アレパンリックス（H1N1）筋注

製造販売承認申請書添付資料

第２部（モジュール２）　CTDの概要（サマリー）

2.7.　臨床概要

グラクソ・スミスクライン株式会社

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Module 2.7: Clinical Summary

2.7.1 SUMMARY OF BIOPHARMACEUTIC STUDIES AND ASSOCIATED ANALYTICAL METHODS

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2.7.1.1 Background and Overview

The "Note for Guidance on Clinical Evaluation of New Vaccines" (CPMP/EWP/463/97, May 19th 1999) specifically details the type of studies to be performed during the clinical development of a new vaccine. Biopharmaceutic studies are typically conducted for drug products and are not mentioned in this guideline. Biopharmaceutic studies were therefore not performed with GSK's candidate pandemic influenza vaccine.

Of note, serological methods used to characterize the immune response in man can be found in Section 5.3.5.4 "Other Study Reports".

2.7.1.2 Summary of Results of Individual Studies

Not applicable.

2.7.1.3 Comparison and Analyses of Results Across Studies

Not applicable.

2.7.1.4 Appendix

Not applicable.

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2.7.2 SUMMARY OF CLINICAL PHARMACOLOGY STUDIES

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2.7.2.1 Background and overview

As mentioned in the "Note for Guidance on Clinical Evaluation of New Vaccines" (CPMP/EWP/463/97, May 19th 1999), "pharmacokinetic studies are generally not required for injectable vaccines. The kinetic properties of vaccines do not provide information useful for establishing adequate dosing recommendations." Pharmacokinetic studies were therefore not conducted during the clinical development of GSK's candidate pandemic influenza vaccine.

In line with the above guideline, pharmacodynamic evaluations were performed. Clinical studies were designed to obtain information on characteristics of the immune response, as follows:

- evaluation of the level of specific antibodies produced
- duration of antibody titres
- assessment of the dose response relationship and basis for dosing recommendation

The safety and reactogenicity of the vaccines tested were also assessed in all clinical studies.

As the primary objectives of all studies were to evaluate the immunogenicity and/or safety of the study vaccines, these results are discussed in Sections 2.7.3 "Summary of Clinical Efficacy" and 2.7.4 "Summary of Clinical Safety" respectively.

All clinical study reports are included in Section 5.3.5 "Reports of Efficacy and Safety Studies" based on the following guidance extracted from Notice to Applicants, Volume 2B "Presentation and format of the dossier CTD, June 2004":

- "Reports of studies with a primary objective of determining the pharmacodynamic (PD) effects of a drug product in humans should be placed in this section (5.3.4 "Reports of Human PD studies"). Reports of studies whose primary objective is to establish efficacy or to accumulate safety data should be placed in Section 5.3.5."

- "In some cases, the short-term PD, dose finding, and/or PK-PD information found in PD studies conducted in patients will provide data that contribute to assessment of efficacy because they show an effect on either an acceptable surrogate marker or a clinical benefit endpoint. Similarly, a PD study can contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in Section 5.3.5, not in Section 5.3.4."

2.7.2.2 Summary of Results of Individual Studies

Not applicable.

2.7.2.3 Comparison and Analyses of Results Across Studies

Not applicable.

2.7.2.4 Special Studies

Not applicable.

2.7.2.5 Appendix

Not applicable.

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2.7.3 SUMMARY OF CLINICAL EFFICACY

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List of abbreviations

Anti-HA	Anti-haemagglutinin antibody
AS03	Adjuvant composed of oil-in-water emulsion
ATP	According to protocol
CHMP	Committee for Human Medicinal Products
CI	Confidence Interval
CRF	Case Report Form
D-Pan	Dresden-sourced adjuvanted pandemic/pre-pandemic influenza vaccine
FLU	Influenza
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titre
GSK	GlaxoSmithKline
HA	Haemagglutinin
HI	Hemagglutination inhibition
IgG	Immunoglobulin G
LL	Lower limit of confidence interval
Max.	Maximum
Min.	Minimum
ml	Millilitre
Q-Pan	Quebec-sourced adjuvanted pandemic/pre-pandemic influenza vaccine
SAS	Statistical analysis system
SCF	Seroconversion factor
SCR	Seroconversion rate
SD	Standard deviation

SNT, SN test	Seroneutralization titre, Seroneutralization test
SPR	Seroprotection rate
SSW	Sächsisches Serumwerk Dresden, Branch of GlaxoSmithKline Pharma GmbH & Co. KG, a GSK-group company
UL	Upper limit of confidence interval
WHO	World Health Organisation
µg	Micrograms

2.7.3.1 Background and Overview of Clinical Efficacy

In the event of pandemic influenza, vaccination will be instrumental in the strategy to protect the human population from a new pandemic influenza strain. Understanding the existing gap between pandemic vaccine supply needs and currently available manufacturing capacities worldwide, GSK Biologicals has explored modified vaccine formulations that would increase supply opportunities and has developed two H5N1 split virus vaccines adjuvanted with AS03, GSK Biologicals' proprietary adjuvant containing an oil–in-water emulsion, consisting of an oil phase containing DL-α-tocopherol and squalene, and an aqueous phase containing the non-ionic detergent Tween 80.

The vaccine based on the antigen manufactured in GSK Biologicals facilities in Dresden (Germany), has been submitted in two parallel Marketing Authorisations Applications (MAAs) for prepandemic (in order to allow priming of the population prior to or at the onset of the pandemic) and pandemic indications, in December 2006 (Prepandrix™) and in February 2007 (Pandemrix™). Prepandrix™ was approved in the European Union on 14 May 2008 and Pandemrix™ on 20 May2008. In the present document, this vaccine is referred to as D-Pan.

In parallel, GSK Biologicals also developed a second AS03 adjuvanted H5N1 vaccine, based on the antigen manufactured in GSK Biologicals facilities in Quebec, Canada (referred to as Q-Pan), and which is subject of the present submission.

Similar to the D-Pan vaccine, the Q-Pan vaccine contains sodium deoxycholate-split, formaldehyde-inactivated H5N1 influenza antigen, adjuvanted with AS03. The manufacturing processes of the D-Pan and Q-Pan antigens are slightly different. The manufacturing process of the antigen included in Q-Pan vaccine is similar to the manufacturing process of the monovalent inactivated split virus bulks of GSK Biologicals' seasonal influenza vaccine FluLaval™ (other TradeName: Fluviral®), while the antigen included in the D-Pan vaccine is manufactured according to the same process as the antigens included in GSK Biologicals' seasonal influenza vaccine Fluarix®.

Clinical trials with the AS03-adjuvanted Q-Pan and D-Pan vaccine were conducted with avian H5N1 strains, which are considered as the leading contenders for the next influenza pandemic. The D-Pan (pre)pandemic vaccines were developed and are under registration with the H5N1 clade 1 strain A/Vietnam/1194/2004, which was the strain considered as the most appropriate for pandemic preparedness at the time of the development of these two vaccines. Since then, several other H5N1 avian strains have emerged. Amongst the strains currently recommended by WHO to be considered for vaccines development and subsequent stockpiling, A/Indonesia/05/2005 clade 2 H5N1 strain was the first one to be available to manufacturers and for which quality control reagents could be obtained. This is therefore the strain which is used for the clinical development of Q-Pan candidate vaccine and which is proposed for initial registration.

The current summary of Clinical Efficacy provides a summary of the immunogenicity data derived from two pivotal trials with the candidate Q-Pan vaccine and one supportive clinical trial proving immunogenicity data generated with D-Pan vaccine.

Pivotal clinical trial Q-Pan-001 provides a direct comparison of the immunogenicity and safety of GSK Biologicals' prepandemic/pandemic vaccines containing Dresden-manufactured antigen or Quebec-manufactured antigen, both using H5N1 clade 2 A/Indonesia/05/2005 strain, administered as a two-dose primary series. This study has also compared the immunogenicity and safety of the monovalent H5N1 vaccine antigens without adjuvant and with two different doses of AS03. It was conducted in North America, in 18-64 years old subjects and was recently completed for the primary immunization phase.

Pivotal clinical trial Q-Pan-002 evaluated the safety and immunogenicity of a two-dose series of the candidate AS03 adjuvanted Q-Pan H5N1 vaccine with strain A/Indonesia/05/2005. The study also assessed the lot-to-lot consistency of the immunogenicity of the AS03 adjuvanted Q-Pan pandemic influenza vaccine (H5N1 A/Indonesia/05/2005 strain).

Immunogenicity data generated from one supportive clinical trial with D-Pan vaccine (H5N1-007) are also described in this application, to support the antigen dose selection of the Q-Pan candidate vaccine. Indeed, the H5N1 antigens contained in the D-Pan and Q-Pan vaccines are manufactured according to a similar manufacturing process. The adjuvant is both qualitatively and quantitatively identical for the two vaccines, i.e AS03, and both vaccines are formulated with the same amount of antigen (3.75µg, rounded to 3.8µg in the present document). These data, which have been previously submitted to EMEA in the context of the two MAAs for the (pre)pandemic D-Pan vaccine, have been used as the primary basis for the dose selection of the Q-Pan vaccine. Study H5N1-007 assessed the reactogenicity and immunogenicity of two administrations of a pandemic virus (H5N1 clade 1 A/Vietnam/1194/2004 strain) vaccine at different antigen doses (30, 15, 7.5 and 3.8µg HA) adjuvanted with AS03.

In the three clinical studies, antibody responses against heterologous strains were also evaluated in order to further assess the potential **cross-protective** properties of the candidate AS03 adjuvanted Q-Pan H5N1 influenza vaccine.

Given the fact that the immunological equivalence for both antigen sources (Dresden and Quebec) was demonstrated in pivotal trial Q-Pan-001, and the fact that the adjuvant system is identical, the Company is of opinion that the clinical database that is currently available is sufficient to support the present Marketing Authorisation Application (MAA).

2.7.3.1.1 Studies presented in the Clinical Summary of Efficacy

Pivotal study Q-Pan-001

Pivotal clinical trial Q-Pan-001 enrolled a total of 680 vaccinated subjects aged 18-64 years. Of these, 303 subjects received the candidate H5N1 Q-Pan vaccine with full or half dose AS03 adjuvant, 78 subjects received non-adjuvanted Q-Pan vaccine and 299 subjects received D-Pan vaccine adjuvanted with full or half dose AS03. The primary endpoint of the study consisted in demonstration of the AS03 adjuvant effect in terms of Day 42 HI antibody against homologous H5N1 vaccine strain A/Indonesia/05/2005 (superiority criteria: > 2 fold increase in GMT and >15% increase in SCR). Importantly, the study was also designed to show equivalence of Quebec-derived vaccine and Dresden-derived vaccine (both with H5N1 Indonesia strain) at 3.8 µg antigen dose level.

