently reported grade 3 solicited systemic AEs considered by the investigator as related to vaccination were irritability/fussiness, drowsiness and fever (≥39.0°C), each reported after 1.0% of doses.

Looking at the above results, in the age group 6 months to <36 months, the majority of subjects, ranging from 60.8% to 89.5%, receiving the primary vaccination with H5N1 vaccine, experienced at least 1 systemic solicited AE.

Of the subjects receiving a quarter adult dose, 090_C, 62.2% experienced at least 1 systemic solicited AE. The most frequently reported systemic AE was drowsiness, reported by 43.2% of subjects after 30.1% of doses. Fever was reported by 40.5% of subjects after 15.8% of doses. Grade 3 fever was reported after 2.7% of doses in 5.4% of subjects.

The most frequently reported systemic solicited AE considered related to the vaccine was irritability, reported after 24.7% of doses, followed by drowsiness, reported after 23.3% of doses. The most frequently reported grade 3 related systemic AE were drowsiness and fever, both reported after 2.7% of doses.

Of the subjects receiving a half adult dose (190_B), 60.8%-89.5% experienced at least 1 systemic solicited AE. The most frequently reported systemic AE was irritability in studies D-PAN H5N1-013 and Q-PAN H5N1-021, reported by 44.0%-51.8% of subjects after 31.0%-38.1% of doses. In study Q-PAN H5N1-023, the most frequently reported systemic AE was overall per dose drowsiness and irritability (after 40.0% of doses) and overall per subject drowsiness and fever, reported by 60.5% of subjects.

Fever was reported by 22.4% to 60.5% of subjects after 12.5% to 38.7% of doses. Grade 3 fever was reported after 3.6%-9.3% of doses. Fever was more frequently reported in study Q-PAN H5N1-023, in 60.5% of subjects after 38.7% of doses, compared to study D-PAN H5N1-013 and Q-PAN H5N1-021, reported by 8.0%-33.0% of subjects after 5.0%-20.2% of doses.

The most frequently reported systemic solicited AE considered related to the vaccine was irritability, reported after 23.0%-38.1% of doses, followed by drowsiness, reported after 18.8%-34.7% of doses, and fever, reported after 4.0%-34.7% of doses. The most frequently reported grade 3 related systemic AEs were irritability, drowsiness and fever, reported after 1.0%-6.7% of doses.

These results indicate that the overall safety profile is comparable between the half and quarter adult dose, in that comparable AEs occur. However, the quarter dose is less reactogenic. Irritability was the most frequently reported systemic AE in all doses.

Fever is an AE of concern as fever due to vaccination has been known to lead to febrile seizures. In study Q-PAN H5N1-023 Vaccine-related fever occurred in 22 subjects (57.9%) in group 190_B and 12 subjects (32.4%) in group 090_C, while Grade 3 fever (39.0-40.0°C) related to the vaccine occurred in 5 subjects (13.2%) in group 190_B and 2 subjects (5.2%) in group 090_C. The mean duration of the fever was short (<2 days) for both groups. These results indicate that the incidence of fever is less after a quarter dose compared to half adult dose.

During study D-PAN H5N1-013 it was shown that after the booster dose, reporting of AEs increased, with an increase seen in irritability/fussiness and fever.

Post-hoc analysis

A higher observed fever incidence post-primary vaccination was noted in subjects 6 to <36 months of age who received the 1.9 µg HA+AS03$_B$ formulation in study Q-PAN H5N1-023 as compared to the same age group administered the same formulation in studies D-PAN H5N1-013 and Q-PAN H5N1-021. Of note the sample size of subjects in this age group was small (N=38) in study Q-PAN H5N1-023. As a result of this notably higher fever rate and the small sample size, the Company conducted a post-hoc analysis

to pool the incidence of solicited local and systemic AEs from the 3 studies that enrolled subjects 6 to <36 months of age.

The subset of subjects (Pooled 190_B) who received 2 doses of H5N1 D-PAN or Q-PAN vaccine (1.9 µg HA+AS03$_B$ formulation) was composed of:

- all subjects from study D-PAN H5N1-013 (N=113);
- all subjects from group 190_B from study Q-PAN H5N1-023 (N=38);
- subjects aged 6 to <36 months from study Q-PAN H5N1-021 (N=206: 199 subjects from Year 1 and 7 subjects from Year 2)

Overall per dose, fever (≥38.0°C) was reported after 17.1% of doses in the Pooled 190_B group and 23.3% of doses in the 090_C group (Table 38). Grade 3 fever (≥39.0°C) was reported after 3.6% of doses in the Pooled 190_B group and 2.7% of doses in the 090_C group.

Table 38 Post hoc analysis: incidence of fever during the 7-day post-vaccination period following H5N1 vaccination of subjects 6 to <36 months, overall per dose (TVC)

		Pooled 190_B					090_C				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Temperature/(Oral) (°C)	All	696	127	**18.2**	15.4	21.3	73	17	**23.3**	14.2	34.6
	≥38	696	119	**17.1**	14.4	20.1	73	17	**23.3**	14.2	34.6
	≥38.5	696	68	**9.8**	7.7	12.2	73	11	**15.1**	7.8	25.4
	≥39.0	696	25	**3.6**	2.3	5.3	73	2	**2.7**	0.3	9.5
	≥39.5	696	7	**1.0**	0.4	2.1	73	1	**1.4**	0.0	7.4
	>40.0	696	0	**0.0**	0.0	0.5	73	0	**0.0**	0.0	4.9
	Related	696	107	**15.4**	12.8	18.3	73	14	**19.2**	10.9	30.1
	≥38 Related	696	103	**14.8**	12.2	17.7	73	14	**19.2**	10.9	30.1
	≥38.5 Related	696	58	**8.3**	6.4	10.6	73	8	**11.0**	4.9	20.5
	≥39.0 Related	696	19	**2.7**	1.7	4.2	73	2	**2.7**	0.3	9.5
	≥39.5 Related	696	5	**0.7**	0.2	1.7	73	1	**1.4**	0.0	7.4
	>40.0 Related	696	0	**0.0**	0.0	0.5	73	0	**0.0**	0.0	4.9

Pooled 190_B = Subjects receiving 1.9 µg HA+AS03$_B$ in the 3 pooled studies (D-PAN H5N1-013, Q-PAN H5N1-021 and Q-PAN H5N1-023)
090_C = Subjects receiving 0.9 µg HA+AS03$_C$ in study Q-PAN H5N1-023
N = number of documented doses
n/% = number/percentage of doses followed by at least 1 type of symptom
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Data source: D-PAN_Pooled_reacto, Tables 8.1 and 8.2.

Fever (≥38.0°C) was reported by 12.5% of subjects in the Pooled 190_B group and 13.5% of subjects in the 090_C group post-dose 1; and by 21.8% of subjects in the Pooled 190_B group and 33.3% of subjects in the 090_C group post-dose 2. Grade 3 fever (≥39.0°C) was reported by 2.8% of subjects in the Pooled 190_B group and was not reported by subjects in the 090_C group post-dose 1; and by 4.4% of subjects in the Pooled 190_B group and 5.6% of subjects in the 090_C group post-dose 2. Fever (≥38.0°C) considered by the investigator as related to vaccination was reported by 9.1% of subjects in the Pooled 190_B group and 8.1% of subjects in the 090_C group post-dose 1; and by 20.6% of subjects in the Pooled 190_B group and 30.6% of subjects in the 090_C group post-dose 2.

Safety database in study Q-PAN H5N1-023 is small, with approximately 38 subjects per group.

Based on the pooled analysis, it appears that the incidence of fever was high in study Q-PAN H5N1-023, as the incidence of fever reported for group 190_B was higher as compared to the same age group administered the same formulation. In the pooled analysis overall per dose fever was reported after 17.1% of doses compared to 38.7% of doses in the 190_B group in study Q-PAN H5N1-023.

This post-hoc analysis showed that the incidence of fever was higher in study Q-PAN H5N1-023, however, this would probably also have applied to the 090_C group. This cannot be tested, as Q-PAN H5N1-023 is the only study to include the quarter dose. The strength of evidence achieved using such a post-hoc analysis is limited, as the groups that are pooled were not randomised potentially leading to bias.

Systemic solicited adverse events in children aged 3 years to 17 years

Study D-PAN H5N1-032

Children 3 to <6 years of age

In children 3 to <6 years, after primary vaccination (overall per dose after 2 D-PAN doses and by dose after 1 Havrix dose), the most frequently reported solicited systemic AEs were:

- All fever in the H5_H5 group, each after 11.7% of D-PAN doses in 23.3% of subjects followed by irritability/fussiness and loss of appetite both after 10.0% of doses in 20.0% of subjects;
- All fever in the H5_Hav group, after 21.0% of D-PAN doses in 35.5% of subjects followed by loss of appetite after 19.4% of doses in 29.0% of subjects;
- Irritability/fussiness, loss of appetite and drowsiness in the Hav_H5 group, each after 13.6% of Havrix doses in 13.6% of subjects;
- Drowsiness in the Hav_Hav group, after 8.3% of Havrix doses in 8.3% of subjects.

The most frequently reported grade 3 solicited systemic AEs were:

- Fever (≥39.0°C) in the H5_H5 group, after 3.3% of D-PAN doses;
- Fever (≥39.0°C) and drowsiness in the H5_Hav group, after 4.8% and 3.2% of D-PAN doses, respectively;
- Fever (≥39.0°C) in the Hav_H5 group, after 2.3% of Havrix doses.
- No grade 3 systemic solicited AEs were observed in the Hav_Hav groups.

The most frequently reported solicited systemic AEs considered by the investigator as related to vaccination were:

- Irritability/fussiness, loss of appetite and fever in the H5_H5 group, reported each after 10.0% of D-PAN doses;
- Fever in the H5_Hav group, reported after 19.4% of D-PAN doses;
- Irritability/fussiness and loss of appetite in the Hav_H5 group, reported each after 13.6% of Havrix doses;
- Drowsiness in the Hav_Hav group, reported after 8.3% of Havrix doses.

The only grade 3 related AE reported was fever in 6.7% of subjects in the H5_H5 group, 6.5% of subjects in the H5_Hav group and 4.5% of subjects in the Hav_H5 group. No related grade 3 systemic solicited AEs were reported in the Hav_Hav group.

After the booster vaccination with D-PAN H5N1 in 3 to <6-year-old subjects primed with 2 doses of D-PAN vaccine (H5N1-H5N1 group), fever (all and ≥38.0°C) was the most frequently reported solicited

systemic AE, grade 3 AE, and solicited systemic AE considered to be related to vaccination, reported after 30.0%, 3.3% and 26.7% of doses, respectively. No grade 4 fever was reported after booster /Day 182 vaccination.

Including the booster dose, fever was reported for 10.0%, 13.3%, 30.0% of subjects respectively, following dose 1, following dose 2 and following dose 3 in Group H5_H5. No subject had fever ≥39.0°C following dose 1. In Group H5_H5, of 30 subjects, two (6.7%) subjects experienced fever ≥39.0°C, two (6.7%) subjects experienced fever ≥39.5°C and one (3.3%) subject experienced fever >40.0°C following dose 2 of the vaccine. Of 30 subjects, one (3.3%) experienced fever ≥39.0°C and one (3.3%) experienced fever ≥39.5°C following dose 3 of the vaccine.

Children ≥6 years of age

In children ≥6 to <18 years, after primary vaccination (overall per dose after 2 D-PAN doses and by dose after 1 Havrix dose), the most frequently reported solicited systemic AEs was headache in all groups, after 28.2% of D-PAN doses in 42.1% of subjects in the H5_H5 group, 24.4% of D-PAN doses in 38.4% of subjects in the H5_Hav group, 17.1% of Havrix doses in 24.4% of subjects in the Hav_H5 group and 23.8% of Havrix doses in 20.3% of subjects in the Hav_Hav group.

Fever (≥38.0°C) was reported after 8.3% of D-PAN doses in 14.3% of subjects in the H5-H5 group, 7.6% of D-PAN doses in 15.2% of subjects in the H5_Hav group, 7.3% of Havrix doses in 12.2% of subjects in the Hav_H5 group and 8.8% of Havrix doses in 8.8% of subjects in the Hav_Hav group.

The most frequently reported grade 3 solicited systemic AEs were:

- Headache in the H5_H5 group, after 2.0% of D-PAN doses in 3.2% of subjects;
- Fever (≥39.0°C) in the H5_Hav group, after 2.4% of D-PAN doses in 4.8% of subjects;
- Fever (≥39.0°C) in the Hav_H5 group, after 1.2% of Havrix doses in 2.4% of subjects;
- Fever (≥39.0°C) and gastrointestinal symptoms in the Hav_Hav group, reported each after 0.6% of Havrix doses in 1.3% of subjects.

The most frequently reported solicited systemic AE considered by the investigator as related to vaccination was headache in all groups, after 27.4% of doses in 41.3% of subjects in the H5_H5 group, 24.0% of doses in 37.6% of subjects in the H5_Hav group, 14.6% of Havrix doses in 22.0% of subjects in the Hav_H5 group and 21.3% of Havrix doses in 27.5% of subjects in the Hav_Hav group.

No grade 4 fever was reported after primary vaccination in any of the study groups.

Including the booster dose, fever was reported for 7.9%, 8.7%, 5.6.% of subjects respectively, following dose 1, following dose 2 and following dose 3 in Group H5_H5. In Group H5_H5, one (0.8%) of 126 subjects experienced fever ≥39.0°C following dose 1 and two (1.6%) of 126 subjects following dose 2. No subject had fever ≥39.0°C following dose 3.

After the booster/Day 182 vaccination with D-PAN H5N1 or Havrix in ≥6 to <18-year old subjects, headache was the most frequently reported systemic solicited AE in all groups: after 31.0% of D-PAN doses in the H5_H5 group, 9.8% of D-PAN doses in the Hav_H5 group, 13.7% of Havrix doses in the H5_Hav group and 15.2% of Havrix doses in the Hav_Hav group. All of these reports were considered by the investigator as related to vaccination. Grade 3 headache was reported in the H5N1-H5N1 group after 0.8% of D-PAN doses and in the Hav_Hav group after 1.3% of Havrix doses. No other grade 3 AEs were reported in any study group. No grade 4 fever was reported after booster/Day 182 vaccination in any of the study groups.

Study Q-PAN H5N1-021

Year 1 children 3 to <6 years of age:

In children 3 to <6 years, after primary vaccination, the most frequently reported solicited systemic AE was irritability/fussiness in both Q-Pan and placebo group, reported after 17.9% of doses in 29.6% of subjects and 13.7% of doses in 22.4% of subjects in the Q-Pan and placebo group respectively.

The most frequently reported grade 3 solicited systemic AEs was fever (≥39.0°C) in the both the Q-Pan and placebo group, reported after 2.6% of doses in 9.2% of subjects and 1.1% of doses in 8.2% of subjects respectively.