A total of 650 subjects vaccinated with Q-Pan or D-Pan H5N1 vaccine were included in the according to protocol (ATP) cohort for immunogenicity. Immunogenicity data (HI antibody response on all subjects and neutralisation antibody response in a subset of subjects) are described for the primary immunization phase (up to Day 42). In addition, the assessment of the persistence of immunogenicity in terms of HI and neutralisation antibody response at six months after the first vaccination (Day 182) is also described.

Pivotal study Q-Pan-002

Pivotal study Q-Pan-002 is a randomized, observer-blind, multi-centered, placebo-controlled eight-arm study. Subjects were randomized in a 3:1 ratio to treatment with 1 of 3 lots of Q-Pan vaccine with Quebec-manufactured H5N1 antigen or placebo. A total of 4561 subjects aged 18 years or older were enrolled and vaccinated, including 3422 subjects who received AS03 adjuvanted Q-Pan vaccine and 1139 subjects who received placebo.

A primary objective of the study was to demonstrate immunogenic equivalence, based on vaccine-homologous HI antibody GMTs, of 3 consecutive lots of H5N1 vaccine antigen manufactured in Quebec combined with 3 consecutive lots of AS03 manufactured in Rixensart, in adults aged 18 to 49 years.

The study was also designed to show that H5N1 antigen in association with AS03 elicits vaccine-homologous HI antibody titers, which meet or exceed CHMP criteria for SCR, SPR, and geometric mean fold-rise in titer (GMFR, or SCF). This was analysed for the 2 age strata (18 to 60 years of age and > 60 years of age). Immunogenicity data (HI and neutralisation antibody response) are described for the primary immunization phase (up to Day 42 after the first dose). In addition, the assessment of the persistence of immunogenicity in terms of HI antibody response at six months after the first vaccination (Day 182) in a subset of subjects is also described.

The safety and reactogenicity of the Q-Pan vaccine was also assessed in comparison to placebo.

Supportive study H5N1-007 with D-Pan vaccine

The immunogenicity of the monovalent pandemic vaccine containing different H5N1 antigen doses was evaluated in the 400 subjects included in study H5N1-007. A total of 394 subjects vaccinated with the H5N1 vaccine were included in the according to protocol (ATP) cohort for immunogenicity of H5N1-007.

As explained in the "Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application" (EMEA/CPMP/VEG/4717/03) and in the "Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context" (EMEA/CHMP/VWP/263499/2006), clinical trials on protective efficacy cannot be performed for mock-up influenza pandemic vaccines or avian influenza vaccines for use in the pre-pandemic phase. No data on protective efficacy are therefore presented in this Summary.

2.7.3.1.2 Ethics

The studies summarised below were carried out by experienced investigators and all these studies were conducted in accordance with Good Clinical Practice (GCP) guidelines. The protocols reflected the Declaration of Helsinki and its amendments as well as the GCP guidelines in use at the study outset. There was an Ethical review committee approval for each study. Written informed consent was obtained from each subject prior to entry into the study.

2.7.3.1.3 Design features

Pivotal studies Q-Pan-001 and Q-Pan-002 were multicentric studies conducted in the US and Canada.

Supportive study H5N1-007 was a monocentric study performed in Belgium.

All studies were observer-blind. Due to the differences in the appearance of adjuvanted and non-adjuvanted formulations, the following steps were taken to maintain the blinding:

- Study personnel who vaccinated the subject were not involved in the evaluation of study endpoints, including safety assessment.
- The access to the vaccines was restricted to the person(s) in charge of the vaccine accountability, preparation and administration.

In case of emergency, access to individual treatment code was available to the local / central GSK Biologicals Safety office.

All studies were randomized. A randomization list was generated at GSK Biologicals, Rixensart. In pivotal studies Q-Pan-001 and Q-Pan-002, the randomization list was generated using MATEX and used to assign treatments to subjects. In supportive study H5N1-007, the randomization list was generated using a standard SAS® (Statistical

Analysis System) program and was used to number the vaccines. A randomization blocking scheme was used to ensure that the balance between treatments was maintained. A treatment number uniquely identified the vaccine doses to be administered to the same subject.

In all studies, the treatment allocation at the investigator site was performed using a central randomisation call in system on Internet (GlaxoSmithKline Simply the Best Internet Randomisation, SBIR). The randomization algorithm used a minimization procedure accounting for center and age (18 to 40 year olds versus 41 to 64 year olds in study Q-Pan-001; 18 to 30 years, 31 to 49 years, 50 to 64 years, 65 to 75 years, and > 75 years in Q-Pan-002; 18-30 year old versus 30-60 year olds in H5N1-007). Center and age minimization factors had an equal weight in the minimization algorithm.

Study H5N1-007 had a staggered design. In order to ensure maximal safety to the subjects, especially those vaccinated with the formulations containing the highest antigen dose (30µg), and to minimise potential risks of serious adverse reactions, vaccination was performed in a step-by-step manner:

- Initially, subjects from groups receiving vaccine formulations containing either 3.8µg, 7.5µg and 15µg HA received their first dose.
- Safety data (in terms of solicited general symptoms and SAEs) were collected for a subset of 20 subjects from each of these groups (120 subjects in total) up to 7 days following vaccination. These safety data were reviewed by an internal safety committee.
- Following demonstration of a satisfactory safety profile after the first dose, vaccination with the formulations containing 30 µg HA was allowed.
- A similar safety evaluation was performed after the second vaccination.

Study duration for each subject was approximately 6 months in studies Q-Pan-001 and H5N1-007 and will be approximately 1 year in study Q-Pan-002.

All subjects enrolled in the clinical trials were healthy volunteers as established by medical history and clinical examination before entering into the study. Of note, in study Q-Pan-002, subjects > 49 years of age could be enrolled when they had a stable health status. All vaccinees were above 18 years of age.

Two doses of vaccine (or placebo) were administered in the three studies according to a 0, 21 day schedule. No concomitant vaccines were administered during any of the studies.

The interval of 21 days between doses is derived from the routine interval between vaccination and blood sampling in the serological evaluation of seasonal influenza vaccines. It appeared to be the most convenient time point to administer the second dose, followed by a further blood sampling after an additional 21 days (i.e Day 42). In addition, in the context of the development of a candidate influenza vaccine for pre-pandemic use, it is recommended to evaluate the minimum dose interval that might be employed when more than one vaccine dose is needed to achieve an optimal immune response. As the

candidate H5N1 vaccine adjuvanted with AS03 is intended for use during a pre-pandemic and pandemic phase, the use of a 0, 21 day schedule therefore appears to offer some advantages as compared to a 0, 28 day regimen in terms of onset of protection.

Brief details of the objectives and design of each study are summarised in Table 4 and Table 5.

Copies of all study reports are located in Module 5, Section 5.3.5.

2.7.3.1.4 Vaccine composition

GSK Biologicals'candidate (pre)pandemic influenza vaccine is a monovalent, split virion (H5N1), inactivated, vaccine adjuvanted with AS03 (oil-in-water emulsion). The H5N1 virus is one of the reference viruses indicated as suitable for use in a mock-up vaccine by the Committee for Human Medicinal Products (CHMP) in the "Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application" (EMEA/CPMP/VEG/4717/03).

The influenza strain contained in the candidate vaccine is a recombinant A/H5N1/Indonesia/5/2005 strain from Clade 2, i.e. the first pandemic vaccine prototype strain from the new phylogenetic group released by WHO in May 2006 (WHO, 2006). The A/Indonesia/05/2005 reassortant H5N1 strain was produced by the Centres for Disease Control and Prevention (CDC) using the reverse genetics technology (CDC reassortant identification code: Indo/05/2005(H5N1)/PR8-IBCDC-RG2).

The vaccine is a 2-component vaccine consisting of concentrated inactivated split virion (H5N1) antigens (suspension) presented in a multidose glass vial (10 doses) and of the AS03 adjuvant (emulsion) presented in a multidose glass vial (10 doses). The composition of the candidate Q-Pan vaccine is provided in Table 1.

The vaccine contains the following residuals from the manufacturing process of the drug substance: formaldehyde, ovalbumin, sucrose and sodium deoxycholate. Thiomersal is added as a preservative at a concentration of 5 μg per dose. Thiomersal is added since the presentation is multidose, for which presence of a preservative was requested by several Regulatory Authorities.

Table 1 Composition of the reconstituted AS03 adjuvanted pandemic influenza candidate vaccine

Component	Quantity per dose	Analytical Reference
ACTIVE INGREDIENTS		
Split-virion monovalent, A/Indonesia/5/2005 (rH5N1)	3.75 g HA	Ph. Eur. 0158
AS03 ADJUVANT		
Squalene	10.69mg	GSK 100346
DL--tocopherol	11.86mg	Ph. Eur. 0692
Polysorbate 80 (Tween 80)	4.86mg	Ph. Eur. 0428
EXCIPIENTS		
Sodium Chloride	3.895 mg	USP/ Ph. Eur. 0193
Potassium Chloride	0.09 mg	USP/Ph. Eur. 0185
Disodium Hydrogen Phosphate	0.613 mg	USP/ Ph. Eur. 0118
Potassium Dihydrogen Phosphate	0.09 mg	NF/ Ph. Eur. 0920
Thimerosal	5ug	USP
WFI	qs 0.5mL	USP/Ph. Eur. 0169

Abbreviations: USP = United States Pharmacopoeia, NF = United States National Formulary, Ph. Eur, = European Pharmacopoeia

The registered D-Pan (pre)pandemic vaccine is formulated from an attenuated recombinant H5N1 prototype vaccine strain derived from the highly pathogenic avian strain influenza A/Vietnam/1194/2004. This strain was developed by a WHO collaborating centre [National Institute for Biological Standards and Control (NIBSC), UK].

D-Pan and Q-Pan vaccines are both AS03-adjuvanted, preservative-containing vaccines (5 µg thiomersal/dose – 20 µg thiomersal/mL in the formulated antigen vial), which present the same amount of A/H5N1 inactivated split virion antigens (3.75 µg/dose – 15 µg HA/ml in the formulated antigen vial).

With respect to the individual components of the Q-Pan and D-Pan vaccines, the same AS03 adjuvant component is used for both vaccines. Regarding the antigen component, Table 2 provides a comparison of the D-Pan and Q-Pan antigen final container compositions. The main difference between the D-Pan and the Q-Pan vaccines relates to the presence of Tween-80, Triton X-100 and Magnesium Chloride that are used as excipients during formulation of the D-Pan antigen.