The most frequently reported solicited systemic AEs considered by the investigator as related to vaccination was irritability/fussiness in both the Q-Pan and placebo group, reported after 15.8% of doses in 26.5% of subjects and 9.5% of doses in 16.3% of subjects respectively. The most frequently reported solicited systemic grade 3 AEs were fever and irritability/fussiness reported by 2.0% of subjects in the Q-Pan group, no grade 3 related AEs were reported in the placebo group.

Fever was reported after 8.2% of D-PAN doses in 15.3% of subjects in the Q-Pan group and 7.6% of placebo doses in 18.4% of subjects in the placebo group.

Fever was reported for 7.1% and 9.2% of subjects respectively, following dose 1 and following dose 2 in the Q-Pan group.

Year 2 children 3 to <6 years of age:

The most frequently reported systemic solicited AE reported was irritability/fussiness reported after 10.5% of doses in 20.7% of subjects. The most frequently reported related solicited systemic AE was irritability/fussiness, reported after 10.5% of doses in 20.7% of subjects. No grade 3 systemic solicited AEs were reported. No fever was reported.

Year 1 children ≥6 years of age:

In study year 1, headache and muscle aches were the most frequently reported symptoms in the Q-Pan group and were reported after 21.4% and 27.3% of doses, respectively, in this group. Headache and muscle aches assessed by the investigator as related to vaccination were reported after 18.0% and 24.9% of doses in the Q-Pan group. Grade 3 headache and muscle aches were reported after 1.3% and 1.1% of doses in this group. Grade 3 headache and muscle aches assessed as related to vaccination were reported after 1.1% and 1.0% of doses in the Q-Pan group.

Fatigue, gastrointestinal symptoms and headache were the most frequently reported symptoms for the placebo group reported after 10.9%, 9.5% and 10.9% of doses respectively. Fatigue, gastrointestinal symptoms and headache assessed by the investigator as related to vaccination were reported after 9.0%, 5.7% and 9.0% of doses in this group. Grade 3 fatigue, gastrointestinal symptoms and headache were reported after 0.9%, 0.9% and 1.4% of doses in the placebo group. Grade 3 fatigue, gastrointestinal symptoms and headache, assessed as related to vaccination, were reported after 0.5% of doses each.

Fever was reported after 3.4% and 1.4% of doses in the Q-Pan and placebo groups. Fever, assessed by the investigator as related to vaccination, was recorded after 2.5% and 0.9% of doses, in the Q-Pan and placebo groups. Grade 3 fever (temperature ≥39°C) was reported after 0.8% and 0.5% of doses in the Q-Pan and placebo groups. Grade 3 fever, assessed as related to vaccination, was reported after 0.7% and 0.5% of doses in the Q-Pan and placebo groups. No grade 4 fever (temperature > 40°C) was reported.

No increases in the frequency or intensity of solicited systemic AEs were noted after the second dose of Q-Pan vaccine in either study year 1 or study year 2.

Year 2 children ≥6 years of age:

The most frequently reported systemic solicited AE reported muscle ache reported after 31.5% of doses in 45.3% of subjects, followed by headache reported after 18.8% of doses in 32.0% of subjects. The most frequently reported related solicited systemic AE was muscle ache, reported after 24.2% of doses in 37.3% of subjects, followed by headache reported after 14.8% of doses in 26.2% of subjects. No grade 3 systemic solicited AEs were reported. The most frequently reported grade 3 related solicited systemic AEs were headache and fatigue, both reported after 0.7% of doses in 1.3% of subjects.

Only 1 case of fever was reported.

In children aged 3 to <6 years, the most frequently reported systemic solicited AE after the primary vaccination with H5N1 vaccine was fever in study D-PAN H5N1-032 (reported after 11.7%-21.0% of D-PAN doses in 23.3%-35.5% of subjects). In study Q-Pan H5N1-021 the most frequently reported systemic solicited AE was irritability/fussiness reported in 13.7% of doses in 22.4% of subjects.

In both studies, the most frequently reported grade 3 systemic solicited AE was fever ≥39.0°C, reported after 2.6%- 4.8% of doses by 2.0% to 6.7% of subjects.

Both studies showed a similar pattern with irritability/fussiness and fever being the dominant systemic solicited AEs. A trend for an increase in the incidence of fever after multiple doses was seen in both studies. In study D-Pan H5N1-032 not only occurrence increased, but also intensity, as no fever ≥39.0°C was seen following dose 1 in the H5_H5 group, but it did occur after dose 2 and 3.

In children aged ≥6 years of age the most frequently reported systemic solicited AE after the primary vaccination with H5N1 vaccine was headache in study D-PAN H5N1-032 (reported after 24.4%-28.2% of D-PAN doses in 38.4%-42.1%). In study Q-Pan H5N1-021 the most frequently reported systemic solicited AE was muscle ache reported in 27.3% of doses in 39.8% of subjects, followed by headache reported in 21.4% of doses in 32.4% of subjects.

In both studies, the most frequently reported grade 3 systemic solicited AE was headache, reported after 1.3%- 2.0% of doses and fever reported after 0.8%-4.8% of doses.

The most frequently reported related systemic solicited AEs was headache in study D-PAN H5N1-032 and muscle ache followed by headache in study Q-Pan H5N1-021. In both studies, headache was the most frequently reported grade 3 related systemic solicited AE reported by 0.8% to 3.2% of subjects.

In study D-PAN H5N1-032 an increase in fever was reported after Dose 2 compared to Dose 1, however, the incidence of fever was lower after Dose 3.

Unsolicited adverse events in children age 6 months to 36 months

Study Q-PAN H5N1-023

The percentage of subjects reporting at least 1 unsolicited AE within 21 days post-vaccination, ranged from 54.1% (090_C group) to 68.4% (190_C group).

The percentage of subjects for whom at least 1 unsolicited AE with causal relationship to vaccination was reported within the 21-day (Days 0-20) postvaccination period, was reported for 7.9%, 10.5%, 8.1% and 11.4% of subjects in the 190_B, 190_C, 375_C and 375_D groups, respectively, see Table 39. None of the unsolicited AEs in the 090_C group was considered related to the vaccine.

Table 39 Percentage of subjects reporting unsolicited AE with causal relationship to vaccine within 21-days post vaccination (Q-PAN H5N1-023)

		190_B N = 38				090_C N = 37				190_C N = 38				375_C N = 37				375_D N = 35			
				95% CI				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		3	7.9	1.7	21.4	0	0.0	0.0	9.5	4	10.5	2.9	24.8	3	8.1	1.7	21.9	4	11.4	3.2	26.7
Eye disorders (10015919)	Periorbital oedema (10034545)	0	0.0	0.0	9.3	0	0.0	0.0	9.5	1	2.6	0.1	13.8	0	0.0	0.0	9.5	0	0.0	0.0	10.0
Gastrointestinal disorders (10017947)	Diarrhoea (10012735)	0	0.0	0.0	9.3	0	0.0	0.0	9.5	0	0.0	0.0	9.3	0	0.0	0.0	9.5	1	2.9	0.1	14.9
	Vomiting (10047700)	1	2.6	0.1	13.8	0	0.0	0.0	9.5	0	0.0	0.0	9.3	0	0.0	0.0	9.5	1	2.9	0.1	14.9
General disorders and administration site conditions (10018065)	Feeling hot (10016334)	1	2.6	0.1	13.8	0	0.0	0.0	9.5	2	5.3	0.6	17.7	1	2.7	0.1	14.2	0	0.0	0.0	10.0
Investigations (10022891)	Body temperature increased (10005911)	1	2.6	0.1	13.8	0	0.0	0.0	9.5	2	5.3	0.6	17.7	1	2.7	0.1	14.2	1	2.9	0.1	14.9
Nervous system disorders (10029205)	Headache (10019211)	0	0.0	0.0	9.3	0	0.0	0.0	9.5	0	0.0	0.0	9.3	0	0.0	0.0	9.5	1	2.9	0.1	14.9
Skin and subcutaneous tissue disorders (10040785)	Rash (10037844)	0	0.0	0.0	9.3	0	0.0	0.0	9.5	0	0.0	0.0	9.3	0	0.0	0.0	9.5	1	2.9	0.1	14.9
	Urticaria (10046735)	1	2.6	0.1	13.8	0	0.0	0.0	9.5	0	0.0	0.0	9.3	1	2.7	0.1	14.2	0	0.0	0.0	10.0

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

At least 1 Grade 3 unsolicited AE was reported within the 21-day (Days 0-20) postvaccination period in all groups. The percentage of subjects ranged from 2.6% (190_C group) to 14.3% (375_D group). None of the Grade 3 AEs were assessed to be related to vaccination by the investigator.

Study D-PAN H5N1-013

From Day 0 to Day 84 (reporting for the 2 primary doses only) at least 1 unsolicited AE was reported by 68.1% of subjects, the most frequently being upper respiratory tract infection, reported by 21.2% of subjects. At least 1 grade 3 unsolicited AE was reported by 8.8% of subjects, the most frequently being upper respiratory tract infection and cough, reported each by 1.8% of subjects

At least 1 unsolicited AE considered by the investigator as related to vaccination was reported by 15.9% of subjects, the most frequently reported AEs were upper respiratory tract infection and rhinitis, 3.5% each, see Table 40. In total, 2 of the reported grade 3 unsolicited AEs (1.8% of subjects) were considered by the investigator as related to vaccination (nasopharyngitis and swelling face).

Table 40 Percentage of subjects reporting the occurrence of unsolicited AE with causal relationship to vaccine up to Day 84 – TVC (D-PAN H5N1-013)

		6<12 M N = 46				12<24 M N = 34				24<36 M N = 33				All N = 113			
				95% CI				95% CI				95% CI				95% CI	
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL	n	%	LL	UL
At least one symptom		9	19.6	9.4	33.9	3	8.8	1.9	23.7	6	18.2	7.0	35.5	18	15.9	9.7	24.0
General disorders and administration site conditions (10018065)	Injection site induration (10022075)	0	0.0	0.0	7.7	0	0.0	0.0	10.3	1	3.0	0.1	15.8	1	0.9	0.0	4.8
	Injection site scab (10066210)	0	0.0	0.0	7.7	1	2.9	0.1	15.3	0	0.0	0.0	10.6	1	0.9	0.0	4.8
	Pyrexia (10037660)	1	2.2	0.1	11.5	0	0.0	0.0	10.3	0	0.0	0.0	10.6	1	0.9	0.0	4.8
Infections and infestations (10021881)	Nasopharyngitis (10028810)	0	0.0	0.0	7.7	2	5.9	0.7	19.7	0	0.0	0.0	10.6	2	1.8	0.2	6.2
	Rhinitis (10039083)	2	4.3	0.5	14.8	0	0.0	0.0	10.3	2	6.1	0.7	20.2	4	3.5	1.0	8.8
	Upper respiratory tract infection (10046306)	2	4.3	0.5	14.8	0	0.0	0.0	10.3	2	6.1	0.7	20.2	4	3.5	1.0	8.8
Respiratory, thoracic and mediastinal disorders (10038738)	Cough (10011224)	2	4.3	0.5	14.8	1	2.9	0.1	15.3	0	0.0	0.0	10.6	3	2.7	0.6	7.6
	Pharyngeal inflammation (10065716)	1	2.2	0.1	11.5	0	0.0	0.0	10.3	0	0.0	0.0	10.6	1	0.9	0.0	4.8
	Rhinorrhoea (10039101)	2	4.3	0.5	14.8	0	0.0	0.0	10.3	1	3.0	0.1	15.8	3	2.7	0.6	7.6
Skin and subcutaneous tissue disorders (10040785)	Rash (10037844)	1	2.2	0.1	11.5	0	0.0	0.0	10.3	0	0.0	0.0	10.6	1	0.9	0.0	4.8
	Rash macular (10037867)	1	2.2	0.1	11.5	0	0.0	0.0	10.3	0	0.0	0.0	10.6	1	0.9	0.0	4.8
	Swelling face (10042682)	1	2.2	0.1	11.5	0	0.0	0.0	10.3	0	0.0	0.0	10.6	1	0.9	0.0	4.8

Study Q-PAN H5N1-021

Year 1:

Within 21 days after the 2 primary doses of D-PAN vaccine (A/Indonesia, 1.9 µg HA+AS03$_B$), 49.2% of Q-Pan subjects and 52.0% of placebo subjects reported at least one symptom; 3.0% of Q-Pan subjects and 5.0% of placebo subjects reported at least one grade 3 symptom. None of the grade 3 AEs were related to the vaccine.

In total, 7.5% of subjects reported a related unsolicited symptom in the Q-PAN group and 2.7% of subjects in the Placebo group, see Table 41.

Table 41 Percentage of subjects reporting occurrence of unsolicited AE with causal relationship to vaccine up to 42 days after first vaccination – (TVC- year 1) (Q-PAN H5N1-021)

Primary System order class	Preferred Term	Q-PAN (N=199)		Placebo (N=75)	
		n	% (95% CI)	n	% (95% CI)
At least 1 symptom		15	7.5 (4.3-12.1)	2	2.7 (0.3-9.3)
Gastrointestinal disorders	Diarrhoea	1	0.5 (0.0-2.8)		
	Vomiting	4	2.0 (0.6-5.1)	1	1.3 (0.0-7.2)
General disorders and administration site conditions	Injection site bruising	2	1.0 (0.1-3.6)		
	Injection site eczema	1	0.5 (0.0-2.8)		
	Pain	1	1.3 (0.0-7.2)		
	Vaccination site nodule	1	0.5 (0.0-2.8)		
Infections and infestations	Bronchiolitis	1	0.5 (0.0-2.8)		
	Ear infection	1	0.5 (0.0-2.8)		
Nervous system disorders	Headache			1	1.3 (0.0-7.2)
Respiratory, thoracic and mediastinal disorders	Cough	1	0.5 (0.0-2.8)		
	Epistaxis	1	0.5 (0.0-2.8)		
	Nasal congestion	1	0.5 (0.0-2.8)		
	Pharyngeal erythema	1	0.5 (0.0-2.8)		
	Rhinorrhoea	2	1.0 (0.1-3.6)		
Skin and subcutaneous tissue disorders	Rash	2	1.0 (0.1-3.6)		

Year 2:

No differentiation was made per age category. Within 21 days after the 2 primary doses of D-PAN vaccine (A/Indonesia, 1.9 µg HA+AS03$_B$), 26.5% of Q-Pan subjects reported at least one symptom; 0.6% of Q-Pan subjects reported at least one grade 3 symptom. In total, 1.9% of subjects reported a related unsolicited symptom.

In all studies, the percentage of participants reporting at least 1 unsolicited AE ranged from 49.2% to 68.4%. Of note, during year 2 of study Q-PAN H5N1-021 only 26.5% of subjects reported an unsolicited AE.