Table 2 Comparison of the Q-Pan vs. D-Pan antigen final container composition

Ingredients	Antigen final container composition	
	Q-Pan (quantity per 0.25mL dose)	D-Pan (quantity per 0.25mL dose)
Active Substance		
A/H5N1inactivated, split virions	3.75µg HA	3.75 µg HA
Excipients		
Polysorbate 80 (Tween®-80)	N/Ap	≥ 28.75 µg
Octoxynol 10 (Triton® X-100)	N/Ap	3.75 µg
Sodium chloride (NaCl)	2.13 mg	1.92 mg
Potassium chloride (KCl)	0.025 mg	0.050 mg
Sodium phosphate dibasic heptahydrate ($Na_2HPO_4.7H_20$)	0.050 mg	N/Ap
Disodium phosphate dodecahydrate ($Na_2HPO_4.12H_20$)	N/Ap	0.260 mg
Potassium phosphate monobasic (KH_2PO_4)	0.363 mg	0.094 mg
Magnesium chloride hexahydrate ($MgCl_2.6H_20$)	N/Ap	0.012 mg
Thiomersal	5µg	5µg
Water for Injection	ad 0.25 mL	ad 0.25 mL

N/Ap: Not Applicable

In pivotal study Q-Pan-001, the immunogenicity, reactogenicity and safety of AS03 adjuvanted H5N1 vaccine antigen at the 3.8 µg dose level produced at GSK Biologicals' manufacturing site in Quebec and adjuvanted H5N1 vaccine antigen (3.8 µg) manufactured in Dresden were compared. In this study the immunogenicity, reactogenicity and safety of the Quebec-manufactured H5N1 antigen adjuvanted with AS03 at two different doses (full or half) versus that of non-adjuvanted Quebec-manufactured H5N1 antigen at the 3.8 µg dose level was also assessed.

Monovalent formulations of influenza split virus D-Pan vaccine (H5N1) containing various concentrations of HA per dose, with or without AS03 adjuvantation, were evaluated in supportive study H5N1-007.

The composition of the vaccine formulations tested in the trials and corresponding lot numbers are presented in Table 3.

Vaccinations were administered intramuscularly.

In studies Q-Pan-001 and Q-Pan-002 the antigen component (15 µg HA/mL, to yield 3.8µg HA/final 0.5mL dose) was presented in a multidose vial (antigen container) and a second multidose vial contained the adjuvant (adjuvant container). At the time of injection, the content of the adjuvant container was thoroughly mixed with the adjuvant component. One individual dose of the vaccine corresponded to 0.5 mL of the appropriate mixture.

In study H5N1-007, the presentation consisted of antigens (containing different antigen doses in study H5N1-007) presented in a vial (unique vial for each antigen dose, antigen container) and a pre-filled syringe containing either the adjuvant (adjuvant container) or the diluent. Before human administration, the content of the pre-filled syringe was

injected into the vial containing the antigens. After mixing, the content was withdrawn into the syringe and the used needle was replaced by an intramuscular needle. One dose of the vaccine corresponded to 1 ml.

Table 3 Composition and lot numbers of H5N1 vaccine formulations used in clinical trials

Study	Antigen	Strain	Manufacture Facility	HA (µg /dose)	Adjuvant	Vaccine lot			Placebo lot (Sterile, preserved phosphate-buffered saline)
						Antigen container	Adjuvant container	Diluent container	
Q-Pan-001	Split	A/Indonesia/05/2005 (H5N1)	Quebec	3.8µg*	AS03 full **	AFLPA009A	DA3BA008A	-	-
	Split	A/Indonesia/05/2005 (H5N1)	Quebec	3.8µg*	AS03 half **	AFLPA009A	DA3AA006A	-	-
	Split	A/Indonesia/05/2005 (H5N1)	Quebec	3.8µg*	-	AFLPA009A	-	DD11A003A	-
	Split	A/Indonesia/05/2005 (H5N1)	Dresden	3.8µg*	AS03 full **	DFLSA006A	DA3BA008A	-	-
	Split	A/Indonesia/05/2005 (H5N1)	Dresden	3.8µg*	AS03 half **	DFLSA006A	DA3AA006A	-	-
Q-Pan-002	Split	A/Indonesia/05/2005 (H5N1)	Quebec	3.8µg*	AS03 full **	AFLPA109A, AFLPA110A, AFLPA111A	DA3BA008A, DA3BA007B, DA3BA009A	-	-
	-	-	-	-	-	-	-	-	PFLSA001A
H5N1-007	Split	A/Vietnam/1194/2004 (H5N1)	Dresden	30µg	-	DFLUAD016A	-	DD11A001A	-
	Split	A/Vietnam/1194/2004 (H5N1)	Dresden	15µg	-	DFLUAD017A	-	DD11A001A	-
	Split	A/Vietnam/1194/2004 (H5N1)	Dresden	7.5µg	-	DFLUAD018A	-	DD11A001A	-
	Split	A/Vietnam/1194/2004 (H5N1)	Dresden	3.8µg *	-	DFLUAD019A	-	DD11A001A	-
	Split	A/Vietnam/1194/2004 (H5N1)	Dresden	30µg	AS03 full **	DFLUAD016A	DA3AA001A	-	-
	Split	A/Vietnam/1194/2004 (H5N1)	Dresden	15µg	AS03 full **	DFLUAD017A	DA3AA001A	-	-
	Split	A/Vietnam/1194/2004 (H5N1)	Dresden	7.5µg	AS03 full **	DFLUAD018A	DA3AA001A	-	-
	Split	A/Vietnam/1194/2004 (H5N1)	Dresden	3.8µg *	AS03 full **	DFLUAD019A	DA3AA001A	-	-

HA : haemagglutinin

AS03: GSK Biologicals' proprietary adjuvant containing an oil–in-water emulsion, consisting of an oil phase containing DL-α-tocopherol and squalene, and an aqueous phase containing the non-ionic detergent Tween 80

*: As the vaccine doses were expressed using only one digit throughout the clinical documentation, 3.75 µg HA was rounded up to 3.8 µg HA in the Clinical Overview, Clinical Summaries and clinical study reports.

**: "Full"(or "Half") dose AS03 corresponds to the same (or "Half" the) adjuvant dose as contained in the candidate vaccine formulation

2.7.3.1.5 Assessment of the immunogenicity of the candidate pandemic influenza vaccine

Hemagglutination inhibition (HI) assay

All serology testing of HI antibody response was performed in GSK Biologicals' central laboratory (SSW, Dresden, Germany) using standardized procedures with adequate controls which have been validated by GSK Biologicals. The immune response was determined by measuring hemagglutination-inhibiting (HI) antibodies in paired serum specimens treated to remove non-specific inhibitors (heat and receptor-destroying enzyme). Anti-HA antibody titres were measured using the method described by the WHO (1991) and modified according to Stephenson et al (2004).

Please note that the terms "HI antibodies" and "anti-HA antibodies" are used interchangeably the present application.

Blood samples for evaluation of vaccine immunogenicity were drawn prior to, on Day 21, Day 42 and on Day 180 or 182 after the first vaccination in studies Q-Pan-001 and H5N1-007. In study Q-Pan-002, blood samples were taken prior to vaccination, and on Day 42 and Day 182 after the first vaccination.

HI antibody titres were measured against the vaccine strain (i.e. A/Indonesia/05/2005 in study Q-Pan-001 and Q-Pan-002; A/Vietnam/1194/2004 in study H5N1-007) as well as against one or more heterologous strain (A/Vietnam/1194/2004 in study Q-Pan-001; A/Indonesia/05/2005, A/turkey/ Turkey/1/05 (a clade 2.2 virus) and A/Anhui/1/05 (a clade 2.3 virus) in study H5N1-007).

Method description - Measurements were performed on frozen thawed serum samples with a standardized and comprehensively validated micromethod using four HI units of the appropriate antigen and a 0.5% horse erythrocyte suspension. Horse red blood cells were used instead of chicken red blood cells to investigate hemagglutinating antibodies against avian influenza viruses in order to increase assay sensitivity by improving the binding of the avian viruses to the indicator cells, as detailed below. The methodology used to measure HI antibody titres is identical to the standard methodology applied to evaluate the immune response to GSK Biologicals' seasonal influenza vaccine Fluarix™, except for some minor differences, including a) use of horse erythrocytes instead of chicken erythrocytes; b) the use of phosphate-buffered saline (PBS) containing 0.5% bovine serum albumin (BSA) (w/v) as assay buffer instead of PBS; and c) an increased sedimentation time of 2 hours instead of 1 to 1.5 hours.

Avian influenza viruses preferentially bind to sialic acid receptors containing N-acetylneuraminic acid α2,3-galactose (α2,3Gal) linkages. The low proportion of α2,3Gal linkages on chicken erythrocytes is likely to be responsible for the insensitivity of HI tests for antibody to avian influenza viruses. Horse erythrocytes contain a high proportion of α2,3 linkages thus making them more sensitive for the detection of antibody to avian HA in the HI assay [Stephenson et al., 2004]. Because horse red blood cells are non-nucleated, sedimentation is not as rapid and clear-cut as when using chicken red blood

cells. The addition of 0.5% BSA allows a better sedimentation of the horse red blood cells as does the extended sedimentation time of two hours.

All HI assays were performed in duplicate in the same run. The assay variability is also controlled by the use of control sera included in each run. The results obtained for the controls have to meet acceptance criteria; in case the acceptance criteria are not fulfilled the assay run has to be repeated.

Subjects with titres below the detection limit (1:10) were considered as seronegative. Subjects with a demonstrable titre (≥ 1:10) after vaccination were considered as seropositive. A titre ≥ 1:40 is considered as a titre correlating with protection against influenza disease ("seroprotection level").

Validation of the method - The validation results of the assay based on the Vietnam strain are presented in the validation report"QVALR-PF-015 version 04/E" (Module 5, section 5.3.5.4). The assay characteristics tested are precision, specificity and robustness. The robustness has been investigated in order to check whether red blood cells could be used one week after collection of the red blood cells.

The validation results of the assay based on the Indonesia strain are presented in the validation report "QVAL-PF-015 version 05/E" The assay characteristics tested are precision and specificity. The assay variability has been estimated during the validation of the assay. The results of assay variability are described in the validation reports and are similar to the results obtained for these types of assay with other virus antigens. Moreover, the reproducibility over time is monitored during the testing of clinical samples (see section 5.3 of the HI validation report as an example of assay variability in routine testing conditions).

Serum neutralization test (SNT)

In all 3 studies (Q-Pan-001, Q-Pan-002, H5N1-007), serum neutralization tests were performed in GSK Biologicals' central laboratory (SSW, Dresden, Germany) in order to demonstrate and quantify serum antibodies inhibiting the multiplication of influenza viruses. Serum neutralization antibodies were assessed against the vaccine strain as well as against one or more heterologous strains: against drifted clade 1 strain A/Vietnam/1194/2004 and 2 other clade 2 strains A/turkey/ Turkey/1/05 (a clade 2.2 virus) and A/Anhui/1/05 (a clade 2.3 virus) in study Q-Pan-001; against A/Vietnam/1194/2004 in study Q-Pan-002; and against A/Indonesia/05/2005, A/turkey/ Turkey/1/05 and A/Anhui/1/05 in study H5N1-007.

In studies Q-Pan-001 and H5N1-007, serum neutralizing antibodies were measured at Days 0, 21, 42 and 180 following initial vaccination. In study Q-Pan-002, serum neutralizing antibody results are available for Days 0 and 42 in subset of subjects vaccinated with Q-Pan vaccine.

Method description - Virus neutralisation by antibodies contained in the serum was determined in a microneutralization assay on thawed frozen serum samples. The sera are heat-inactivated before being tested. A standardised amount of virus was mixed with serial dilutions of serum and incubated to allow binding of the antibodies to the virus. A

cell suspension, containing a defined amount of Madin-Darby Canine Kidney (MDCK) cells was then added to the mixture of virus and antiserum and incubated at 37°C. After the incubation period, virus replication is determined by testing the supernatant of each well in a hemagglutination assay using chicken erythrocytes.

All SN assays were run in triplicate in the same run. Each control serum was tested ten times by different validated technicians on ten different days to obtain the control sample.

The geometric mean of the titres derived from these tests was calculated and the titre next to it was termed the "declared titre". The declared titres correspond to the list of computable titres of the Reed and Muench method by using triplicates in serial 2-fold dilutions. The value of the titre that is the nearest to the calculated geometric mean is determined as the "declared titre".

Validation methods - The assay variability is also controlled by the use of control sera included in each run. The results obtained for the controls have to meet acceptance criteria; in case the acceptance criteria are not fulfilled the assay run has to be repeated.

The assay variability has been estimated during the validation of the assay; the results of assay variability are described in the validation reports and are similar to the results obtained for these types of assay.

The specificity of the neutralization assay has been estimated by testing a set of samples from naïve (i.e. previously unvaccinated) children (6 to 9 years) collected before vaccination with the seasonal vaccine: out of 46 subjects, one was slightly positive. These data are described in the Validation Report. Based on this result, the specificity of the SNA can be estimated to be 98%.

Cut-off determination – The neutralization titre of a serum is the dilution for which 50% of the wells are protected against virus infection (ND50). The assay cut-off was defined as 1:28. This assay cut-off of 1:28 is a consequence of the predilution of the sera and is the first computable ND50 value.

Details of the serological methods used to evaluate vaccine immunogenicity can be found in Module 5, Section 5.3.5.4.

2.7.3.1.6 Immunogenicity endpoints

Geometric mean titres (GMTs) of HI antibodies were calculated by taking the anti-log of the mean of the log transformations reciprocal titres. Antibody titres below the cut-off value (1:10) were given an arbitrary value of half the cut-off for the purpose of GMT calculation, that is a reciprocal titre of 5.

Based on the GMTs, the following serological parameters were assessed as defined in the "Note for Guidance on Harmonisation of requirements for influenza vaccines" (CPMP/BWP/214/96):

- The mean increase in the antibody titer (**seroconversion factor,** SCF) defined as the ratio of the post-vaccination GMT divided by the pre-vaccination GMT. Please note that "SCF" and geometric mean fold rise ("GMFR") are interchangeable terms, and both used in the present Summary.
- The **seroconversion rate** (SCR) defined as the proportion of subjects who were either seronegative prior to vaccination and have a protective post-vaccination titre of ≥ 1:40 or who were seropositive prior to vaccination and have at least 4-fold increase in titre post-vaccination.
- The **seroprotection rate** (SPR) defined as the proportion of subjects in each group having a protective post-vaccination titre of ≥ 1:40.

In the above mentioned "Note for Guidance on Harmonisation requirements for influenza vaccines" (CPMP/BWP/214/96), immunological criteria were established for the annual relicensing procedure of influenza vaccines in the European Union (see table below). Currently, at least one of the assessments in each age group should meet the European requirements for seasonal influenza vaccines.

	Age groups	
	18–60 years	**> 60 years**
Seroconversion factor (SCF) (factor of increase in the geometric mean)	> 2.5	> 2.0
Seroconversion rate (SCR)	> 40%	> 30%
Seroprotection rate (SPR)	> 70%	> 60%

In the absence of specific criteria for influenza vaccines derived from non-circulating strains, it is anticipated that a candidate pandemic vaccine or an avian influenza vaccine for use in the pre-pandemic phase should at least be able to elicit sufficient immunological responses to meet all three of the current standards set for existing vaccines in adults or elderly subjects. This requirement is specified in the "Guideline on dossier structure and content of marketing authorisation applications for influenza vaccines derived from strains with a pandemic potential for use outside of the core dossier context." (EMEA/CHMP/VWP/263499/2006).

Results of neutralizing serum antibodies were expressed as follows:

- GMTs of serum neutralizing antibodies pre- and post-vaccination (with 95%CI)
- Seropositivity rates, defined as the percentage of subjects with a serum neutralizing titre ≥1:28
- Percentage of subjects with a serum neutralizing titre ≥ 1:40 and ≥1:80.
- **Vaccine response rate for neutralizing antibody titers** was defined in studies Q-Pan-001 and Q-Pan-002 as the incidence rate of vaccinees at least a 4-fold increase in post vaccination reciprocal titre. Samples which were seronegative at baseline were presumed to have a reciprocal titre of 14 (i.e. half of the assay cut-off).

2.7.3.1.7 Statistical analysis

Statistical methods are described extensively in the study reports (Module 5, Section 5.3.5).

Descriptive analyses of the humoral immune response in terms of both anti-HA antibodies and neutralizing antibodies were presented for all studies.

Inferential analyses of immunogenicity performed in study Q-Pan-001 were as follows:

- The primary objective was to demonstrate the adjuvant activity of AS03 by comparing the immunogenicity of the Quebec-manufactured H5N1 antigen at the 3.8 µg dose level with AS03 at two different doses (full and half) versus that of Quebec-manufactured H5N1 antigen alone.
- Superiority of the Quebec-manufactured antigen plus adjuvant formulation versus Quebec-manufactured antigen alone was established if:

  1) the lower bound of the 95% confidence interval (CI) on the HI GMT ratio for antibody against the vaccine strain, exceeded 2.0;

  2) the lower bound of the 95% CI on the difference (H5N1 antigen with adjuvant minus H5N1 antigen alone) in HI SCR against the vaccine strain, exceeded 15%.

- The equivalence of the Quebec and Dresden sources of antigen was assessed as a secondary objective based on vaccine-homologous virus HI GMTs at Day 42. The analysis used data from the two groups receiving AS03-adjuvanted (half or full dose) H5N1 antigen manufactured in Quebec (Q-Pan) and the two groups receiving AS03-adjuvanted (half or full dose) H5N1 antigen manufactured in Dresden (D-Pan). A 95% CI on the mean difference in $\log_{10}$ reciprocal titres between the pooled Quebec antigen and Dresden antigen groups was calculated, and the anti-log of these limits used to calculate the CI on the GMT ratio. If these limits were between 0.67 and 1.5, equivalence was considered achieved.

Criteria used for the lot-to-lot consistency analysis in study Q-Pan-002, were as follows:

- Consistency at Day 42 (21 days after dose 2) was reached if, for all pairs of lots, the two-sided 95% CIs for the ratio of HI antibody GMTs are within the [0.67;1.5] clinical limit interval, in the age group 18-49 years old. The 95% CI for HI antibody GMT ratio between vaccine groups was computed using the analysis of co-variance (ANCOVA) model on the log_{10}-transformed reciprocal titres.

Inferential analyses of immunogenicity performed in study H5N1-007 were as follows:

- The analysis of variance (ANOVA) model was used to test "haemagglutinin-dose" (3.8, 7.5, 15 or 30 µg HA) effect and "adjuvantation" effect (with or without AS03). In case of non-significant interaction between the two factors "haemagglutinin-dose" and "adjuvantation", a factorial design approach was to be used to assess the effect of these two factors.
- For the comparison between groups, 95% CI for haemagglutinin GMT ratio between H5N1 AS03-adjuvanted vaccine formulations were computed using the ANOVA model on the logarithm10 transformed titres. The ANOVA model included the vaccine group effect. The GMT ratio was derived from the contrast of the vaccine group effect. Pairwise comparisons were performed using a Tukey adjustment for the haemagglutinin-dose effect in non-adjuvanted formulations.

The datasets used for the analyses were created from each subject's CRF or serological assay result. No mathematical computation technique was performed to replace confirmed missing values, they remained blank.

Two cohorts were defined for the statistical analysis: the Total Vaccinated cohort (TVC) and the According-to-Protocol (ATP) cohort.

The Total Vaccinated cohort included all vaccinated subjects for whom data were available. Thus, the Total cohort for the analysis of immunogenicity included all vaccinated subjects for whom data concerning immunogenicity endpoint measures were available.

The ATP cohort for analysis of immunogenicity included all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures are available. This included subjects for whom assay results are available for antibodies against at least one study vaccine antigen component after vaccination.

The primary analysis of the humoral response was based on the ATP immunogenicity cohort. An analysis on the TVC was only to be performed if more than 5% of the subjects were excluded from the ATP cohort. The purpose of the TVC analysis was to ensure that protocol violations were not treatment related and did not lead to any selection bias in results. In the event, the conditions for a TVC analysis were not met in either H5N1-007 or Q-Pan-001, but were met in Q-Pan-002. The TVC analysis in Q-Pan-002 confirmed the ATP cohort analysis for every endpoint and hypothesis test, as detailed in the study report.

2.7.3.2 Summary of Results of Individual Studies

All studies were analysed according to pre-specified statistical plans.

Table 4 summarizes pivotal studies Q-Pan-001 and Q-Pan-002 which provide pivotal immunogenicity data with the candidate AS03 adjuvanted H5N1 (A/Indonesia) vaccine containing Quebec-manufactured antigen, when administered as a two-dose primary series.

Supportive study H5N1-007 performed with the registered monovalent pandemic influenza A vaccine (Dresden-manufactured H5N1) is summarized in Table 5.