Of the subjects receiving a quarter adult dose, 090_C, 20 subjects (54.1%) experienced at least 1 unsolicited AE. Most frequently reported unsolicited AEs were in the system organ class (SOC) of infections and infestations. None of the unsolicited AEs were considered related to the vaccine.

Of the subjects receiving a half adult dose (190_B), 49.2%-68.1% experienced at least 1 unsolicited AE, with only 26.5% of subjects reporting an unsolicited AE during study year 2. The most frequently reported unsolicited AEs were in the system organ class (SOC) of infections and infestations. The percentage of subjects reporting a vaccine-related unsolicited AE was 3 ranged from 7.5% to 15.9%.

Grade 3 unsolicited AEs were reported by 3.0% to 8.8% of subjects. In only 2 cases in the D-PAN H5N1-013 study (1.8% of subjects) was the grade 3 unsolicited AE related to the vaccine (nasopharyngitis and swelling face). None of the other grade 3 unsolicited AEs in the other 2 studies were considered vaccine-related.

Unsolicited AEs children aged 3 years to 17 years

Study D-PAN H5N1-032

At least one unsolicited AE was reported for 128 subjects (41.0%) in the Pooled H5N1 Group and 76 subjects (36.5%) in the Pooled control group. At least one grade 3 unsolicited AE was reported for one subject (0.3%) in the Pooled H5N1 Group. None of the subjects in the Pooled control group reported any grade 3 unsolicited AE.

At least one unsolicited AE with causal relationship to vaccination was reported for 13 subjects (4.2%) in the Pooled H5N1 Group and six subjects (2.9%) in the Pooled control group, see Table 42. None of the grade 3 AEs were considered related to the vaccine.

Table 42 Percentage of subjects with unsolicited AE with causal relationship to vaccination, from Day 0 to Day 42 after the first vaccination - pooled groups according to primary schedule (Total vaccinated cohort) (D-PAN H5N1-032)

		Pooled H5N1 N = 312				Pooled control N = 208			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
At least one symptom		13	4.2	2.2	7.0	6	2.9	1.1	6.2
General disorders and administration site conditions (10018065)	Injection site anaesthesia (10022046)	0	0.0	0.0	1.2	1	0.5	0.0	2.6
	Injection site haematoma (10022066)	0	0.0	0.0	1.2	1	0.5	0.0	2.6
	Pyrexia (10037660)	1	0.3	0.0	1.8	0	0.0	0.0	1.8
Infections and infestations (10021881)	Gastroenteritis (10017888)	0	0.0	0.0	1.2	1	0.5	0.0	2.6
	Nasopharyngitis (10028810)	2	0.6	0.1	2.3	0	0.0	0.0	1.8
	Upper respiratory tract infection (10046306)	5	1.6	0.5	3.7	2	1.0	0.1	3.4
	Viral infection (10047461)	2	0.6	0.1	2.3	1	0.5	0.0	2.6
Nervous system disorders (10029205)	Dizziness (10013573)	1	0.3	0.0	1.8	0	0.0	0.0	1.8
	Headache (10019211)	1	0.3	0.0	1.8	0	0.0	0.0	1.8
	Syncope (10042772)	1	0.3	0.0	1.8	0	0.0	0.0	1.8

Pooled H5N1 = H5N1_H5N1 + H5N1_Havrix:[2 doses (D0,D21) of H5N1 Indo]
Pooled control = Havrix_H5N1 + Havrix_Havrix:[1 dose (D0) of Havrix]
At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI= exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Study Q-PAN H5N1-021

Year 1 children aged 3 years to <9 years:

Within 21 days after the 2 primary doses of D-PAN vaccine (A/Indonesia, 1.9 µg HA+AS03$_B$), 41.9% of Q-Pan subjects and 40.8% of placebo subjects reported at least one symptom; 3.0% of Q-Pan subjects and 6.9% of placebo subjects reported at least one grade 3 symptom. One subject reported 2 grade 3 unsolicited AEs in the Q-PAN group which were considered related to the vaccine: chills and myalgia.

In total, 7.6% of subjects reported a related unsolicited symptom in the Q-PAN group and 2.6% of subjects in the Placebo group, see Table 41.

Table 43 Percentage of subjects reporting occurrence of unsolicited AE with causal relationship to vaccine up to 42 days after first vaccination – (TVC- year 1) (Q-PAN H5N1-021)

Primary System order class	Preferred Term	Q-PAN (N=199)		Placebo (N=75)	
		n	% (95% CI)	n	% (95% CI)
At least 1 symptom		15	7.6 (4.3-12.2)	2	2.6 (0.3-9.2)
Gastrointestinal disorders	Abdominal pain upper	1	0.5 (0.0-2.8)		
	Gastrointestinal disorder	1	0.5 (0.0-2.8)		
General disorders and administration site conditions	Administration site reactions	1	0.5 (0.0-2.8)		
	Chills	1	0.5 (0.0-2.8)		
	Fatigue	1	0.5 (0.0-2.8)		
	Injections site bruising	1	0.5 (0.0-2.8)	1	1.3 (0.0-7.1)
	Injection site pruritus	2	1.0 (0.1-3.6)		
Infections and infestations	Pharyngitis	1	0.5 (0.0-2.8)		
	Upper respiratory tract infection	2	1.0 (0.1-3.6)		
Musculoskeletal and connective tissue disorders	Myalgia	1	0.5 (0.0-2.8)		
	Pain in extremity	2	1.0 (0.1-3.6)		

Nervous system disorders	Dizziness	1	0.5 (0.0-2.8)		
	Headache	2	1.0 (0.1-3.6)		
Respiratory, thoracic and mediastinal disorders	Asthma	1	0.5 (0.0-2.8)		
	Cough	2	1.0 (0.1-3.6)	1	1.3 (0.0-7.1)
	Pneumonitis	1	0.5 (0.0-2.8)		
	Rhonchi	1	0.5 (0.0-2.8)		
Skin and subcutaneous tissue disorders	Skin ulcer	1	0.5 (0.0-2.8)		

Year 1 children aged 9 years to <18 years:

Within 21 days after the 2 primary doses of D-PAN vaccine (A/Indonesia, 1.9 µg HA+AS03$_B$), 29.5% of Q-Pan subjects and 33.8% of placebo subjects reported at least one symptom; 4.8% of Q-Pan subjects and 2.5% of placebo subjects reported at least one grade 3 symptom. One subject in the Q-PAN group reported 2 grade 3 unsolicited AEs which were considered related to the vaccine: abdominal pain and nausea.

In total, 3.3% of subjects reported a related unsolicited symptom in the Q-PAN group and 3.8% of subjects in the Placebo group, see Table 41.

Table 44 Percentage of subjects reporting occurrence of unsolicited AE with causal relationship to vaccine up to 42 days after first vaccination – (TVC- year 1) (Q-PAN H5N1-021)

Primary System order class	Preferred Term	Q-PAN (N=199)		Placebo (N=75)	
		n	% (95% CI)	n	% (95% CI)
At least 1 symptom		7	3.3 (1.4-6.7)	3	3.8 (0.8-10.6)
Gastrointestinal disorders	Abdominal pain	1	0.5 (0.0-2.6)		
	Nausea	1	0.5 (0.0-2.6)		
General disorders and administration site conditions	Application site anaesthesia	1	0.5 (0.0-2.6)		
	Axillary pain	1	0.5 (0.0-2.6)		
	Pain	1	0.5 (0.0-2.6)		
Infections and infestations	Nasopharyngitis	1	0.5 (0.0-2.6)		
Musculoskeletal and connective tissue disorders	Musculoskeletal stiffness	1	0.5 (0.0-2.6)		
Nervous system disorders	Dizziness	1	0.5 (0.0-2.6)	1	1.3 (0.0-6.8)
	Hypoaesthesia	1	0.5 (0.0-2.6)		
	Tremor	1	0.5 (0.0-2.6)		
Respiratory, thoracic and mediastinal disorders	Nasal discomfort	1	0.5 (0.0-2.6)		
	Nasal congestion			1	1.3 (0.0-6.8)
Skin and subcutaneaous tissue disorders	Rash generalised			1	1.3 (0.0-6.8)

Year 2:

No differentiation was made per age category. Within 21 days after the 2 primary doses of D-PAN vaccine (A/Indonesia, 1.9 µg HA+AS03$_B$), 26.5% of Q-Pan subjects reported at least one symptom; 0.6% of Q-Pan subjects reported at least one grade 3 symptom. In total, 1.9% of subjects reported a related unsolicited symptom.

In the studies, the percentage of participants receiving H5N1 vaccine during the primary vaccination series reported at least 1 unsolicited AE ranged from 29.5% to 41.0%. The most frequently reported unsolicited AEs were in the SOC of infections and infestations. Unsolicited AEs with a causal relationship to the study vaccine, were reported in 3.3%-7.6% of participants receiving H5N1 vaccine and 2.6%-3.8% in the placebo/active comparator control group.

Grade 3 unsolicited AEs were reported in 0.3%-4.8% of subjects receiving H5N1 vaccine and 2.5%-6.9% in the placebo/active comparator control group. In study D-PAN H5N1-032 none of the grade 3 unsolicited AEs were considered related to the vaccine. In study Q-PAN H5N1-021 during year 1 and 2,

1 subject reported 2 grade 3 unsolicited AEs in the Q-PAN group which were considered related to the vaccine: chills and myalgia for year 1 and abdominal pain and nausea during year 2.

Serious adverse event/deaths

Deaths

No fatal events were recorded in any of the studies.

SAEs children aged 6 months to 36 months

Study Q-PAN H5N1-023

During the entire study, SAEs were reported in 29 of the 185 subjects (15.7%). At least 1 SAE was reported for 13.2% of subjects in the 190_B group, 16.2% of subjects in the 090_C group, 26.3% of subjects in the 190_C group, 10.8% of subjects in the 375_C group and 11.4% of subjects in the 375_C group. None of the SAEs were assessed as being related to the vaccination by the investigator.

One subject in the 190_C group reported a potential immune mediated disease (pIMD) of Kawasaki disease. The event was assessed as not related to vaccination.

Study D-PAN H5N1-013

During the entire study, a total of 18 SAEs were reported for 9 subjects (8.0%). All SAEs were assessed by the investigator as not related and resolved at the time of study end.

Study Q-PAN H5N1-021

During the study year 1, SAEs were reported for 3 subjects (1.5%) in the Q-Pan vaccine group and none in the placebo group. None of the SAEs in the Q-PAN group were considered related to the vaccine.

The percentage of participants reporting an SAE in study Q-PAN H5N1-023 was relatively high, 29 of 185 subjects (15.7%). The percentage of participants experiencing an SAE in the quarter adult dose group was 16.2%. The percentage of participants experiencing an SAE in the half adult dose group was 13.2%. None of the SAEs were considered related to the vaccine, which is agreed.

The percentage of participants experiencing an SAE during study D-PAN H5N1-013 and Q-PAN H5N1-021 ranged from 1.5% to 8.0%. None were considered related to the vaccine, which is agreed.

One subject during study Q-PAN H5N1-021 developed febrile convulsion 11 days after dose 1 and was hospitalized for 3 days. This SAE is not considered related to the vaccine, considering a TTO of 11 days and the fact that during the 7 days post study vaccination the subject did not present with any fever.

SEAs children aged 3 years to 17 years

Study D-PAN H5N1-032

From Day 0 up to the Day 364 visit, SAEs were reported for four subjects (2.6%) in the group H5N1_H5N1, one subject in the group H5N1_Havrix and no subjects for the groups Havrix_H5N1 and Havrix_Havrix. All the SAEs were resolved and none of the SAEs were assessed by the investigator to be related to vaccination.

Study Q-PAN H5N1-021

During the study year 1, SAEs were reported for 5 subjects (1.2%) in the Q-Pan vaccine group and 2 subjects (1.2%) in the placebo group. None of the SAEs were considered related to the vaccine.

Two non-fatal SAEs (wound and scarlet fever) were reported during Study Year 2 (Days U0-U385). They were not considered related to vaccination

The percentage of participants experiencing an SAE during study D-PAN H5N1-032 and Q-PAN H5N1-021 ranged from 1.2% to 2.6%. None were considered related to the vaccine.

Other significant events

In study Q-PAN H5N1-023, AEs of special interest (AESI) were collected throughout the entire study period. These were identified using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) or Standardized MedDRA Queries (SMQs) as recommended in the Committee for Medicinal Products for Human Use (CHMP) Risk Management Plan for Pandemic Vaccines (CHMP, 2009). AESIs included the events listed below; the MedDRA PT or SMQ used to identify reports of these events is provided in parentheses:

- Anaphylaxis (narrow SMQs "Anaphylactic reaction" and "Angioedema")
- Bell's palsy (MedDRA PT "VIIth nerve palsy")
- Convulsion (narrow SMQ "Convulsions")
- Demyelination (narrow SMQ "Demyelination")
- Encephalitis (narrow SMQ "Non-infectious encephalitis")
- Guillain-Barré syndrome (narrow SMQ "Guillain-Barré syndrome")
- Neuritis (MedDRA PT "Neuritis")
- Vasculitis (narrow SMQ "Vasculitis")

During the entire study, the percentage of subjects who had at least 1 AESI was 10.5% (190_B group), 8.1% (090_C group), 7.9% (190_C group), 5.4% (375_C group) and 5.7% (375_D group). Three of these AESIs were assessed to have a causal relationship to vaccination (urticaria in 1 subject in 190_B group and in 1 subject in 375_C group and periorbital oedema in 1 subject in 190_C group).

Pregnancy

During the entire D-PAN H5N1-032 study period, a total of 6 pregnancies were reported. The subjects were exposed to the vaccine before conception. Up to the end of the study, 4 subjects gave birth to male live healthy infants and 2 pregnancies were still ongoing. For these 2 pregnancies, the reported outcome was live births without congenital anomalies.

During Year 1 of study Q-PAN H5N1-021, 2 subjects in group Q-Pan reported a pregnancy. One pregnancy was reported 8 months after receipt of vaccine dose 2. Approximately 1 month after it was reported, the pregnancy ended in a spontaneous abortion. This was not considered by the investigator to be related to vaccination. The second pregnancy was reported 12 months after receipt of vaccine dose 2. This pregnancy ended in a healthy live birth.

No pregnancies were reported during Year 2 of study Q-PAN H5N1-021.

In the CSR of study D-PAN H5N1-032, 6 pregnancies were reported, however, only 3 pregnancy outcomes were reported (all healthy males). No further information was presented. The MAH was asked to update the reports to include all relevant information.

During Study Q-PAN H5N1-021 2 pregnancies were reported, of which 1 ended in spontaneous abortion and 1 in live birth. The abortion was not considered related to the vaccine, which is agreed. Upon request

the MAH provided the CIOMS form for the live birth. The subject delivered healthy infant-female without complications.

All subjects were vaccinated prior to conception. No congenital or other abnormalities were reported.