Table 4 Summary of pivotal studies Q-Pan-001 and Q-Pan-002 with Quebec-manufactured H5N1 influenza vaccine (Total cohort)

Study ID	Study centers Locations Study start Study end	Study groups (Vaccine strain, manufacturing site and dose)	Total enrolment (*enrolment target*) Entered *(Completed)* ‡ per group	Study design	Primary objectives	Study duration (active phase)	Diagnosis Inclusion criteria	Primary endpoints
Q-Pan-001	10 centers US Canada [redacted]20[redacted] [redacted]20[redacted] (end Day 42) [redacted]20[redacted] (end Day 182)	**H5N1 split Quebec** (HA 3.8µg/AS03 full*) **H5N1 split Quebec** (HA 3.8µg/AS03 half*) **H5N1 split Quebec** (HA 3.5µg) **H5N1 split Dresden** (HA 3.8µg/AS03 full*) **H5N1 split Dresden** (HA 3.8µg/AS03 half*)	**680 *(662)*** 152 *(148)* 151 *(150)* 78 *(75)* 151 *(148)* 148 *(141)*	Observer-blind, randomized, phase I/II 2 doses at 0, 21 days	Immunogenicity (humoral immune response) and safety/reactogenicity of AS03-adjuvanted split monovalent vaccines (H5N1) manufactured in Quebec and manufactured in Dresden	Approximately 6 months for each subject	Healthy adults 18-64 years old (18-40 years, 41-64 years)	- Determination of serum HI antibody titres, SCF, SCR and SPR at days 0, 21, 42 and 182 for adjuvanted versus non-adjuvanted Quebec-manufactured H5N1 antigen. Establishment of equivalence of adjuvanted Quebec-manufactured H5N1 antigen and adjuvanted Dresden-manufactured H5N1 antigen. - Assessment of reactogenicity/ safety of Quebec-manufactured and Dresden manufactured H5N1 antigen with full and half dose AS03 in terms of solicited local and general symptoms, unsolicited symptoms and SAEs

"Full"*(or "Half")* AS03 dose corresponds to the same *(or "Half" the)* adjuvant content as contained in the candidate vaccine formulation
H5N1 Quebec: H5N1 antigen produced at GSK Biologicals' manufacturing site in Quebec; H5N1 Dresden: H5N1 antigen produced at GSK Biologicals' manufacturing site in Dresden
‡ number of subjects completed based on Day 182 analysis

Table 4 (cont'd) Summary of pivotal studies Q-Pan-001 and Q-Pan-002 with Quebec-manufactured H5N1 influenza vaccine (Total cohort)

Study ID	Study centers Locations Study start Study end	Study groups (Vaccine strain, manufacturing site and dose)	Total enrolment (*enrolment target)* Entered *(Completed‡)* per group	Study design	Primary objectives	Study duration (active phase)	Diagnosis Inclusion criteria	Primary endpoints
Q-Pan-002	40 centers US, Canada [redacted]20[redacted] [redacted]20[redacted] (data lock D42 analysis: [redacted]20[redacted])	**H5N1 Quebec** (HA 3.8µg/AS03) H5N1 Quebec lot A H5N1 Quebec lot B H5N1 Quebec lot C Placebo	**4561** ***(4343)*** **3422** ***(3263)*** 1141 1141 1140 1139 *(1080)*	Observer-blind, randomized, phase III 2 doses at 0, 21 days	Immunogenicity (humoral immune response) and safety/reactogenicity of AS03-adjuvanted split monovalent vaccines (H5N1) manufactured in Quebec **Immunogenicity analysis was performed in a subset of subjects, by age strata** (18-60 years, N=1666; >60 years, N= 554)	Initially 6 months; amended to approximately 1 year for each subject	Healthy adults At least 18 years old	- Determination of serum HI and neutralization antibody titres, SCF, SCR and SPR at days 0, 42 and 182 (Day 182: HI Ab only) for AS03 adjuvanted Quebec-manufactured H5N1 antigen. - Establishment of equivalence of 3 consecutive lots of adjuvanted Quebec-manufactured H5N1 antigen. - Assessment of reactogenicity/ safety of Quebec-manufactured H5N1 antigen in terms of solicited local and general symptoms, unsolicited symptoms and SAEs

H5N1 Quebec: H5N1 antigen produced at GSK Biologicals' manufacturing site in Quebec
‡ number of subjects completed based on Day 182 analysis

Table 5 Summary of supportive studies conducted with H5N1 influenza vaccine manufactured in Dresden (Total cohort)

Study ID	Study centers Locations Study start Study end	Study groups (Vaccine strain and dose)	Total enrolment (*enrolment target)* Entered *(Completed)* per group	Study design	Primary objectives	Study duration (active phase)	Diagnosis Inclusion criteria	Primary endpoints
H5N1-007	1 center Belgium [redacted] 20[redacted] [redacted] 20[redacted]	**H5N1 split** (HA 30µg) **H5N1 split** (HA 15µg) **H5N1 split** (HA 7.5µg) **H5N1 split** (HA 3.8µg) **H5N1 split** (HA 30µg /AS03) **H5N1 split** (HA 15µg /AS03) **H5N1 split** (HA 7.5µg /AS03) **H5N1 split** (HA 3.8µg /AS03)	**400 *(400)*** 50 *(50)* 50 *(50)* 50 *(50)* 50 *(50)* 49 *(49)* 50 *(50)* 50 *(50)* 51 *(51)*	Observer-blind, randomized, phase I 2 doses at 0, 21 days	Immunogenicity (humoral immune response) and safety/reactogenicity of split monovalent vaccines (H5N1)	Approximately 51 days for each subject	Healthy adults 18-60 years old (18-30 years, 31-60 years)	- Determination of serum HI antibody titres, SCF, SCR and SPR at days 0, 21, 42 and 180 - Assessment of reactogenicity/ safety in terms of solicited local and general symptoms, unsolicited symptoms and SAEs

Study Narratives

The narratives of the pivotal study listed in Table 4 and the supportive studies listed in Table 5 are presented below.

Study Q-Pan-001 (US, Canada)

Design: observer-blind, randomized, phase I/II, multicentre trial with five groups. Subjects were randomized to receive vaccination according to a 2 dose schedule (day 0, day 21) with a monovalent split virus influenza vaccine containing 3.8 µg HA/dose of H5N1 antigen produced either at the Quebec manufacturing site or at the Dresden manufacturing site. Both Dresden and Quebec-derived vaccines were adjuvanted with half or full strength AS03 adjuvant; one control group received non-adjuvanted Quebec-derived H5N1 vaccine.

Objectives: to evaluate the humoral immunogenicity and safety/reactogenicity of the split monovalent H5N1 vaccines.

Population: healthy adults who were 18-64 years old (with half of the subjects pertaining to the 18-40 year old age group, and the other half to the 41-64 year old age group).

Results: 680 subjects aged 38.6 ± 12.11 years old (mean ± SD) at the time of the first vaccine dose were enrolled and vaccinated. Immunogenicity results against vaccine strain H5N1 A/Indonesia/05/2005 based on the ATP cohort are summarized hereafter.

After one vaccine dose, all but one (D-Pan vaccine adjuvanted with half dose AS03) adjuvanted groups reached the CHMP criterion of SCR >40% in terms of HI antibody SCR against homologous vaccine strain.

After a 2-dose vaccination schedule, the adjuvanted Q-Pan and D-Pan vaccines were shown to elicit a strong immune response towards the vaccine strain A/Indonesia/05/2005. At Day 42, all three CHMP criteria were met or exceeded for the vaccine strain, in all treatment groups receiving adjuvanted vaccine (either with full or half dose of AS03). Both SCR and SPR obtained at Day 42 in the adjuvanted groups were >70% and varied from 89.7% to 97.2% (versus 17.3% in non-adjuvanted group). SCF in all adjuvanted groups exceeded 2.5 after the first dose of vaccine. After the second dose, a further important increase in SCF was observed, ranging from 30 to more than 40-fold versus the pre-immunization titres depending on the adjuvant dose.

Of note, two of the three CHMP criteria (SCR and SCF) were also fulfilled for the heterologous virus strain A/Vietnam/1194/2004 in the adjuvanted vaccine groups, indicating that a cross-reactive immune response against strain variation was induced.

The equivalence of the Q-Pan vaccine and the D-Pan vaccine was statistically demonstrated with respect to the homologous anti-HI GMTs (i.e. the limits of the 95% CI on the GMT ratio were between 0.67 and 1.5). On the basis of the highly overlapping confidence intervals, Q-Pan and D-Pan also presented similar results for the other

immunogenicity parameters against homologous vaccine strain, when formulated with the same adjuvant content.

The primary outcomes for immunogenicity were met: immunogenicity of the Q-Pan vaccine with full dose adjuvant was superior to the Q-Pan vaccine antigen without adjuvant, as determined by HI antibody SCR and GMTs at Day 42. Similarly, immunogenicity of Q-Pan vaccine with half dose adjuvant was also substantially superior to vaccine without adjuvant.

AS03 adjuvanted H5N1 vaccine with strain A/Indonesia/05/2005 was able to induce high neutralizing antibody responses to both the vaccine virus and to drift-variant virus A/Vietnam/1194/2004, irrespective of the defined threshold (≥1:28, ≥1:40 or ≥1:80). The neutralizing antibody responses with the Q-Pan vaccine and the D-Pan vaccine when formulated with the same amount of AS03 were similar.

While HI antibody titers against H5N1 viruses at Month 6 (Day 182) were not as high as at Day 42, a persistent antibody response was clearly present in those groups that had received adjuvanted Q-Pan or D-Pan vaccine, but not in the unadjuvanted vaccine group. The decline in neutralizing antibody titers at Day 182 appeared to be less pronounced than the decline in HI titres, suggesting persistence of this important class of antibodies.

Q-Pan and D-Pan vaccines presented a similar reactogenicity profile with clinically acceptable incidence rates of local and general solicited symptoms. The incidence of unsolicited adverse events was relatively low in all treatment groups, with no statistically notable difference between adjuvanted and unadjuvanted vaccine. No deaths or vaccine-related SAEs were reported during the study period, including the 6-month safety follow-up (up to Day 182).

Study Q-Pan-002 (US, Canada)

Design: observer-blind, randomized, phase III, placebo-controlled multicentre trial with eight study groups. Subjects were randomized in a 1:1:1:1 ratio to receive 1 of 4 treatments: i.e., 1 of 3 lots of AS03 adjuvanted influenza vaccine with Quebec-manufactured H5N1 antigen (3.8 µg HA/dose), or placebo, according to a 2 dose schedule (day 0, day 21).

Objectives: to evaluate the humoral immunogenicity and safety/reactogenicity of the AS03 adjuvanted split monovalent vaccines with H5N1 antigen manufactured in Quebec.

Population: healthy adults aged ≥ 18 years. Within each treatment, the randomization was to target an age interval ratio of 1.5 (18 to 30 years): 1.5 (31 to 49 years): 1 (50 to 64 years): 1.5 (65 to 75 years): 0.5 (> 75 years).