Narcolepsy

Beginning in August 2010, cases of narcolepsy were reported in children and adolescents vaccinated with Pandemrix, initially in Finland and Sweden (Läkemedelsverket, 2011; Sarkanen 2018a). A series of retrospective epidemiological single country studies were conducted in several European countries in addition to the multinational VAESCO (in 8 European countries) and SOMNIA (in 4 continents) studies (Sarkanen, 2018a, Sarkanen , 2018b; Sturkenboom, 2015; Verstraeten, 2016; Weibel, 2018; Wijnans, 2013). In the population under 20 years of age, most studies found an increase in relative risk of narcolepsy in those vaccinated with Pandemrix compared to those unvaccinated (Sturkenboom, 2015; Verstraeten, 2016; Weibel, 2018; Wijnans, 2013). Increased risk was mostly identified in the younger population (Sturkenboom, 2015; Verstraeten, 2016; Weibel, 2018; Wijnans, 2013). In the various studies, the relative risk estimates of narcolepsy following vaccination with Pandemrix ranged from 1.5 to 25.0 (95% CI range: 0.3 to 48.5) in children, and from 1.1 to 18.8 (95% CI range: 0.6 to 207.4) in adults (Cohet, 2019; Thebault, 2013).

Arepanrix, while having a slightly different viral antigen manufacturing process, has not been associated with a similar increased risk narcolepsy as compared to Pandemrix. The association between Arepanrix and narcolepsy has been assessed in a specific study in Quebec (Canada), based on validated cases of narcolepsy from sleep centres (Montplaisir, 2014). In their primary analysis, the relative risk was estimated as 4.3 (95% CI: 1.5, 11.1). This estimate is not incompatible with the ranges observed for Pandemrix (Sarkanen, 2018a). The authors of the Quebec study concluded their study by stating that their results were consistent with a risk of narcolepsy following administration of Arepanrix, but that the attributable risk was of small magnitude (approximately 1 case per million). Attributable risk for Pandemrix was approximately 1 per 20,000 (Sarkanen, 2018a).

Arepanrix vaccination occurred mostly in Canada and South America, while vaccination with Pandemrix occurred mostly in Europe.

Overall, there is no robust evidence that the 2 vaccines are likely to invoke intrinsically different immunologic responses. In addition, to the extent the currently leading hypothesis suggests that the increased risk of narcolepsy reported in Europe is likely the result of molecular mimicry between an epitope within the H1N1pdm09 virus and peptides from proteins produced by hypocretin (HCRT)-secreting neurons there are no data that would suggest that the 2 vaccines would differentially trigger such mimicry. The experts convened by the International Alliance for Biological Standardization (IABS) in 2018 concluded that explanation for the apparent differences remain an open question (Edwards, 2019). Possible explanations include: regional difference in the background incidence of narcolepsy between the populations that received Pandemrix and Arepanrix; regional difference in the expression of the HLA-DQB1*06:02 allele and other HLA types; regional differences in the timing of large-scale vaccination programs relative to H1N1pdm09 wild-type virus circulation; regional differences in narcolepsy referral and diagnosis processes; and difference in media interest and/or public perceptions.

Furthermore, while neither Pandemrix nor Arepanrix were licensed or used in China, an increased incidence of narcolepsy was reported in China, following the 2009 H1N1 pandemic (Han, 2011; Han, 2013). Similarly, an increased incidence of narcolepsy was observed in Germany (Oberle, 2015) and in Canada (province of Quebec) (Montplaisir, 2014) during the first wave of the 2009 pandemic, prior to initiation of the respective vaccination campaigns in those locations, and in Taiwan following H1N1pdm09

virus circulation (Huang, 2020). Finally, outside of the pandemic vaccination period a 2013 incidence peak in childhood narcolepsy was reported in several European countries, using the European Narcolepsy network 9EU-NN database (Zhang, 2020).

It therefore appears that influenza infection can be a confounder and renders it difficult to separate risk associated with infection from risk associated with vaccination. Indeed, because the A/H1N1pdm09 pandemic preceded the vaccination campaign by a small margin in many European countries, including Ireland, Finland, Sweden and Norway, interpretation of the epidemiological data is confounded by the influenza viral infection data.

Molecular mimicry

One proposed mechanism to explain an auto-immune aetiology of narcolepsy involves molecular mimicry, also referred to as cross-reactivity, at the CD4 T cell level. Type 1 narcolepsy with cataplexy is strongly associated with (HLA) DQB1*0602 (termed DQ0602 in this document) (Bassetti, 2019; Faraco, 2013; Fontana, 2010), with 90–99% of narcolepsy patients being positive for this genetic marker (Dauvilliers, 2007; Fontana, 2010; Mahoney, 2019; Mieda, 2016; Ollila, 2015; Sarkanen, 2018a; Sarkanen, 2018b). The population prevalence of the DQ0602 marker is much higher (12–38%) (Ollila, 2015) than the prevalence of narcolepsy, indicating that DQ0602 is necessary but not sufficient for development of disease (Bomfim, 2017). DQ0602 belongs to the family of HLAs which play a key role in immune system regulation by interacting with CD4 T helper cells.

The CD4 T cell cross-reactivity hypothesis asserts that cross-reactive CD4 T cells exist that can recognize peptides originating from A/H1N1pdm09 influenza proteins as well as peptides from proteins produced by (HCRT)-secreting neurons. Thus, CD4 T cells responding to the A/H1N1pdm09 influenza HA peptide would also recognize HCRT, which is secreted by the neurons and most likely presented to T cells by DQ0602-expressing microglia. It has been further hypothesised that these peptides are uniquely presented by the DQ0602 molecule and that this explains the importance of DQ0602 as a genetic marker. The same HA peptide is present in the H1N1pdm09 vaccines (both Pandemrix and Arepanrix) and in the A/H1N1pdm09 influenza virus itself, which could explain why narcolepsy incidence increases have been observed in relation to A/H1N1pdm09 influenza virus in the absence of vaccination (Han, 2011; Han, 2013; Han, 2014; Huang, 2020; Zhang, 2020).

Aligned with this proposed mechanism and with the confounding effect of H1N1pdm09 influenza infection, a "two-hit" hypothesis of auto-immune aetiology of narcolepsy has been proposed involving both H1N1pdm09 viral infection and vaccination (Edwards, 2019; Partinen, 2014). On the basis of a specific genetic background (i.e., most importantly, the HLA DQ0602 allele), according to this "two-hit" hypothesis, an environmental trigger such as A/H1N1pdm09 influenza virus could increase risk of narcolepsy by inducing a cross-reactive immune response. Subsequent vaccination could then potentially increase the frequency of the cross-reactive CD4 T cells.

The "two-hit" hypothesis explains the observed effects of A/H1N1pdm09 influenza virus infection because the H1N1pdm09 influenza virus and the vaccine share the same peptide that has been hypothesized to act as a mimicry epitope because of structural similarity between this HA peptide and peptides in HCRT. If the putative mimicry peptide is specific for the A/H1N1pdm09 virus proteins, which is believed to be the case, it would explain why the increased risk of narcolepsy was not detected before 2009 (i.e., because the mimicry peptide was absent) and why the narcolepsy incidence peak in China was higher in 2010 with very limited vaccination (with a vaccine other than Pandemrix) (Han, 2011; Han, 2012). A role of a mimicry peptide would further explain why, in a study in Sweden, the risk of narcolepsy was so specific, with no increases in incidence for any other disorder after vaccination (Schinkelshoek, 2019), because the risk would have been driven by peptide specificity.

Supporting data

To study cross-reactivity, CD4 T cells specific for the peptides listed HA275-287, HCRT56-68 and HCRT87-100, were analysed at the single cell level and their T-cell receptor sequences were analysed (Luo, 2018; Jiang, 2019; Pandemrix EPAR, 2016). Shared T-cell receptors were identified, and this provided evidence that the same T cell could recognize both HA and HCRT peptides (Luo, 2018).

Table 45 Peptide sequence of the purported cross-reactive peptides from HCRT-1, HCRT-2 and HA (HA from A/H1N1pdm09)

Protein/Position			**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**		
HCRT1 56-68	A	G	***N***	H	*A*	*A*	**G**	***I***	**L**	T	*L*	G	K
HCRT2 87-100	S	G	***N***	H	*A*	*A*	**G**	***I***	**L**	T	*M*	G	K
HA 275-287	E	R	***N***	A	*G*	*S*	**G**	***I***	**I**	I	*S*	D	T

Amino acids in the peptides are indicated by their single-letter code. Each letter indicated a specific amino acid. Positions refer to how the peptides are expected to 'sit' in the HLA-DQ0602 groove. Amino acids that are the same or very similar (I/L) between HCRT and HA are indicated in bold. Five amino acids identified as critical for DQ0602 HLA binding are indicated in italics.

Even though the peptides present relatively low homology in their primary amino acid sequence, the three-dimensional conformation of the peptide, as it is bound to the HLA groove was remarkably similar on the three-dimensional level, providing a potential molecular basis for cross-reactivity. The similarity between the HA and HCRT peptides was also demonstrated on the 3-dimensional level using X-ray diffraction (Schinkelshoek, 2019).

The cross-reactive CD4 T cells were detected in narcolepsy patients but also in DQ0602-matched healthy controls (Jiang, 2019; Pandemrix EPAR, 2016), suggesting that the mere presence of such cross-reactive T cells is not enough to trigger symptomatic disease. The "two-hit" model (Edwards, 2019; Partinen, 2014), involving H1N1pdm09 viral infection, could explain this by postulating the H1N1pdm09 viral infection would be the essential trigger and that risk would be increased if vaccination happens shortly after the infection. Further T cell data have been published that are consistent with this hypothesis (Latorre, 2018).

A T-cell based aetiology is further supported by pre-clinical data reported by Liblau and coworkers (Bernard-Valnet, 2016). These authors designed a transgenic mouse model in which HA is artificially expressed in HCRT neurons, allowing to bypass mimicry because the shared protein (HA) is already expressed in situ (Bernard-Valnet, 2016). In this model, they demonstrated that the injection of HA-specific CD8 T cells but not HA specific CD4 T cells was able to launch an immune attack, specific for HA, to the HCRT neurons, leading to mice with narcolepsy-like symptoms. It is possible that once an immune response is triggered by cross-reactive CD4 T cells, CD8 T cells are engaged at a next step. It is worth noting that various studies to date have been unable to detect any CD8 T cell responses induced by AS03-adjuvanted vaccines (Couch, 2014; Moris, 2011; Roman, 2011).

The putative cross-reactive pHA1275-287 epitope (HA from A/H1N1pdm09) is located at the border of the HA1 globular domain of the H1N1pdm09 pandemic strain (Luo, 2018). Of this sequence, 5 amino acids were identified as critical for DQ0602 HLA binding (De la Herrán-Arita, 2013). A review of this corresponding sequence alignment has been performed for 4 additional analogous HA sequences in the context of the FLU-D-SUIV-ADJ-001 study, i.e., the chimeric HAs (cHA) used in the project (i.e., cH5/1, cH8/1 [which has the identical sequence as H8N4], cH11/1 and cH12/1) (Figure 4). These data are relevant because they include the analogous sequence from the H5 HA protein. DQ0602-binding data are shown in Figure 5 and demonstrate that the analogous peptide in the H5 HA protein does not bind to DQ0602 and it is therefore extremely unlikely that the same peptide mimicry as observed with H1 HA will occur. Binding is expressed as the percentage of the reference peptide EBV displaced by a given concentration of competitor test peptide and expressed as the concentration of competitor peptide that replaces 50% of the EBV reference peptide. Concentrations below ~50 µM are considered to reflect good

binding of the competitor peptide. Results from the competition experiments with the cH peptides are shown. None of the experimental peptides achieve EBV peptide replacement of >50%.

Position				P1	P2	P3	P4	P5	P6	P7	P8	P9			% identity
H1 AA nr		275	276	277	278	279	280	281	282	283	284	285	286	287	
HCRT 56		A	G	N	H	A	A	G	I	L	T	L	G	K	23.08
HCRT 87		S	G	N	H	A	A	G	I	L	T	M	G	R	23.08
H1N1	A/California/09	E	R	N	A	G	S	G	I	I	I	S	D	T	100
H1N1	A/Michigan/14	E	R	N	A	G	S	G	I	I	I	S	D	T	100
H3N2	A/Hong Kong/14	I	R	S	G	K	S	S	I	M	R	S	D	A	38.46
H2N2	A/Japan/57	S	K	R	G	S	S	G	I	M	K	T	E	G	23.08
H5N1	A/Vietnam/04	V	K	K	G	D	S	G	I	M	K	S	E	L	23.08
cH5/1		V	K	K	G	D	S	G	I	M	K	S	E	L	23.08
H8N4	A/Mallard/02	K	G	E	S	H	G	R	I	I	Q	N	E	D	7.69
cH11/1		V	S	V	G	N	G	K	L	F	R	S	E	L	7.69
cH12/1		T	G	K	S	H	G	R	I	L	K	N	N	L	7.69

Figure 4 Amino acid sequence alignment of DQ0602-binding epitopes of hypocretin (HCRT), relevant pandemic influenza strains and chimeric HAs (cHAs). Sequence homology to predicted HA sequence is indicated blue. Impact of mutations on DQ0602 binding: significant decrease indicated in red (P3/P6); medium decrease indicated in yellow (P1/P4/P5).

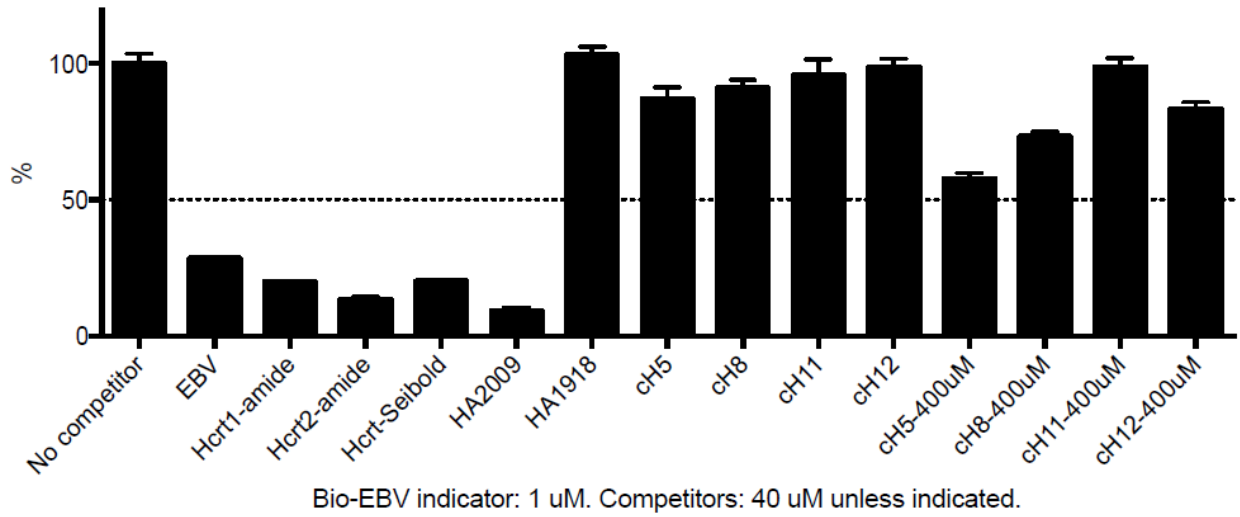


Figure 5 HLA DQ0602 binding of peptides generated based on HA1275-287 sequence of the 4 cHAs (i.e., cH5/1, H8N4, which has the identical sequence of cH8, cH11/1 and cH12/1, Figure 4) was assessed in vitro by using a peptide binding competition assay with an DQ0602-binding peptide from Epstein-Barr virus (EBV) as reference peptide (De la Herrán-Arita, 2013; Jiang, 2019).

Current epidemiological and immunological data support the hypothesis that cases of narcolepsy seen immediately following the 2009/2010 influenza pandemic were the result of an immune cascade triggered by CD4 T cell cross-reactivity to Haemagglutinin (HA) proteins from the H1N1 virus itself (DQ0602-restricted epitopes) and the HCRT neuropeptide (Luo, 2018). The HA275 cross-reactive peptide was identified in the H1 HA protein but its counterpart in H5 was shown to not bind DQ0602. This implies that the mechanism postulated for H1N1 cannot be extrapolated to H5N1, which does not therefore raise additional concerns for narcolepsy as a safety issue for Adjupanrix D-Pan H5N1.

As stated above, an increase in relative risk of narcolepsy in those vaccinated with Pandemrix compared to those unvaccinated, especially in the younger population, has been observed. However, increased incidences of narcolepsy have been observed following H1N1pdm09 virus circulation not associated with Pandemrix vaccination, indicating that influenza infection can be a confounder.

A current hypothesis is that molecular mimicry between H1N1pdm09 influenza HA peptide and HCRT could play a role in the development of narcolepsy. Cross-reactive CD4 T have been shown to occur that recognize both peptides originating from A/H1N1pdm09 influenza proteins as well as peptides from proteins produced by (HCRT)-secreting neurons, which could ultimately leads to the destruction of hypocretin secreting neurons. The peptides that induced cross-reactivity once bound to the HLA groove looked very similar, giving credence to the molecular mimicry hypothesis. However, the fact that cross-reactive T-cells were found in both narcoleptic and not-narcoleptic individuals, means that having cross-reactive T-cells is not enough. This inspired the "double-hit" hypothesis, which could explain the involvement of natural infection and why only narcolepsy is so specifically increased after vaccination with Pandemrix.

The molecular mimicry hypothesis seems plausible; however, it is still a hypothesis and other mechanisms should not be ignored. However, this does indicate that the MAH should continue their research into biological mechanism to how the cross-reactive CD4 T-cells and potentially CD8 T-cells are involved in the aetiology of narcolepsy. Upon request, the MAH presented information to their ongoing commitment to investigate the biological mechanisms how cross-reactive CD4 T-cells could potentially be involved in the aetiology of narcolepsy. The molecular mimicry hypothesis will be further investigated using a novel transgenic mouse model, which could be interesting. In addition, the MAH indicated that once an influenza pandemic is declared and the Influenza strain identified, the research plan would then be to identify the corresponding putative cross-reactive pHA1275-287 sequence and assess the probability of the peptide to bind DQ0602 based on amino acid sequence using bioinformatic tools.

The MAH has committed to closely monitoring narcolepsy should the product be used in a situation of mass immunisation, such as a next influenza pandemic, which is of the utmost importance. The MAH actively searches for relevant published data regarding the incidence of narcolepsy and incorporates this information within currently existing background incidence rates of narcolepsy. In addition, the MAH is aware of the potential bias induced by narcolepsy referral and diagnosis processes and difference in media interest and/or public perceptions and will endeavour to account for these at time of analysis.

Laboratory findings

Clinical laboratory evaluations were carried out only in study Q-PAN H5N1-021.

Eight subjects (1.3%) in the Q-Pan group and 3 subjects (1.3%) in the placebo group reported haematological and/or biochemical abnormalities that were deemed by the investigators to be qualified as MAEs through the Day 385 contact.

The information on laboratory assessments is considered extremely limited.

Safety in special populations

Not applicable. Only healthy children were enrolled in the studies.

Safety related to drug-drug interactions and other interactions

Children aged 6 months to <36 months

Study Q-PAN H5N1-023

Overall per subject, the incidence of the use of any medication within the 21-day postvaccination period was 63.2% (190_B group), 59.5% (090_C group), 65.8% (190_C group), 70.3% (375_C) and 65.7% (375_D) of which 63.2%, 45.9%, 47.4%, 40.5% and 34.3% of subjects from 190_B, 090_C, 190_C, 375_C and 375_D groups, respectively, received antipyretics. Prophylactic antipyretics were administered to none of the participants in groups 190_B and 090_C and to 1 subject in each of the groups 190_C, 375_C and 375_D.

Study D-PAN H5N1-013

Overall, during the entire period up to Day 203, any concomitant medications were used by 101 (89.4%) subjects. Ninety (79.6%) subjects took an antipyretic. Antipyretics were taken prophylactically in anticipation of reaction to vaccination by five (4.4%) subjects.

There was an apparent increase in the use of antipyretics from 31.0% following Dose 1 to 50.0% following Dose 2 to 65.7% following Dose 3.

Study Q-PAN H5N1-021

Study Year 1: Considering the 21-day interval after each dose of vaccine/product, a total of 124 subjects (62.3%) in the Q-Pan group and 40 (53.3%) of subjects in the placebo group used a concomitant medication. Antipyretics were used by 95 Q-Pan subjects (47.7%) and by 29 placebo subjects (38.7%).

In total, 2 participants used prophylactic antipyretics in during year 1 in the Q-PAN group and none in the placebo group.

Concomitant medication was not split per age category for year 2.

The majority of participants receiving H5N1 vaccination in all studies received concomitant medications, ranging from 59.5%-89.4%.

Of the subjects receiving a quarter adult dose, 090_C, 59.5% received concomitant medication and 45.9% received antipyretics. None received prophylactic antipyretics.

Of the subjects receiving a half adult dose (190_B), 62.3-89.4% received concomitant medication and 47.7%-79.6% received antipyretics. None to 4.4% of subjects received prophylactic antipyretics. A trend towards increased use of concomitant medication and antipyretics was seen in subjects using half adult dose.

Children aged 3 years to <18 years

Study D-PAN H5N1-032

Overall, during the entire period up to Day 364, concomitant medication was used by 199 subjects (63.8%) in the pooled H5N1 groups (H5_H5 and H5_Hav) and by 122 subjects (58.7%) in the pooled control groups (Hav_H5 and Hav_Hav). Antipyretics were used by 164 Q-Pan subjects (52.6%) and by 100 placebo subjects (48.1%).

In total, 5 (1.6%) participants used prophylactic antipyretics in the pooled H5N1 group and one (0.5%) in the placebo group.

Study Q-PAN H5N1-021

Study Year 1: Considering the 21-day interval after each dose of vaccine/product, a total of 222 subjects (54.4%) in the Q-Pan group and 74 (47.4%) of subjects in the placebo group used a concomitant medication. Antipyretics were used by 152 Q-Pan subjects (37.2%) and by 41 placebo subjects (26.3%).

In total, 1 participant used prophylactic antipyretics in during year 1 in the Q-PAN group and none in the placebo group.

Concomitant medication was not split per age category for year 2.

The majority of participants receiving H5N1 vaccination in all studies received concomitant medications, ranging from 54.4%-63.8%, of which 37.2%-58.7% received antipyretics. Of the subjects in the placebo/active comparator group, 47.4%-58.7% of subjects received concomitant medications and 26.3%-48.1% used antipyretics.

Prophylactic antipyretics were used in 0.2%-1.6% of subjects receiving H5N1 vaccination and none to 0.5% in the active comparator/placebo group.

Discontinuation due to adverse events

No (S)AEs leading to premature discontinuation of study were reported in studies D-PAN H5N1-013, D-PAN H5N1-032 and Q-PAN H5N1-021. In study Q-PAN H5N1-023, 1 subject (from 190_B group) experienced an AE (injection-site pain) that led to withdrawal from the treatment.

Therefore, the number of discontinuations due to AEs is considered low, only 1 subject in all 4 studies. As only 1 subject was withdrawn no trends could be observed.

Post marketing experience

N/A

2.5.1. Discussion on clinical safety

The evaluation of safety in children and adolescents aged 6 months to <18 years is based upon 4 studies, in which a total of 1,372 subjects who received 2,741 doses of A/Indonesia containing H5N1 vaccine during the primary vaccination series. Reactogenicity was followed for 7 days when concerning local injection-site reactions and systemic reactions, which is considered appropriate (see Guideline on clinical evaluation of vaccines). Non-serious, unsolicited AEs were followed for an appropriate duration and sufficient to identify AEs potentially related to vaccination.

Children aged 3 years to <17 years

Solicited Adverse Events

In the age group **3 years to 17 years**, the majority of subjects, ranging from 78.8% to 88.5%, receiving the primary vaccination with H5N1 vaccine experienced at least 1 solicited AE. Grade 3 solicited AEs, were reported by <12% of subjects (<6.9% overall/dose) in both studies. This is numerically slightly higher compared to the solicited AEs experienced by the active comparator/placebo control groups in these studies, ranging from 47.5% to 76.0%. Grade 3 solicited AEs were reported by 1.3% to 7.1% of subjects.

In the age group **3 years to 17 years**, injection site pain was the most frequently reported solicited local AE in all age stratums after primary vaccination with H5N1 vaccine. The percentage of subjects reporting injection site pain ranged from 70.5% to 82.7%. Grade 3 pain was reported by 1.9%-5.4% of subjects. The majority of subjects experiencing injection site pain experienced mild to moderate pain. In the active comparator/placebo group, pain was experienced by 22.5% to 70.2% of subjects, with 1.0% to 2.7% reporting Grade 3 pain.

Both redness and swelling occurred much less frequently. Redness was reported by 1.3% to 5.6% of subjects, while 2.1% to 9.6% of subjects reported swelling. No grade 3 redness or swelling were reported in both studies after primary vaccination with H5N1 vaccine. In the active comparator/placebo group, redness and swelling was experienced by 0.0% to 1.0% of subjects and 0.0% to 1.9%. As with the H5N1 primary vaccination, no grade 3 redness or swelling was observed in the active comparator/placebo group.

In children aged **3 to <6 years**, the most frequently reported systemic solicited AE after the primary vaccination with H5N1 vaccine was fever in study D-PAN H5N1-032 (reported after 11.7%-21.0% of D-PAN doses in 23.3%-35.5% of subjects) and irritability/fussiness in study Q-PAN H5N1-021 (reported in 13.7% of doses in 22.4% of subjects).

In both studies, the most frequently reported grade 3 systemic solicited AE was fever ≥39.0°C, reported after 2.6%- 4.8% of doses by 2.0% to 6.7% of subjects.

Both studies showed a similar pattern with irritability/fussiness and fever being the dominant systemic solicited AEs. A trend for an increase in the incidence of fever after multiple doses was seen in both studies. In study D-Pan H5N1-032 not only occurrence increased, but also intensity, as no fever ≥39.0°C was seen following dose 1 in the H5_H5 group, but it did occur after dose 2 and 3.

In children aged **≥6 years of age** the most frequently reported systemic solicited AE after the primary vaccination with H5N1 vaccine was headache in study D-PAN H5N1-032 (reported after 24.4%-28.2% of D-PAN doses in 38.4%-42.1% of subjects). In study Q-Pan H5N1-021 the most frequently reported systemic solicited AE was muscle ache reported in 27.3% of doses in 39.8% of subjects, followed by headache reported in 21.4% of doses in 32.4% of subjects.

In both studies, the most frequently reported grade 3 systemic solicited AE was headache, reported after 1.3%- 2.0% of doses and fever reported after 0.8%-4.8% of doses

The most frequently reported related systemic solicited AEs was headache in study D-PAN H5N1-032 and muscle ache followed by headache in study Q-Pan H5N1-021. In both studies, headache was the most frequently reported grade 3 systemic solicited AE reported by 0.8% to 3.2% of subjects.

In study D-PAN H5N1-032 an increase in fever was reported after Dose 2 compared to Dose 1, however, the incidence of fever was lower after Dose 3 (i.e. a booster 6 months after primary vaccination).

Overall, these results indicate that Adjupanrix is a reactogenic vaccine, with the majority of participants experiencing at least 1 solicited AE. Reactogenicity was higher compared to the active comparator (Havrix or Havrix junior) and placebo control group. Across studies, the observations about solicited AEs were consistent, with the majority of participants experiencing 1 or more solicited AEs and injection-site pain being the most frequently reported local solicited AE. In children aged 3 to <6 years of age, the dominant systemic solicited AEs were irritability/fussiness and fever. Fever was the most frequently reported grade 3 systemic solicited AE and a trend for an increase in the incidence of fever was observed. In children aged 6years to <18 years, headache was the most frequently reported systemic AE. The most frequently reported grade 3 systemic solicited AE was headache, reported after 1.3%- 2.0% of doses and fever reported after 0.8%-4.8% of doses. Most AEs were mild to moderate in intensity.

Unsolicited Adverse Events

The percentage of participants receiving H5N1 vaccine during the primary vaccination series reported at least 1 unsolicited AE ranged from 29.5% to 41.0%, of which the most frequently reported unsolicited AEs were in the SOC of infections and infestations. Grade 3 unsolicited AEs were reported in 0.3%-4.8% of subjects receiving H5N1 vaccine and 2.5%-6.9% in the placebo/active comparator control group.

Unsolicited AEs with a causal relationship to the study vaccine, were reported in 3.3%-7.6% of participants receiving H5N1 vaccine and 2.6%-3.8% in the placebo/active comparator control group. These numbers appear balanced between the groups.

In study D-PAN H5N1-032 none of the grade 3 unsolicited AEs were considered related to the vaccine. In study Q-PAN H5N1-021 during year 1 and 2, 1 subject reported 2 grade 3 unsolicited AEs in the Q-PAN group which were considered related to the vaccine: chills and myalgia for year 1 and abdominal pain and nausea during year 2.

Serious Adverse Events and Death

The percentage of participants experiencing an SAE during study D-PAN H5N1-032 and Q-PAN H5N1-021 ranged from 1.2% to 2.6%. None were considered related to the vaccine. No deaths occurred during the studies.

Pregnancy

In total 6 participants in Study D-PAN H5N1-032 (two 15-year old, three 16-year old and one 17-year old), and 2 in Study Q-PAN H5N1-021 (1 17-year old, 1 unknown), got pregnant after vaccination including Adjupanrix. Of the known infant outcomes, no congenital or other abnormalities were reported. These data do not indicate an unusual risk or safety concern; however, exposure to the vaccines in all cases was before the pregnancy. Currently, there is no clinical data of the use of these vaccines in women who are pregnant.