Results: A total of 4561 subjects were enrolled and vaccinated including 2889 subjects aged 37 ± 12.58 years (mean ± SD) at the time of the first vaccine dose in the 18-60 years group and 1672 subjects aged 70.9 ± 5.93 years in the >60 years group. Immunogenicity results against vaccine strain H5N1 A/Indonesia/05/2005 were obtained in a subset of

subjects (N=1666 in age group 18-60 years and N= 554 in age group >60 years) and are summarized hereafter, based on the ATP cohort.

Immunogenic equivalency of 3 consecutive lots of H5N1 vaccine antigen manufactured in Quebec combined with 3 consecutive lots of AS03 was shown, since the 2-sided 95% confidence intervals for all pairwise GMT ratios were within the interval of 0.67 and 1.5.

After a 2-dose vaccination schedule, the adjuvanted Q-Pan vaccine was shown to elicit a strong immune response against the vaccine strain A/Indonesia/05/2005. All three CHMP criteria based on homologous HI antibody response in both age strata (18 to 60 and >60 years) were fulfilled. The SCR following 2 doses of Q-Pan vaccine at Day 42 were 91.0% for the 18 to 60 years group and 76.4% for the > 60 years age group, which is well above the 40% and 30% CHMP threshold for the respective age groups. The SPR for the 18 to 60 years of age group was 91.0% and 76.8% for the > 60 years of age group. These rates exceeded the CHMP targets of 70% and 60%, respectively. The SCF for the 18 to 60 years age group was 51.4 and 17.2 for the > 60 years age group and thus also exceeded the CHMP targets of 2.5 and 2.0, respectively.

Microneutralization titers at Day 42 indicated that high levels of vaccine-homologous virus-specific and also cross-clade cross-reactive neutralizing H5N1 antibodies against strain A/Vietnam/1194/2004 were induced by the AS03 adjuvanted H5N1 (A/Indonesia) vaccine.

Although HI antibody titers against H5N1 vaccine strain A/Indonesia/05/2005 at at 6 months after first vaccination (Day 182) were not as high as at Day 42, a persistent antibody response was still present in both age groups 18-60 years and >60 years who were vaccinated with adjuvanted Q-Pan vaccine.

The AS03 adjuvanted Q-Pan vaccine presented an acceptable reactogenicity profile compared to placebo, with clinically acceptable incidence rates of local and general solicited symptoms. The incidence of unsolicited AEs was similar in the Q-Pan and placebo groups, with 38% and 35% of subjects reporting at least one event. No vaccine-related SAEs were reported through Day 42 of the study. One death which was assessed by the investigator as unrelated to study vaccine, occurred in the Q-Pan vaccine group due to an SAE of myocardial infarction in a subject with pre-existing cardiac risk factors.

Study H5N1-007 (Belgium)

Design: observer-blind, randomized, phase I, monocentric trial with eight groups. Subjects were randomized to receive vaccination with D-Pan monovalent split virus influenza formulation (H5N1) of different antigen concentrations (3.8 µg, 7.5 µg, 15 µg and 30 µg HA per dose) with or without AS03 adjuvantation according to a 2 dose schedule (day 0, day 21).

Objectives: to evaluate the immunogenicity and safety/reactogenicity of D-Pan split monovalent H5N1 vaccines.

Population: healthy adults who were 18-60 years old (with half of the subjects pertaining to the 18-30 year old age group, and the other half to the 31-60 year old age group).

Results: 400 subjects aged 34.3 ± 12.76 years old (mean ± SD) at the time of the first vaccine dose were enrolled. Immunogenicity results against vaccine strain H5N1 A/Vietnam/1194/2004 based on the ATP cohort are summarized hereafter.

Twenty one days after administration of the first dose, SCR and SPR to HI antibodies ranged between 0.0%-26.5% and 0.0%-28.6% respectively in the plain H5N1 vaccine groups, as compared to 24.0%-58.3% and 26.0%-58.3% respectively in the H5N1 adjuvanted vaccine groups. Twenty one days after the second dose, SCR and SPR rates increased in all vaccine groups (i.e. 4.0%-40.8% and 4.0%-42.9% respectively in the plain H5N1 vaccine groups, versus 82.0%-95.9% and 84.0%-95.9% respectively in the H5N1 adjuvanted vaccine groups). At this timepoint, the SCF ranged from 1.2 to 3.9 in the plain H5N1 vaccine groups, as compared to 27.9 to 60.5 in the H5N1 adjuvanted vaccine groups. For each dosage and at all timepoints, higher immunogenicity results were observed with the adjuvanted formulation as compared to the plain formulation. All four adjuvanted formulations fulfilled the three CHMP criteria for annual registration procedures of influenza vaccines after the second dose, while none of the non-adjuvanted groups fulfilled all three criteria. The measurement of anti-HA antibody titres against an H5N1 heterologous strain (A/Indonesia/05/2005) indicated that a cross-reactive immune response against strain variation was induced in the adjuvanted vaccine groups. A high neutralizing antibody response against the vaccine strain was elicited with all adjuvanted formulations. In the lowest dose group (3.8µg HA/AS03), all subjects except one were seropositive for neutralizing antibodies after the second dose, with a SCR of 85.7%. The seropositivity and SCR for neutralizing antibodies against a heterologous strain (A/Indonesia/05/2005) were 87.5% and 77.1% respectively in the 3.8µg HA/AS03 vaccine group.

At day 180, SCR for anti-HA antibodies against A/Vietnam/1194/2004 remained higher in the adjuvanted vaccine groups (52.0-62.0%) than in the non-adjuvanted vaccine groups (4.0-35.4%). In all adjuvanted groups, the SCF remained above the CHMP criteria. Similarly, SPR for the adjuvanted groups were statistically higher at Day 180 (54.0% to 64.0%), as compared to the non-adjuvanted groups (4.0% to 37.5%) except for the highest antigen dose. None of the vaccine groups reached the CHMP criterion for SPR (>70%) at Day 180. The decline in SPR from Day 42 to Day 180 was between 22.9% and 34.7% in the adjuvanted groups.

SCR, SPR and SCF were 52.0%, 54.0% and 4.4 respectively at Day 180 with the adjuvanted vaccine containing 3.8 µg HA. In terms of neutralizing antibodies at Day 180, seropositivity rates of 98.0% and SCR of 72.0% were obtained in that same vaccine group.

Incidence rates of local and general solicited symptoms with the D-Pan pandemic influenza vaccine were clinically acceptable. No SAEs were reported during the active study period (up to Day 51) in any group. None of the SAEs reported during the extended safety follow-up (up to Day 180) was considered related to vaccination by the investigator.

2.7.3.3 Comparison and Analyses of Results across Studies

2.7.3.3.1 Study Populations

Inclusion/Exclusion criteria

The inclusion and exclusion criteria applied in all studies included in this summary (Q-Pan-001, Q-Pan-002 and H5N1-007) are listed below.

In order to enter the trials, all subjects had to fulfil the following inclusion criteria:

- A male or female between the ages specified in the protocol at the time of the first vaccination.
- Subjects for whom the investigator believed they could and would comply with the requirements of the protocol (e.g., ability to comprehend and comply with procedures for collection of data such as completion of the diary cards, return for follow-up visits).
- Healthy subjects as established by medical history and clinical examination before entering into the study. In study Q-Pan-002, subjects >49 years of age could be enrolled when they had a stable health status (as defined by absence of a health event satisfying the definition of a serious adverse event, or a change in an ongoing drug therapy due to therapeutic failure or symptoms of drug toxicity).
- Written informed consent obtained from the subject.

The exclusion criteria common to all studies included in this summary were:

- Administration of any vaccine during the period before the first administration of the study vaccine and after the second one, as specified in the protocol.

- Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying or cytotoxic drugs within the protocol-define period before first administration of the study vaccine. (For corticosteroids, this meant prednisone, or equivalent, ≥0.5 mg/kg/day for H5N1-007, and ≥ 10 mg/day for Q-Pan-001 and -002. Inhaled and topical steroids are allowed.).

- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination (no laboratory testing required).

- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.

- Acute disease at the time of enrolment. (Acute disease is defined as the presence of a moderate or severe illness with or without fever (defined as axillary temperature ≥37.5°C or oral temperature ≥37.8 ºC).

- Administration of immunoglobulins and/or any blood products within the three months preceding the first administration of the study vaccine or during the study.

- Lactating women.

- Women of child bearing potential that lack a history of reliable contraceptive practices (as defined by the protocol) and pregnant women were excluded from the study. In study H5N1-007, the following inclusion criterion was handled for female subjects: she was to be of non-childbearing potential (i.e., either surgically sterilized or one year post-menopausal); or, if of childbearing potential, she was to be abstinent or using adequate contraceptive precautions for 30 days prior to first vaccination, have a negative pregnancy test and agree to continue such precautions for two months after completion of the vaccination series.

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days prior to the first vaccination, or planned use during the study period.

The following exclusion criteria were specific for pivotal studies Q-Pan-001 and Q-Pan-002:

- Diagnosed with cancer, or treatment for cancer, within 3 years.

- Any significant disorder of coagulation or treatment with Coumadin derivatives or heparin.
- Known receipt of analgesic or antipyretic medication on the day of vaccination.
- Evidence of substance abuse or of neurological or psychiatric diagnoses rendering the subject unable/unlikely to provide accurate safety reports.

Other exclusion criteria applicable in specific studies included:

- Blood pressure abnormalities, defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg (Q-Pan-001 only).

- Administration of an influenza vaccine other than the study vaccines during the entire study period (H5N1-007) or previous administration of any H5N1 vaccine (Q-Pan-002).

- History of hypersensitivity to vaccines (Q-Pan-001 and H5N1-007).

- Acute clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests (H5N1-007). Significant acute or chronic, uncontrolled medical or psychiatric illness (Q-Pan-001).

The number of subjects enrolled in pivotal studies Q-Pan-001 and Q-Pan-002, and the number of subjects excluded from the ATP analyses with reasons for exclusion are given in Table 6 and Table 7, respectively.

The number of subjects enrolled in supportive study H5N1-007 and the number of subjects excluded from the ATP analyses with reasons for exclusion are given in Table 8.