Children aged 6 months to <36 months

Solicited Adverse Events

In the age group 6 months to <36 months, the majority of subjects, ranging from 70.3% to 94.6%, receiving the primary vaccination with H5N1 vaccine, experienced at least 1 AE (solicited or unsolicited). Injection site pain was the most frequently reported solicited local AE in all doses and all groups.

Of the subjects receiving a half adult dose (190_B), enrolled in study D-PAN HN1-013, Q-PAN H5N1-023 and Q-PAN H5N1-021, 74.9% to 94.6% experienced at least 1 AE. A solicited systemic AE was reported by 60.8%-89.5% of subjects and a local AE by 42.1%-48.2% of subjects. A grade 3 solicited AE was reported by 12.1%-23.7% of subjects of which, 8.5%-18.4% were considered related to the vaccine.

The local solicited AE of injection pain was reported after >29% of doses and in >42% of subjects. Grade 3 injection pain was reported after >1.6% of doses in >2.6% of subjects. In study Q-PAN H5N1-021, it was observed that Grade 3 injection site pain occurred at comparable frequencies in the Q-PAN and placebo group: Grade 3 pain was reported after 1.6% of doses in 2.6% of subjects from the Q-Pan group and 1.4% of doses in 2.7% of subjects in the Placebo group.

The most frequently reported systemic AE was irritability in studies D-PAN H5N1-013 and Q-PAN H5N1-021, reported by 44.0%-51.8% of subjects after 31.0%-38.1% of doses. In study Q-PAN H5N1-023, the most frequently reported systemic AE was overall per dose drowsiness and irritability (after 40.0% of doses) and overall per subject drowsiness and fever, reported by 60.5% of subjects.

Fever was reported by 22.4% to 60.5% of subjects after 12.5% to 38.7% of doses. Grade 3 fever was reported after 3.6%-9.3% of doses. Fever was more frequently reported in study Q-PAN H5N1-023, in 60.5% of subjects after 38.7% of doses, compared to study D-PAN H5N1-013 and Q-PAN H5N1-021, reported by 8.0%-33.0% of subjects after 5.0%-20.2% of doses.

The most frequently reported systemic solicited AE considered related to the vaccine was irritability, reported after 23.0%-38.1% of doses, followed by drowsiness, reported after 18.8%-34.7% of doses, and fever, reported after 4.0%-34.7% of doses. The most frequently reported grade 3 related systemic AEs were irritability, drowsiness and fever, reported after 1.0%-6.7% of doses.

Of the subjects receiving a quarter adult dose, 37 subjects in study Q-PAN H5N1-023, 70.3% experienced at least 1 AE. A solicited systemic AE was reported by 62.2% of subjects and a local AE by 29.7% of subjects. A grade 3 solicited AE was reported by 13.5% of subjects, of which 10.8% were considered related to the vaccine.

The most frequently reported local solicited AE was injection pain reported after 26.0% of the doses and in 29.7% of subjects. No grade 3 injection pain was reported. No redness or swelling were reported.

The most frequently reported systemic AE was drowsiness, reported by 43.2% of subjects after 30.1% of doses. Fever was reported by 40.5% of subjects after 15.8% of doses. Grade 3 fever was reported after 2.7% of doses in 5.4% of subjects.

The most frequently reported systemic solicited AE considered related to the vaccine was irritability, reported after 24.7% of doses, followed by drowsiness, reported after 23.3% of doses. The most frequently reported grade 3 related systemic AE were drowsiness and fever, both reported after 2.7% of doses.

Overall, these results indicate that Adjupanrix is a reactogenic vaccine in children aged 6 months to <36 months, with the majority of participants experiencing at least 1 solicited AE. Reactogenicity was slightly higher in the half adult dose group compared to the quarter adult dose group.

Across studies, the observations about solicited AEs were consistent, with the majority of participants experiencing 1 or more solicited AEs and injection-site pain being the most frequently reported local solicited AE. In children aged 6 months to <36 months, the dominant systemic solicited AEs were irritability/fussiness and drowsiness. The most frequently reported grade 3 systemic solicited AE was irritability, drowsiness and fever. Most AEs were mild to moderate in intensity.

Fever is an AE of concern as fever due to vaccination has been known to lead to febrile seizures. In study Q-PAN H5N1-023 Vaccine-related fever occurred in 22 subjects (57.9%) in group 190_B and 12 subjects (32.4%) in group 090_C, while Grade 3 fever (39.0-40.0°C) related to the vaccine occurred in 5 subjects (13.2%) in group 190_B and 2 subjects (5.2%) in group 090_C. The mean duration of the fever was short (<2 days) for both groups. These results indicate that the incidence of fever is less after a quarter dose compared to half adult dose. A post-hoc analysis relying on comparisons across studies showed that incidence of fever in study Q-PAN H5N1-023 was high, as the incidence of fever reported for group 190_B was higher as compared to the same age group administered the same formulation. The strength of evidence achieved using such a post-hoc analysis is limited, as the groups that are pooled were not randomised potentially leading to bias.

Unsolicited Adverse Events

The percentage of participants reporting at least 1 unsolicited AE ranged from 49.2% to 68.4%. Of note, during year 2 of study Q-PAN H5N1-021 only 26.5% of subjects reported an unsolicited AE.

Of the subjects receiving a half adult dose (190_B), 49.2%-68.1% experienced at least 1 unsolicited AE, with only 26.5% of subjects reporting an unsolicited AE during study year 2. The most frequently

reported unsolicited AEs were in the system organ class (SOC) of infections and infestations. The percentage of subjects reporting a vaccine-related unsolicited AE was 3 ranged from 7.5% to 15.9%.

Grade 3 unsolicited AEs were reported by 3.0% to 8.8% of subjects. In only 2 cases in the D-PAN H5N1-013 study (1.8% of subjects) was the grade 3 unsolicited AE related to the vaccine (nasopharyngitis and swelling face). None of the other grade 3 unsolicited AEs in the other 2 studies were considered vaccine-related.

Of the subjects receiving a quarter adult dose, 090_C, 20 subjects (54.1%) experienced at least 1 unsolicited AE. Most frequently reported unsolicited AEs were in the system organ class (SOC) of infections and infestations. None of the unsolicited AEs were considered related to the vaccine.

These results point to a more reactogenic profile when using the half adult dose compared to the quarter adult dose, which is expected. It has to be noted that only 37 children were treated with the quarter adult dose, which is only enough to pick up the most frequently reported solicited AEs. The MAH was asked to discuss the relationship of the unsolicited AEs judged by the investigator as related to the vaccine and add unsolicited vaccine-related AEs to the SmPC.

Serious Adverse Events and Death

The percentage of participants reporting an SAE in study Q-PAN H5N1-023 was relatively high, 29 of 185 subjects (15.7%). The percentage of participants experiencing an SAE in the quarter adult dose group was 16.2%. The percentage of participants experiencing an SAE in the half adult dose group was 13.2%. None of the SAEs were considered related to the vaccine, which is agreed.

The percentage of participants experiencing an SAE during study D-PAN H5N1-013 and Q-PAN H5N1-021 ranged from 1.5% to 8.0%. None were considered related to the vaccine, which is agreed.

No deaths occurred during the studies.

Narcolepsy

An increase in relative risk of narcolepsy in those vaccinated with Pandemrix (H1N1-AS03 adjuvanted pandemic influenza vaccine) compared to those unvaccinated, especially in the younger population, has been observed. However, increased incidences of narcolepsy have been observed following H1N1pdm09 virus circulation not associated with Pandemrix vaccination, indicating that influenza infection can be a confounder.

A current hypothesis is that molecular mimicry between H1N1pdm09 influenza HA peptide and HCRT could play a role in the development of narcolepsy. Cross-reactive CD4 T have been shown to occur that recognize both peptides originating from A/H1N1pdm09 influenza proteins as well as peptides from proteins produced by (HCRT)-secreting neurons, which could ultimately leads to the destruction of hypocretin secreting neurons. The peptides that induced cross-reactivity once bound to the HLA groove looked very similar, giving credence to the molecular mimicry hypothesis. However, the fact that cross-reactive T-cells were found in both narcoleptic and not-narcoleptic individuals, means that having cross-reactive T-cells is not enough. This inspired the "double-hit" hypothesis, which could explain the involvement of natural infection and why narcolepsy is so specifically increased after vaccination with Pandemrix.

The molecular mimicry hypothesis seems plausible, however it is still a hypothesis and other mechanisms should not be ignored. This does indicate that the MAH should continue their research into biological mechanism to how the cross-reactive CD4 T-cells and potentially CD8 T-cells are involved in the aetiology of narcolepsy. In addition, the MAH should ensure that the type of peptides that can cause cross-reactive T-cells will be investigated further. The MAH stated that if an influenza pandemic is declared and the Influenza strain identified, the research plan would then be to identify the corresponding putative cross-

reactive pHA1275-287 sequence and assess the probability of the peptide to bind DQ0602 based on amino acid sequence using bioinformatic tools. In addition, the MAH is further investigating the theoretical possibility of molecular mimicry of Pandemrix leading to narcolepsy using a novel transgenic animal model, which is appreciated.

Considering the seriousness of this theoretical risk, the MAH has committed to closely monitoring narcolepsy should the product be used in a situation of mass immunisation, such as a next influenza pandemic. The MAH actively searches for relevant published data regarding the incidence of narcolepsy and incorporates this information within currently existing background incidence rates of narcolepsy. In addition, the MAH is aware of the potential bias induced by narcolepsy referral and diagnosis processes and difference in media interest and/or public perceptions and will endeavour to account for these at time of analysis.

Concomitant medication

The majority of participants receiving H5N1 vaccination in all studies received concomitant medications, ranging from 54.4%-89.4%, of which 37.2%-79.6% received antipyretics. Of the subjects in the placebo/active comparator group, 47.4%-58.7% of subjects received concomitant medications and 26.3%-48.1% used antipyretics.

Of the subjects receiving a half adult dose (190_B) in the 6 Months to <36 month old age category, 62.3%-89.4% received concomitant medication and 47.7%-79.6% received antipyretics. None to 4.4% of subjects received prophylactic antipyretics. A trend towards increased use of concomitant medication and antipyretics was seen in subjects using half adult dose. Of the subjects receiving a quarter adult dose, 090_C, 59.5% received concomitant medication and 45.9% received antipyretics. None received prophylactic antipyretics.

The results indicate that over all studies, the majority of subjects receiving H5N1 primary vaccination also received concomitant medication. A large portion of the subjects received antipyretics, indicating that fever is an important AE. In the 6 month to <36 month old age category, when using the half adult dose a trend towards increased antipyretics was seen, which was not present in the group administered a quarter adult dose.

Discontinuation due to AE

In total, only 1 participant experienced an AE that led to study vaccine discontinuation.

2.5.2. Conclusions on clinical safety

No new safety concerns arose during the studies in children. The safety profile of Adjupanrix is dominated by solicited AEs. Injection site pain was the most commonly reported local solicited AE. The most frequently reported systemic solicited AE depends on the age category, with irritability/fussiness and drowsiness being most frequently reported by children aged 6 months to <36 months, irritability/fussiness and fever in children aged 3 years to <6 years and headache in children 6 years to <18 years. Most AEs were mild to moderate in intensity. None of the SAEs that occurred during the studies were related to the vaccine.

The quarter adult dose was found to be slightly less reactogenic compared to half adult dose. A decrease in incidence of fever of approximately 50% was seen in study Q-PAN H5N1-023.

As there is a theoretical risk of narcolepsy with AS03-adjuvanted influenza vaccines in children, the MAH

committed to closely monitoring narcolepsy should the product be used in a situation of mass immunisation, such as a next influenza pandemic.

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 13.2 with this application.

The PRAC considered that the risk management plan version 13.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 13.2 with the following content:

Part I – PRODUCT OVERVIEW

In Table Product Overview, *Indication(s) and module Dosage in EEA* were updated with the paediatric population from 6 months of age.

Part II – SAFETY SPECIFICATION

Module SI *Epidemiology of the indication(s) and target population(s)* was updated with general updates and the updated indication.

Module SVII.2 *New safety concerns and reclassification with a submission of an updated RMP*: deleted text, risks reclassified in previous version, however no changes to this version.

Please note that during the Adjupanrix renewal procedure (EMEA/H/C/001206/R/0062, finalized 29 May 2019) the RMP was updated to comply with GVP Module V rev 2, hence the safety concerns 'Vaccination failure/ vaccine effectiveness', 'Fever', 'Medical errors/ misidentification of vaccine' and 'Coring of the rubber stopper on the vial' and 'Contamination of multiple-dose vials' were removed from the RMP.

Module SVII.3.1. *Presentation of important identified risks and important potential risks*: updated table to be consistent with recent PBRER update.

Module SVIII – ***Summary of the safety concerns*** (no changes were proposed, but this summary is reflected in this AR for overview)

Summary of safety concerns

Important identified risks	None
Important potential risks	Anaphylaxis Autoimmune hepatitis Bell's palsy Convulsion Demyelinating Disorders Encephalitis Guillain-Barré syndrome Increased concentrations of hepatic enzymes Narcolepsy Neuritis Vasculitis Potential immune-mediated disorders (pIMD)
Missing information	Use in pregnancy and lactating women Use in persons with clinically severe underlying medical conditions, including immunocompromised

Part III PHARMACOVIGILANCE PLAN (INCL. POST AUTHORISATION SAFETY STUDIES)

III.1 ***Routine pharmacovigilance activities*** (no changes are proposed; however, the assessor chooses to reflect some of the routine pharmacovigilance (PV) activities in this AR for overview and to comment)

III.1.1 *Specific adverse reaction follow-up questionnaires for the following events*:

- Liver and hepatobiliary events
- Anaphylaxis
- Bell's Palsy
- Convulsions
- Demyelination
- Encephalitis
- GBS
- Narcolepsy
- Neuritis
- Vasculitis

III.1.2 *Spontaneous reporting*

Enhanced passive surveillance

GSK Biologicals performs close monitoring of GBS, thrombocytopenia, and sudden unexplained infant death reported to occur following the administration of any GSK vaccine. For Adjupanrix, GSK Biologicals will perform close monitoring of the three events listed above plus the events designated as AESIs in the CHMP recommendations for the PhV plans of pandemic influenza vaccines (EMEA/359381/2009). The additional AESIs include anaphylaxis, Bell's palsy, convulsion, demyelinating disorders, encephalitis, neuritis and vasculitis. Close monitoring will also be performed for AIH, increased aminotransferase concentrations and narcolepsy. For all events subject to close monitoring, targeted questionnaires will be used in order to maximise the consistent documentation of the case reports.

III.1.3 *Periodic safety update reports*

In order to effectively monitor the safety profile of *Adjupanrix* during an officially declared H5N1 influenza pandemic, GSK Biologicals will prepare monthly simplified PSURs, accompanied by a summary of vaccine distribution, as described in the CHMP recommendations for PhV plans of pandemic influenza vaccines (EMEA/359381/2009). The preparation and submission of the safety reports are described in detail in this section and in Annex IIC (Other conditions and requirements of the marketing authorisation).

Objectives of the simplified PSUR
The objectives of the simplified PSUR, as indicated by CHMP, include the following:

- To notify regulatory authorities of the AERs that have been received within a pre-specified time period and that may have the greatest implications for risk-benefit balance in a pandemic;
- To flag any preliminary safety concerns and prioritise them for further evaluation within an appropriate timeframe.

Frequency of submission
- The clock will start on the first Monday after shipment of the first batch of vaccine.
- First data-lock point is 28 days later.
- Report submission will be no later than day 43 (15 days after data-lock point), as agreed with European Medicines Agency (EMA) during the H1N1 influenza pandemic, because Day 14 after data-lock point will always fall on a Sunday.
- Reports will be submitted monthly for the first 6 months of the pandemic.
- Periodicity will be reviewed by GSK Biologicals and the (Co-)Rapporteur at 6-month intervals.

Format of the simplified PSUR
The report will include the following tables of aggregate data, using the format specified in the CHMP recommendations (EMEA/359381/2009) in the order listed below:

1. An overview for all spontaneous reports per country, stratified according to type of report (medically confirmed or non-medically confirmed) and seriousness, for the period covered by the report and cumulatively.
2. An overview for all spontaneous adverse events by SOC, High Level Term (HLT), and PT, stratified according to type of report (medically confirmed or non-medically confirmed) and including the number of fatal reports, for the period covered by the report and cumulatively.
3. Adverse Events of Special Interest stratified according to type of report (medically confirmed or non-medically confirmed). AESIs will be defined as follows:
    - Neuritis: PT "Neuritis".
    - Convulsion: narrow standardised MedDRA query (SMQ) "Convulsions".
    - Anaphylaxis: narrow SMQ "Anaphylactic reaction" and narrow SMQ "Angioedema".
    - Encephalitis: narrow SMQ "Non-infectious encephalitis."
    - Vasculitis: narrow SMQ "Vasculitis".
    - Guillain-Barré syndrome: narrow SMQ "Guillain-Barré syndrome" (the PTs 'Chronic inflammatory demyelinating polyradiculoneuropathy' and 'Demyelinating polyneuropathy' will be tabulated in the "Demyelination" category).
    - Demyelination: narrow SMQ "Demyelination" (as GBS is also included in this SMQ, there will be an overlap in the number of cases for these 2 categories).
    - Bell's palsy: PT "Bell's Palsy"
    - Narcolepsy: PT Narcolepsy; SMQ "Convulsions," SMQ "Generalised convulsive seizures following immunisation," SMQ "Immune-mediated/autoimmune disorders"
    - Autoimmune hepatitis: PT "Autoimmune hepatitis," SMQ "Immune-mediated autoimmune disorders"
    - Increased concentrations of hepatic enzymes: PT "Hepatic enzyme increased," SMQ "Liver related investigations, signs and symptoms"
    - Potential immune-mediated diseases: GSKMQ_pIMD (see Annex 9 for complete list)
4. Serious unlisted adverse reactions (SOC, HLT, PTs) stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

5. All spontaneous adverse reactions by age group, per SOC, HLT and PT, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively. The following age groups will be used: <2 years, 2 to 8 years, ≥9 years, and age unknown.
6. All spontaneous adverse reactions (SOC, HLT, PT) occurring in pregnant women, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

The following principles will be followed when compiling the data:

- Table 1 of the PSUR will be based on the number of reports, while all other tables will be based on number of reactions (presented on PT level, sorted by SOC and HLT).
- All tables will be based on generic and not product-specific data, based on the assumption that product name will not be provided in a significant proportion of cases. Product-specific data will be evaluated during signal evaluation.
- "Cumulatively" means all adverse events since the use of the vaccine.
- All non-medically confirmed events will be those that had been entered into GSK's worldwide clinical safety database (referred to as ARGUS) by the data-lock point. Those which have not yet been entered will be reported in subsequent simplified PSURs.
- "Serious" refers to the seriousness using regulatory criteria based on outcomes; this definition will be used in all tables.
- CIOMS I forms for fatal cases and reports of GBS will be provided in annexes.

A short summary will be provided in which the total number of new AERs since the last simplified PSUR will be outlined and validated signals and areas of concern will be highlighted, signal evaluation prioritised (in the event of multiple signals), and appropriate timelines for submission of a full signal evaluation report provided.
Signals occurring in pregnant women will be summarised in a table that will include the following data elements: gestational age at time of vaccination, gestational age at time of occurrence of adverse event, adverse event, and outcome.

Vaccine distribution report
To put the safety report into context, a summary of vaccine distribution will be included and will provide details of the number of doses of vaccine distributed in

i) EU member states for the reporting period by batch number,
ii) EU member states cumulatively and
iii) the rest of the world.

Upon request narcolepsy has been included as AESI.

III.3 ***Summary Table of Additional Pharmacovigilance activities*** was updated with editorials only.

Table On-going and Planned Additional Pharmacovigilance Activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional PhV activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional PhV activities which are Specific Obligations in the context of a conditional marketing authorisation under exceptional circumstances				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Post-authorisation cohort study (planned)	To determine the incidence of important safety outcomes in all participants; To assess immunogenicity in a subset of participants; To determine the incidence of certain influenza-related outcomes in all participants.	Bell's palsy; convulsion; demyelinating disorders; encephalitis; Guillain-Barre Syndrome; neuritis; vasculitis; hospitalisations; pneumonia	Planned to start if a pandemic is declared	To be determined

Background incidence of narcolepsy per narcolepsy type, per age cohort, and per HLA haplotype should be clear in a pre-pandemic situation. The MAH will take genetic factors, such as HLA type, influence the susceptibility of individuals to narcolepsy, as well as that the prevalence and incidence estimates may vary by methodology and populations tested (e.g., age), into account when establishing a background incidence rate. In addition, the MAH, will pro-active process for identifying potential safety signals with several components; systematic and regular review of the literature is a key component of these pharmacovigilance activities. When relevant data regarding the incidence of narcolepsy is published, this information is incorporated within currently existing background IRs, to continuously assess the benefit/risk profile of GSK vaccines for which narcolepsy adverse events have been reported.

Part V RISK MINIMISATION MEASURES (INCL. EVALUATION OF THE EFFECTIVENESS OF RMM)

V.3 *Summary of risk minimization measures* was updated to remove section of table on missing data in pregnant women, per RMP template.

Part VI SUMMARY OF THE RISK MANAGEMENT PLAN

II.B *Summary of important risks*: updated table to be consistent with recent PBRER update (dated 21 July 2020).

2.7. Update of the Product information

As a result of this variation sections, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated and the Package Leaflet is updated in accordance. Section 4.4 has also been updated with information on sodium and potassium content in line with the excipients guideline, as well as to add wording on traceability. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, Annex II C has been updated regarding PSUR frequency of submission

and format of the 'simplified PSUR' and Vaccine distribution report, the PI has been brought in line with the latest QRD template version 10.2, and the MAH performed minor editorial changes and removed information related to the withdrawn of the Prepandrix marketing authorisation. Version 13.2 of the RMP has been agreed with this procedure.

4.2

Paediatric population

Children aged 6 months to <36 months:
One dose of 0.125 ml (equals quarter the adult dose per injection) at an elected date.
A second dose of 0.125 ml at least three weeks after the first dose for maximum efficacy.

Children and adolescents aged 36 months to <18 years:
One dose of 0.25 ml (equals half the adult dose per injection) at an elected date.
A second dose of 0.25 ml at least three weeks after the first dose for maximum efficacy.

Children aged <6 months:
The safety and efficacy of Adjupanrix in children less than 6 months have not been established.

~~There are limited safety and immunogenicity data available on the administration of Adjupanrix and on administration of half a dose of the vaccine (i.e. 1.875 µg HA and half the amount of AS03 adjuvant) at 0 and 21 days in children aged 3 to 9 years.~~

~~Currently available data are described in section 4.4, 4.8 and 5.1 but no recommendation on a posology can be made.~~

~~For further information, see sections 4.4, 4.8 and 5.1.~~

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 has been submitted by the MAH and has been found acceptable for the following reasons: the product is not commercialised, changes are minimal.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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 is a global outbreak of influenza disease that occurs when a type A influenza strain to which most or all humans are immunologically naïve emerges to cause clinically apparent illness, and then spreads easily from person to person worldwide. 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.

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).

3.1.2. Available therapies and unmet medical need

Vaccination is the most effective way of preventing and controlling the spread of influenza in the human population. GlaxoSmithKline Biologicals (GSK) has developed H5N1 pandemic influenza vaccines. GSK manufactures split virion seasonal influenza vaccines at two GSK facilities, one in Dresden Germany and the other in Québec Canada (the subsequent vaccines are indicated with the prefix D and Q respectively). The pandemic vaccine H5N1 split virus antigens are produced using a process similar to that used for the production of seasonal influenza vaccine and are adjuvanted with GSK's AS03 adjuvant system.

Of note, the vaccine used during the studies will not be deployed during a pandemic. It is considered a "mock-up" vaccine. During an officially declared pandemic, the pandemic strain will be included in the vaccine.

3.1.3. Main clinical studies

The main clinical trials to support dosing regimens in children aged 6 to <36 months and 3 to <18 years were Q-PAN H5N1-023 and D-PAN H5N1-032 respectively.

Study D-PAN H5N1-032 was a phase III, single-centre, randomized, open-label, active-controlled, prime-boost study, enrolling healthy children aged 3 to 17 years old. Children were randomised to receive 2 doses containing 1.9 µg HA antigen/AS03$_B$ (half adult dose) or comparator vaccine (Havrix/Havrix junior). The primary objective was to assess the superiority of the HI antibody response against A/turkey/Turkey/01/2005 (H5N1) 10 days following a booster dose (1.9 µg A/turkey/Turkey/01/2005 [H5N1] HA antigen adjuvanted with AS03$_B$) on Day 182 in subjects previously primed with two doses of heterologous A/Indonesia/5/2005 (H5N1) vaccine versus non primed subjects. Criterion used: lower limit of the 2-sided 95% confidence interval (CI) for the HI GMT ratio on Day 192 (Group H5N1_H5N1 compared to Group Havrix_H5N1) was greater than 1.0.

Study Q-PAN H5N1-023, is a Phase II, observer-blind, randomized, dose-ranging study enrolling healthy children aged 6 and 35 months (inclusive) at time of first vaccination. Q-PAN H5N1-023 investigated a range of doses including a quarter and half adult dose. The co-primary objectives of the study were to assess the performance of alternative dosing regimens for primary immunization with Q-Pan H5N1 vaccine using an immunogenicity-fever index that considers immunogenicity by HI assay / MN assay 21 days after the second priming dose and fever scores after the first and second priming doses, and to assess the performance of dosing regimens for booster immunization with Q-Pan H5N1 vaccine

considering immune response by HI / MN assay 7 days after a 12 month booster dose of 3.75 µg HA Q-Pan H5N1 unadjuvanted antigen. As this is the only study providing information on a quarter dose (0.9 µg HA antigen/AS03$_B$), this study is considered pivotal.

3.2. Favourable effects

Children aged 6 months to <36 months

Homologous immune response. At 21 days after primary vaccination SCR and VRR were 100% in all dose groups. HI and MN GMTs were numerically higher in the half adult dose group (1118.6 [884.4-1414.9] and 1498.5 [1181.7-1900.1] respectively) compared to the quarter adult dose group (858.8 [659.2-1118.8] and 1214.3 [921.3-1600.6] respectively). Both HI and MN antibodies persisted for at least 12 months as they remained substantially above baseline for both quarter adult dose and half adult dose, leading to SCR of 78.8% (61.1%-91.0%) and 97.1% (84.7%-99.9%) respectively and VRR of 100% (100% [89.1-100] and 100% [89.7-100] respectively).

Heterologous immune response. At 21 days after primary vaccination SCR and VRR were slightly higher in the half adult dose group compared to the quarter adult dose group, 100% (88.4-100 and 89.7-100) for both in the half adult dose vs 91.7% (73.0-99.0) and 96.9% (83.8-99.9) for SCR and VRR respectively in the quarter adult dose. Both HI and MN antibodies persisted for at least 12 months as they remained above baseline for both quarter adult dose and half adult dose, leading to SCR of 27.6% (12.7-47.2) and 38.7% (21.8-57.8) respectively and VRR of 84.4% (67.2-94.7) and 87.1% (70.2-96.4). At 12 months MGI was higher in the half adult dose compared to the quarter dose for both HI (4.7 [3.5-6.2] and 4.1 [4.2-8.1] respectively) and MN (7.6 [5.5-10.3] and 5.8 [4.2-8.1] respectively) antibodies.

Effect of boost. A booster dose of unadjuvanted vaccine 1 year after the primary vaccination was able to elicit an immune response in all groups. An anamnestic primary vaccine-homologous HI response was seen at 7 days after the boost SCR was 100% in both quarter adult dose and half adult dose groups. Heterologous HI antibodies were also elicited, leading to an SCR of 100% (88.1-100) in the quarter adult dose and 96.7% (82.8-99.9) in the half adult dose. The anamnestic response seen for MN antibodies yielded a VRR of 100% for vaccine-homologous MN antibodies and 96.9% for vaccine-heterologous MN antibodies in both groups.

Children aged 3 years to <18 years

Homologous immune response. At 21 days after primary vaccination SCR and VRR were 99.3% (96.4-100) - 99.4% (96.5-100) and 98.7% (95.4-99.8) respectively in the groups receiving H5N1 primary vaccination. In unprimed individuals, SCR was 1.0% (0.0-5.3 and 0.0-5.4) and VRR ranged from 0.0-2.0%. Both HI and MN antibodies persisted for at least 6 months as they remained substantially above baseline for both primed groups, leading to SCR of 78.7% (71.4-84.9) and 79.6% (72.3-85.7) respectively and VRR of 79.7% (72.5-85.8) to 85.7% (79.2-90.8). In unprimed individuals, numbers remained similar to baseline levels.

Heterologous immune response. At 21 days after primary vaccination vaccine-heterologous HI response was robust, leading to SCR ranging from 98.0% (94.3-99.8) to 98.7% (95.4-99.8) in the primed individuals, while in unprimed individuals SCR was 3.9% (1.1-9.6) to 4.0% (1.1-9.8). Vaccine-heterologous HI antibodies declined over time, but persisted for at least 6 months as they remained above baseline for the primed individuals leading to an SCR of 48.4% (40.3-56.5) to 66.4% (58.3-73.9). In unprimed individuals, SCR at 6 months after primary vaccination ranged from 1.0% (0.0-5.3) to 2.0% (0.2-7.0).