Table 6 Number of subjects enrolled in pivotal study Q-Pan-001 and the number of subjects excluded from ATP analyses at Day 182 with reasons for exclusion (Total cohort)

Study	**Q-Pan-001**				
Study groups	**H5N1 Split Quebec source (HA 3.8 µg) AS03 full**	**H5N1 split Quebec source (HA 3.8 µg) AS03 half**	**H5N1 split Quebec source (HA 3.8 µg) Without AS03**	**H5N1 split Dresden source (HA 3.8 µg) AS03 full**	**H5N1 split Dresden source (HA 3.8 µg) AS03 half**
Number of subjects enrolled and vaccinated (Total Vaccinated Cohort)	**152**	**151**	**78**	**151**	**148**
Administration of vaccine(s) forbidden in the protocol (code 1040)	1	1	0	2	1
Randomisation failure (code 1050)	1	0	0	0	0
Others (reacto) (code 1500)	1	1	0	0	0
Subjects included in the ATP analysis of safety (ATP Safety cohort)	**149**	**149**	**78**	**149**	**147**
Non compliance with vaccination schedule (including wrong and unknow dates) (code 2080)	5	3	3	8	3
Non compliance with blood sampling schedule (including wrong and unknow dates (code 2090)	0	0	0	1	1
Subjects included in the ATP analysis of immunogenicity (AT Immunogenicity cohort)	**144**	**146**	**75**	**140**	**143**

Note: subjects may have more than one elimination code assigned. The number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number is presented.

Full"*(or "Half")* AS03 dose corresponds to the same *(or "Half" the)* adjuvant content as contained in the vaccine formulation

H5N1 Quebec source: H5N1 antigen produced at GSK Biologicals' manufacturing site in Quebec; H5N1 Dresden source: H5N1 antigen produced at GSK Biologicals' manufacturing site in Dresden

Table 7 Number of subjects enrolled by age strata in pivotal study Q-Pan-002 and the number of subjects excluded from ATP analyses at Day 42 with reason for withdrawal (Total vaccinated cohort)

Study groups	Age group 18-60 years			Age group >60 years		
	Total	Q-Pan	Placebo	Total	Q-Pan	Placebo
Number of subjects enrolled and vaccinated (Total vaccinated cohort)	**2889**	**2172**	**717**	**1672**	**1250**	**422**
Administration of vaccine(s) forbidden in the protocol (code 1040)	18	12	6	7	5	2
Study vaccine dose not administered according to protocol (code 1070)	98	68	30	39	30	9
Subjects included in the ATP analysis of safety (ATP Safety cohort)	**2773**	**2092**	**681**	**1626**	**1215**	**411**
Number of Subjects to be tested for Immunogenicity Analysis	**1666**	**1594**	**72**	**554**	**506**	**48**
Protocol violation (inclusion/exclusion criteria) (code 2010)	0	0	0	6	3	3
Administration of any medication forbidden by the protocol (code 2040)	4	4	0	11	6	5
Non compliance with vaccination schedule (including wrong and unknown dates) (code 2080)	25	21	4	7	4	3
Non compliance with blood sampling schedule (including wrong and unknown dates) (code 2090)	32	24	8	23	16	7
Essential serological data missing (code 2100)	18	17	1	1	1	0
Subject not planned to be tested for their all blood samples (code 2130)	1138	538	600	1051	706	345
Subjects included in the ATP analysis of immunogenicity (ATP Immunogenicity cohort)	**1556**	**1488**	**68**	**527**	**479**	**48**

Note: Subjects may have more than one elimination code assigned
The number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number is presented
No subjects were excluded from analyses due to protocol deviations occurring after Day 42; i.e., all subjects in the ATP cohorts for immunogenicity and for safety in the Day 42 analysis remained so for the Day 182 analysis, providing they had data.

Table 8 Number of subjects enrolled in supportive study H5N1-007 and the number of subjects excluded from ATP analyses with reasons for exclusion (Total cohorts)

Study N°	**H5N1-007**							
Study groups	**H5N1 split** (HA 30 µg)	**H5N1 split** (HA 15 µg)	**H5N1 split** (HA 7.5 µg)	**H5N1 split** (HA 3.8 µg)	**H5N1 split** (HA 30 µg, AS03)	**H5N1 split** (HA 15 µg, AS03)	**H5N1 split** (HA 7.5 µg, AS03)	**H5N1 split** (HA 3.8 µg, AS03)
Number of subjects enrolled (Total Cohort)	**50**	**50**	**50**	**50**	**49**	**50**	**50**	**51**
Administration of vaccine(s) forbidden in the protocol (code 1040)	0	0	0	0	1	0	0	0
Subjects included in the ATP analysis of safety (ATP Safety cohort)	**50**	**50**	**50**	**50**	**48**	**50**	**50**	**51**
Non compliance with blood sampling schedule (including wrong and unknown dates (code 2090)	1	1	1	0	0	1	0	1
Subjects included in the ATP analysis of immunogenicity (ATP Immunogenicity cohort)	**49**	**49**	**49**	**50**	**48**	**49**	**50**	**50**

Note: subjects may have more than one elimination code assigned. The number of subjects with the elimination code assigned excluding subjects who have been assigned a lower elimination code number is presented.

Demographic characteristics

The demographic characteristics of subjects enrolled in pivotal studies Q-Pan-001 and Q-Pan-002 are presented for the ATP immunogenicity cohort in Table 9 and Table 10, respectively. All subjects were above 18 years of age. In both studies, the majority of subjects were White Caucasians (86.7% in Q-Pan-001 and 86.2%-94.9% in the two age strata in Q-Pan-002).

The demographic profile for the different treatment groups and the two age strata in Q-Pan-002 were comparable with respect to gender and racial distribution.

Table 9 Summary of Demographic Characteristics of subjects included in pivotal study Q-Pan-001 (all study groups) - ATP cohort for immunogenicity

		Total N = 650	
Characteristics	**Parameters or Categories**	**Value or n**	**%**
Age (years)	Mean	38.7	-
	SD	12.14	-
	Median	39.0	-
	Minimum	18	-
	Maximum	64	-
Age Category	18-40	355	54.8
	41-64	293	45.2
Gender	Female	372	57.4
	Male	276	42.6
Ethnic	American hispanic or latino	97	15.0
	Not american hispanic or latino	551	85.0
Race	African heritage / african american	36	5.5
	American indian or alaskan native	1	0.2
	Asian - central/south asian heritage	1	0.2
	Asian - east asian heritage	5	0.8
	Asian - japanese heritage	0	0.0
	Asian - south east asian heritage	8	1.2
	Native hawaiian or other pacific island	3	0.5
	White - arabic / north african heritage	6	0.9
	White - caucasian / european heritage	562	86.7
	Other	26	4.0

N = total number of subjects; n/% = number / percentage of subjects in a given category
Value = value of the considered parameter; SD = standard deviation

Table 10 Summary of Demographic Characteristics of subjects included in pivotal study Q-Pan-002 by age strata (all study groups) - ATP cohort for immunogenicity

Age group		18-60 years N =1556		> 60 years N =527	
Characteristics	**Parameters / Categories**	**Value or n**	**%**	**Value or n**	**%**
Age (years)	Mean	37.1	-	70.3	-
	Sd	12.75	-	6.17	-
	Median	37.0	-	69.0	-
	Minimum	18	-	61	-
	Maximum	60	-	89	-
Gender	Male	891	57.3	302	57.3
	Female	665	42.7	225	42.7
Race	African heritage / african american	145	9.3	14	2.7
	American indian or alaskan native	11	0.7	1	0.2
	Asian - central/south asian heritage	2	0.1	1	0.2
	Asian - east asian heritage	1	0.1	2	0.4
	Asian - japanese heritage	2	0.1	0	0.0
	Asian - south east asian heritage	7	0.4	1	0.2
	Native hawaiian or other pacific islande	1	0.1	0	0.0
	White - arabic / north african heritage	20	1.3	7	1.3
	White - caucasian / european heritage	1341	86.2	500	94.9
	Other	26	1.7	1	0.2

N = total number of subjects
n = number of subjects in a given category
Value = value of the considered parameter
% = n / Number of subjects with available results x 100; SD= standard deviation

The demographic characteristics of subjects enrolled in supportive study H5N1-007 are presented in Table 11 for the ATP immunogenicity cohort. All subjects were above 18 years of age. The majority of subjects were White Caucasians (99.7%). There were no major differences in demographic characteristics between the individual groups.

Table 11 Summary of Demographic Characteristics of subjects included in supportive D-Pan study H5N1-007 - ATP cohort for immunogenicity

Study		**H5N1-007**	
Characteristics	**Parameters/**	**N = 394**	
	Categories	Value or n	%
Age	Mean	34.3	-
(years)	SD	12.79	-
	Median	30.5	-
	Minimum	18	-
	Maximum	60	-
Gender	Male	181	45.9
	Female	213	54.1
Race	African heritage / African American	0	0.0
	American Indian or Alaskan native	0	0.0
	Asian - Central/South Asian heritage	1	0.3
	Asian - East Asian heritage	0	0.0
	Asian - South East Asian heritage	0	0.0
	Native Hawaiian or other pacific islanders	0	0.0
	White - Arabic / North African heritage	0	0.0
	White - Caucasian / European heritage	393	99.7
	Other	0	0.0

*Immunogenicity subset
N = total number of subjects
Value or n = value of the considered parameter or number of subjects in a given category
% = n / Number of subjects with available results x 100; SD= standard deviation

Study completion and drop-out

A total of 236 subjects (4.18%) from the total vaccinated cohort dropped out from the 3 clinical trials included in this summary: 18 subjects or 2.6% by Day 182 in study Q-Pan-001 and 218 subjects or 4.8% by Day 182 in study Q-Pan-002. Of note, no subjects were withdrawn from supportive study H5N1-007.

The reasons for drop-out are summarized in Table 12.

Table 12 Study completion and reasons for drop-out in pivotal studies Q-Pan-001 and Q-Pan-002, and in supportive D-Pan study H5N1-007 (total vaccinated cohort)

	Study			Total
	Q-Pan-001	Q-Pan-002	H5N1-007	
Number of subjects enrolled and vaccinated	680	4561	400	**5641**
Number of subjects completed	662	4343	400	**5405**
Number of subjects dropped-out	18	218	0	**236**
Reasons for drop-out				
Serious adverse event	0	9	-	9
Non-serious adverse event	0	5	-	5
Protocol violation	0	2	-	2
Consent withdrawal (not due to an adverse event)	5	40	-	45
Migrated/moved from study area	4	22	-	26
Lost to follow-up (subjects with incomplete vaccination course)	0	37	-	37
Lost to follow-up (subjects with complete vaccination course)	9	82	-	91
Others	0	21	-	21

Q-Pan-001 and Q-Pan-002: number of subjects who dropped out by Day 182:

The majority of subjects who dropped out were either lost to follow up or withdrew their consent for reasons not associated with an adverse event. Two subjects (study Q-Pan-002) were identified as drop-out due to protocol violation.

In pivotal study Q-Pan-001, none of the subjects dropped out due to a serious or a non-serious adverse event.