Effect of boost. Both primed and unprimed individuals showed an increase in H5N1/turkey HI GMT after the booster vaccination with H5N1/turkey, however, the response was significantly higher in the primed individuals, indicating the presence of an anamnestic immune response to an antigenically drifted strain after primary vaccination with H5N1/Indonesia. The response was higher compared to the primary response. In group without primary vaccination series, 10 days after the heterologous booster dose A/Indonesia HI antibody response as measured by GMTs, SCR and MGI increased only slightly.

3.3. Uncertainties and limitations about favourable effects

Efficacy/effectiveness data. No efficacy or effectiveness data is available for Adjupanrix. The evaluation of the vaccine regimen is based on immunogenicity data.

Correlate of protection. Both HI and MN titers were measured, but as there is no cut-off value known that can be associated with clinical benefit the clinical relevance of the observed responses and differences between different doses and timepoints or strains is not entirely clear.

Children with immune deficiencies. No efficacy or immunogenicity data are available in children with immune deficiencies.

3.4. Unfavourable effects

Children aged 6 months to <36 months receiving quarter dose

The incidence of solicited AEs, vaccine-related Grade 3 solicited AEs and unsolicited AEs was higher in group 190_B, half adult dose, compared to 090_C, quarter adult dose.

Of the subjects receiving a **quarter adult dose**, 70.3% experienced at least 1 AE. A solicited systemic AE was reported by 62.2% of subjects and a local AE by 29.7% of subjects. A grade 3 solicited AE was reported by 13.5% of subjects, of which 10.8% were considered related to the vaccine.

The most frequently reported local solicited AE was injection pain reported after 26.0% of the doses and in 29.7% of subjects. No grade 3 injection pain was reported. No redness or swelling were reported.

The most frequently reported systemic AE was drowsiness, reported by 43.2% of subjects after 30.1% of doses. Fever was reported by 40.5% of subjects after 15.8% of doses. Grade 3 fever was reported after 2.7% of doses in 5.4% of subjects.

The most frequently reported systemic solicited AE considered related to the vaccine was irritability, reported after 24.7% of doses, followed by drowsiness, reported after 23.3% of doses. The most frequently reported grade 3 related systemic AE were drowsiness and fever, both reported after 2.7% of doses.

There were no SAEs related to Adjupanrix or deaths. One subject discontinued the study treatment due to an AE: 1 subject in the 190_B group experienced injection-site pain that led to withdrawal.

Children aged 3 years to <17 years receiving half adult dose

Adjupanrix is a reactogenic vaccine, with the majority of participants experiencing at least 1 solicited AE 78.8% to 88.5% following the primary vaccination. Reactogenicity was higher compared to the active comparator and placebo control groups, which reported experiencing at least 1 solicited AE by 47.5% to 76.0% of subjects.

Across studies, the observations about solicited AEs were consistent, with the majority of participants experiencing 1 or more solicited AEs and injection-site pain being the most frequently reported local solicited AE, being reported by 70.5%-82.7% of subjects. Most AEs were mild to moderate in intensity.

In children aged **3 to <6 years of age**, the dominant systemic solicited AEs were irritability/fussiness and fever reported by 22.4% and 23.3%-35.5% of subjects respectively. Fever was the most frequently reported grade 3 systemic solicited AE, reported by 2.0%-6.7% of subjects, and a trend for an increase in the incidence of fever with increasing number of doses was observed.

In children aged **6 years to <18 years**, the most frequently reported systemic AE were headache and muscle ache reported by 32.4%-42.1% and 15.9%-39.8% of subjects respectively. The most frequently reported grade 3 systemic solicited AE was headache, reported after 1.3%- 2.0% of doses and fever reported after 0.8%-4.8% of doses.

There were no SAEs related to Adjupanrix or deaths.

3.5. Uncertainties and limitations about unfavourable effects

Narcolepsy. As Pandemrix, a H1N1pdm09 vaccine using an identical vaccine platform, was associated with an increased risk of narcolepsy in children following vaccination, a theoretical risk exists that this will also occur using Adjupanrix. In the various studies, the relative risk estimates of narcolepsy following vaccination with Pandemrix ranged from 1.5 to 25.0 (95% CI range: 0.3 to 48.5) in children

Safety database. In total, 1,372 subjects received A/Indonesia containing H5N1 vaccine during the primary vaccination series. The size of the safety database limits the detection of more rare adverse events. Information on rare but serious AEs should be systematically collected post-licensure. Since the dose selected for children aged 6 months to <36 months is a quarter dose, which has only been investigated in 37 children, the safety database is extremely limited. However, data obtained with a higher dose (half adult dose) in this age group, given to n=350 children aged 6 to <36 months are considered supportive for the safety of the lower dose.

3.6. Effects Table

Table 1. Effects Table for Adjupanrix

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Children aged 6 months to <36 months						
			¼ dose (090_C)	½ dose (190_B)		
SCR	Vaccine-homologous HI antibodies 21 days after vaccination	%	100	100	*SoE*: As immune response to half adult dose was comparable between studies Q-PAN H5N1-023, D-PAN H5N1-013 and Q-PAN H5N1-021, the immune response is considered to be robust. *Uncertainty*: No correlate	CSR Q-PAN H5N1-023 CSR Q-PAN H5N1-021 CSR D-PAN H5N1-013
VRR	Vaccine-homologous MN (virus neutralizing) antibodies 21 days after vaccination	%	100	100		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
					of protection therefore clinical relevance of 4-fold increase in both HI and MN antibodies is unknown.	
Children aged 3 years to <18 years						
			½ dose	Havrix		
SCR	HI antibodies 21 days after vaccination	%	99.3-99.4	1.0	*SoE*: supported by study Q-PAN H5N1-021	CSR D-PAN H5N1-032
VRR	Virus neutralizing antibodies 21 days after vaccination	%	98.7	0.0-2.0	*Uncertainty*: No correlate of protection therefore clinical relevance of 4-fold increase in both HI and MN antibodies is unknown.	CSR Q-PAN H5N1-021
Unfavourable Effects						
Children aged 6 months to <36 months						
			¼ dose (090_C)	½ dose (190_B)		
LS AE	Injection site pain	%	26.0	29.3	*SoE*: injection site pain is most frequently reported local solicited AE in all studies. *Uncertainty*: safety data base very small	CSR Q-PAN H5N1-023
Fever	All ≥38.0°C	%	32.4	57.9	*Uncertainty*: fever in half adult dose reported more frequently in study Q-PAN H5N1-023 compared to D-PAN H5N1-013 and Q-PAN H5N1-021	
	Grade 3 vaccine-related fever	%	5.2	13.2		
Children aged 3 years to <18 years						
			½ dose	Havrix		
Children aged 3 years to <6 years						
LS AE	Injection site pain	%	73.3-87.7	41.7-68.2	*SoE*: injection site pain is most frequently reported local solicited AE in all studies.	
Fever	All ≥38.0°C		23.3-35.5	0.0-22.8	*Uncertainty*: fever much less frequently reported in study Q-PAN H5N1-021	
	Grade 3 vaccine-related fever		6.5-6.7	0.0-4.5		
Children aged 6 years to <18 years						
L AE	Injection site pain		75.4-80.8	53.8-70.7	*SoE*: injection site pain is most frequently reported local solicited AE in all studies.	
S AE	Headache		38.4-42.1	24.4-30.0	*SoE*: Headache also commonly reported during study Q-PAN H5N1-021	
Fever	All ≥38.0°C		14.3-15.2	8.8-12.2	*Uncertainty*: fever much less frequently reported in study Q-PAN H5N1-021	
	Grade 3 vaccine-related fever		1.6-4.0	1.2-1.3		

Abbreviations: S AE = systemic solicited AE; L AE= local solicited AE; SCR= seroconversion rate; SoE= strength of evidence; VRR=vaccine response rate

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In all studies, using all doses, Adjupanrix was found to be highly immunogenic, especially at Day 42, 21 days after primary vaccination, which is considered most relevant for a pandemic vaccine. The fact that cross-reactive HI and MN antibodies are robustly elicited is considered relevant, as influenza is known to mutate quickly therefore there is a risk of antigenic drift of a pandemic influenza virus after it starts circulating in the population. In addition, 6 months after the primary vaccination, a boost using a heterologous vaccine is able to elicit an anamnestic response, which was greater than the response to the primary vaccination. One year after the primary vaccination, a boost using an unadjuvanted vaccine, still was able to elicit an immune response, however, this was lower compared to the primary response.

Across all age groups and doses, the majority of participants experienced local and systemic AEs. Most of the solicited AEs were grade 1 or 2 in severity.

As previously concluded by the VWP, the data support use of half the adult dose down to 3 years of age, as the immune response is robust and safety profile acceptable.

Dose selection for children aged 6 months to <36 months

The MAH proposes a half adult dose for children aged 6 to 36 months, and has performed several studies with the half dose in this age group. However, PDCO requested further dosefinding in this age group due to concerns surrounding the relatively high reactogenicity. In the dose ranging study Q-PAN H5N1-023 the MAH compared the responses to half adult dose (190_B), quarter adult dose (090-C), half adult dose with less adjuvant (190_C), full adult dose with less adjuvant (375_C) and full adult dose (375_D) in a single study.

At 21 days after vaccination, a numerically lower vaccine-homologous GMT response was seen when using the quarter adult dose (GMT 858.8 [659.2-1118.8]) compared to the half adult dose (GMT 1118.6 [884.4-1414.9]), however SCR was 100% using both doses. The vaccine-homologous immune response shortly after vaccination could be considered the most relevant in a pandemic setting, as the goal of vaccination is to induce an immune response quickly. The immunogenicity data showed that a quarter adult dose was only slightly less immunogenic compared to a half adult dose in the 6 month to 36 month old age category, as 95% CI of the GMTs overlap at Day 42. As there is no correlate of protection, the clinical relevance of this slight decrease in immunogenicity is unknown. However, considering the fact that study Q-PAN H5N1-021 showed that the immune response was highest in the 6 month to <36 month age category when compared to 3 years to <9 years and 9 year to <18 year old age category, the slightly reduced immunogenicity when using the quarter dose in this age category is considered of limited relevance.

The safety profile is better when using the quarter adult dose (090_C) compared to the half adult dose (190_B). Injection site pain was the most frequently reported solicited local AE, reported by 42.1% of subjects in the half adult dose group and 29.7% of subjects in the quarter adult dose group in study Q-PAN H5N1-023. The most frequently reported systemic solicited AEs in the half adult dose group were drowsiness and fever, both reported by 60.5% of subjects and drowsiness in the quarter adult dose group reported by 43.2% of subjects. Vaccine-related fever occurred in 22 subjects (57.9%) in group 190_B and 12 subjects (32.4%) in group 090_C. Grade 3 fever (39.0-40.0°C) related to the vaccine occurred in 5 subjects (13.2%) in group 190_B and 2 subjects (5.2%) in group 090_C.

Based on the fact that the slightly reduced immunogenicity when using the quarter dose in this age category could be acceptable considering the improved safety profile overall, the quarter dose is

recommended in children aged 6 months to <36 months. The MAH was requested to update the posology in children aged 6 months to 36 months at time of first vaccination to a quarter adult dose . This also affected the data to be presented in section 5.1.

This conclusion is in line with previous advice from VWP given in relation to scientific advice (EMEA/H/SA/3998/1/2018/PED/II). In infants and toddler from 6 months to 36 months of age the VWP concluded that a quarter adult dose may be preferable since it seemed sufficiently immunogenic (including in cross-immunogenicity studies) and had a slightly better safety profile than the half adult dose. In addition, the VWP concluded that a further study of the quarter adult dose in this age was not required as the data would be sufficient to conclude on a posology. When deciding this, the VWP took into account the ethical controversies around vaccinating children with H5N1 in lack of an imminent threat.

Narcolepsy

Pandemrix has been associated with an increased risk of narcolepsy, especially in the young population. Considering the fact that Pandemrix uses the same platform as Adjupanrix and a definite cause has not been identified for the increased risk, a theoretical risk exist that Adjupanrix could also be associated with an increased risk.

A current plausible hypothesis is that molecular mimicry between H1N1pdm09 influenza HA peptide and HCRT could play a role in the development of narcolepsy. Cross-reactive CD4 T have been shown to occur that recognize both peptides originating from A/H1N1pdm09 influenza proteins as well as peptides from proteins produced by (HCRT)-secreting neurons and once bound to the HLA groove both peptides looked very similar. The MAH will continue their research into biological mechanism to how the cross-reactive CD4 T-cells and potentially CD8 T-cells are involved in the aetiology of narcolepsy using a novel transgenic animal model. In addition, once an influenza pandemic is declared, the influenza strain will be investigated to determine whether putative cross-reactive pHA1275-287 sequence is present and assess the probability of the peptide binding to DQ0602 using bioinformatic tools. .

Considering the seriousness of this theoretical risk, the MAH has committed to closely monitoring narcolepsy should a pandemic vaccine be used in a situation of mass immunisation, such as a next influenza pandemic. The MAH actively searches for relevant published data regarding the incidence of narcolepsy and incorporates this information within currently existing background incidence rates of narcolepsy to be able to assess the benefit/risk profile of Adjupanrix. A warning has been included in section 4.4 which will create alertness to the potential risk.

3.7.2. Balance of benefits and risks

Adjupanrix elicits a robust immune response, as measured by an increase in both vaccine-homologous HI and MN antibodies.

The data support use of half the adult dose proposed by the MAH down to 3 years of age, as the immune response is robust and safety profile acceptable.

In infants and toddler from 6 months to 36 months of age, a quarter adult dose is preferable since it seems sufficiently immunogenic (including in cross-immunogenicity studies) and had a better safety profile than the half adult dose

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Adjupanrix is positive. Posology for children aged 6 months to <36 months and 36 months to <18 years has been added to the SmPC.

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, IIIA and IIIB

Extension of indication to include use in children from 6 months to <18 years for Adjupanrix based on the results of two studies: study H5N1-013, a phase II, non-randomized, open-label study to evaluate the safety and immunogenicity in children aged 6 to 35 months and study H5N1-032, a phase III, randomized, open, active-controlled study to evaluate the safety and immunogenicity in children aged 3 to 17 years. As a consequence, sections, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated and the Package Leaflet is updated in accordance. Section 4.4 has also been updated with information on sodium and potassium content in line with the excipients guideline, as well as to add wording on traceability. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, Annex II C has been updated regarding PSUR frequency of submission and format of the 'simplified PSUR' and Vaccine distribution report, the PI has been brought in line with the latest QRD template version 10.2, and the MAH performed minor editorial changes and removed information related to the withdrawn of the Prepandrix marketing authorisation. Version 13.2 of the RMP has been agreed with this procedure.

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

Amendments to the marketing authorisation

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

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 Adjupanrix-H-C-1206-II-74