In pivotal study Q-Pan-002, 9 subjects dropped out due to a SAE by Day 182 (4 subjects vaccinated with Q-Pan vaccine and 5 placebo recipients). None of these SAEs were considered by the investigator to be related to vaccination. These SAEs are briefly described below and are also detailed in Section 2.7.4.2.1.3:

Four SAEs (including 3 fatal cases) resulted in premature discontinuation from study Q-Pan-002 among Q-Pan vaccine recipients. In addition, one subject (1663), which was recorded as lost to follow-up in the Q-Pan group, experienced a fatal SAE that was reported at later stage and is described below as well:

- a 59-year-old male (Subject 4253), experienced a myocardial infarction 17 days following one dose of the Q-Pan vaccine, and died. The subject had a history of diabetes mellitus and hypercholesterolemia.
- a 53-year-old male (Subject 6568), presented with aggravated diabetes mellitus and exacerbation of liver disease 154 days following 2 doses of Q-Pan vaccine, and died. The subject had a history of high blood pressure and type II diabetes, an additional history of alcohol abuse, hepatic cirrhosis, and gastrointestinal bleeding as the proximate cause of death were obtained post mortem.
- a 69-year-old female (Subject 4308), presented with a malignant neoplasm of unknown type 155 days following 2 doses of Q-Pan vaccine, and died.
- a 76-year old male (Subject 1041) was hospitalized and found to have septic arthritis of the knee 133 days after his second dose of Q-Pan vaccine. The subject had a history of rheumatic heart disease, hypertension, mitral valve regurgitation, peripheral vascular disease, left bundle branch block, increased ocular pressure, right rotator cuff tear, osteoarthritis, right inguinal hernia, and benign prostatic hyperplasia. While hospitalized, he experienced a pulmonary embolus on Day 142, and subsequently developed a lumbar spinal cord compression due to a lumbar abscess on Day 158. The latter event was treated surgically. The events were ongoing at the cut-off date for the study report.
- a 78-year-old female (Subject 1663), had metastases to the liver and presumptive metastatic ovarian cancer 168 days following one dose of Q-Pan vaccine, and died after a brief clinical course. The subject had a remote history of ovarian cancer in 1988; histology of the liver metastases was compatible with, but apparently not diagnostic of, ovarian origin

Five SAEs (including 2 fatal SAEs) resulted in premature discontinuation from study Q-Pan-002 among placebo recipients:

- a 73-year old male (Subject 6120) with hypertension and chronic obstructive lung disease was diagnosed with a malignant brain neoplasm of unknown type on [redacted] 20[redacted], Day 42 following 2 doses of placebo. Palliative therapy was given on an outpatient basis and the subject died on [redacted] 20[redacted]
- a 60-year-old male (Subject 6567) developed cardiomegaly secondary to chronic obstructive pulmonary disease, 25 days following 2 doses of placebo, and died. A coroner's report listed cardiomegaly as the proximate cause of death. The subject also had a history of morbid obesity and sleep apnea.
- a 68-year-old male (Subject 6307) with a history of myocardial infarction, coronary artery disease, diabetes mellitus, dyslipidemia, hypotension, hypothyroidism, and shoulder pain was hospitalized for dehydration on Day 3 following the first dose of placebo. While hospitalized he experienced shoulder pain similar to his prior episodes. Cardiac catheterization was performed, significant coronary artery disease was noted, and coronary artery stents were placed. The event resolved in 3 days.
- a 39-year-old female (Subject 3701), presented with flu-like symptoms 18 days after the first dose of placebo. Two days later, the subject was diagnosed with influenza B and was treated with oseltamivir. However, the diagnosis subsequently was changed

to pneumococcal pneumonia and she was hospitalized briefly for antibiotic treatment. The event resolved 13 days after onset.

- a 58-year old male (Subject 7937) experienced a cerebrovascular stroke and carotid artery dissection on Day 51 following 2 doses of placebo. The event of carotid artery dissection resolved the following day. Stroke resolved 83 days after onset.

Five subjects included in pivotal study Q-Pan-002 experienced non-serious AEs leading to discontinuation up to Day 182 (3 subjects in Q-Pan vaccine group and 2 subjects in the placebo group). Further details regarding the non serious AEs that led to premature discontinuation of the study can be found in Section 2.7.4.2.1.4 and in the individual study report, located in Module 5.3.5.

2.7.3.3.2 Comparison of Efficacy Results of all Studies

2.7.3.3.2.1 Homologous HI antibody response (against vaccine strain)

Pivotal studies with the candidate Q-Pan pandemic influenza vaccine (Q-Pan-001 and Q-Pan-002)

The HI antibody response (in terms of GMTs, SCF, SCR and SPR) against vaccine strain H5N1 A/Indonesia/05/2005 in the ATP immunogenicity cohort of pivotal study Q-Pan-001 is presented in Table 13. Seropositivity rates for HI antibodies at pre-vaccination in study Q-Pan-001 are presented in Appendix Table 1.

The HI antibody response (in terms of GMTs, SCF, SCR and SPR) against vaccine strain H5N1 A/Indonesia/05/2005 in the ATP immunogenicity cohort of pivotal study Q-Pan-002 is presented in Table 14 for subjects aged 18-60 years and subjects aged >60 years.

A primary objective of study Q-Pan-001 was to demonstrate the AS03 adjuvant activity after receiving two doses of Q-Pan vaccine. Analyses to further evaluate the AS03 adjuvant activity for the Q-Pan vaccine in this study are presented in detail in Section 2.7.3.4.2.

The effect of age at vaccination based on immunogenicity results in healthy adults (18-60 years old) and in elderly subjects (>60 years old) in study Q-Pan-002 is further discussed in Section 2.7.3.3.1.

Study Q-Pan-001

Significantly higher GMTs were observed in the adjuvanted groups when compared to the non-adjuvanted group already after the first dose, and the observed difference is more significant after the second dose (Table 13). The amplitudes of the Day 42 HI antibody responses for the D-Pan and Q-Pan formulations were very similar when comparing results obtained by the groups receiving the same amount of adjuvant (i.e groups Q-Pan full dose AS03 versus D-Pan full dose AS03 and Q-Pan half dose AS03 versus D-Pan half dose AS03).

In terms of homologous SCR after a single vaccine dose, all adjuvanted groups, except one (D-Pan half dose AS03), reached the CHMP criterion of >40%. This criterion was easily fulfilled in all adjuvanted groups after Dose 2, while, in the non-adjuvanted group, the SCR after 2 doses (Day 42) was 17.3%. When comparing SCR obtained at Day 42 in the Q-Pan and D-Pan groups, the response was similar between groups receiving the same adjuvant doses (full or half dose), as evidenced by the broadly overlapping confidence intervals.

Similar conclusions can be drawn when evaluating the Day 42 seroprotection rates: SPR obtained in the adjuvanted groups range from 89.7% (Q-Pan half dose AS03) to 97.2% (Q-Pan full dose AS03), whereas the SPR obtained in non-adjuvanted group was 17.3%. The CHMP criterion of SPR >70% was met and exceeded for all adjuvanted vaccine groups. On the basis of the highly overlapping confidence intervals, Q-Pan and D-Pan vaccines presented similar results when formulated with the same adjuvant content. The Day 42 SPR for the full dose adjuvant groups was 97.2% (95%CI: 93.0 – 99.2%) with Q-Pan and 96.4% (95%CI: 91.9 – 98.8%) with D-Pan. For the half dose adjuvant groups this was 89.7% (95% CI: 83.6 – 94.1%) versus 92.3% (95% CI: 86.6 – 96.1%), respectively.

The third CHMP criterion requires that SCF exceed 2.5. This criterion is already fulfilled by all adjuvanted groups after the first dose of vaccine, whereas it is not met at any timepoint by the non-adjuvanted group. After the second dose, a further increase to high SCF values is observed for the adjuvanted groups, ranging from 30 to more than 40-fold depending on adjuvant dose. Again, very similar values were obtained for Q-Pan and D-Pan groups when they were formulated with the same adjuvant content. SCFs were 92.9 (95% CI, 76.7 - 112.7) and 95.3 (95% CI, 77.3 - 117.5) when adjuvanted with full dose AS03, and 64.1 (95% CI, 49.4 – 83.3) and 69.0 (95% CI, 54.0 - 88.3) when adjuvanted with half dose AS03, for Q-Pan and D-Pan vaccines, respectively.

Study Q-Pan-002

HI antibody GMTs after a 2-dose vaccination schedule with AS03 adjuvanted Q-Pan vaccine reached 258.0 in subjects aged 18-60 years and to 89.0 in subjects aged >60 years, whereas in the placebo group HI titers at Day 42 remained low or undetectable (5.0-5.5) (Table 14).

After 2 doses of Q-Pan vaccine (Day 42), the SCRs were 91.0% for the 18 to 60 years of age stratum and 76.4% for the > 60 years of age stratum. These rates well exceeded the CHMP targets of 40% SCR for 18-60 year olds and 30% SCR for >60 year olds.

Recipients of Q-Pan vaccine in both age strata also exceeded the CHMP thresholds for SPR (70% for 18-60 years; 60% for >60 years), with a SPR of 91.0% for the 18 to 60 years age stratum and a SPR of 76.8% for the > 60 years age stratum.

The SCR and SPR in the adult age group of study Q-Pan-002 (both 91.0%) was similar to the SCR and SPR obtained in adults in study Q-Pan-001 (range 89.7% to 97.2% in adjuvanted groups).

SCFs measured by HI titer from baseline to Day 42 in study Q-Pan-002 were 51.4 for the 18 to 60 years age stratum and 17.2 for the > 60 years age stratum, both of which results exceeded the CHMP criteria (2.5 and 2.0 for the 2 age strata respectively).

Supportive study H5N1-007 with D-Pan H5N1 pandemic influenza vaccine

Supportive immunogenicity results with D-Pan vaccine (GMTs of HI antibodies, SCF, SCR and SPR) against vaccine strain H5N1 A/Vietnam/1194/2004 in the ATP immunogenicity cohort are presented for study H5N1-007 in Table 15. Results in initially seronegative subjects from the ATP immunogenicity cohort of dose-finding study H5N1-007 are included in Table 16. Seropositivity rates for HI antibodies at pre-vaccination are presented in Appendix Table 2.

Analyses performed to evaluate, in study H5N1-007, the effect of antigen dose and the interaction between antigen dose and adjuvantation are presented in Section 2.7.3.4.1.

In study H5N1-007 (0, 21 day schedule), the immunogenicity of different doses (30, 15, 7.5 and 3.8µg HA) of D-Pan monovalent split virus vaccine (H5N1) adjuvanted with AS03 was assessed, in comparison with similar dose groups formulated without AS03. The following discussion will focus on results from the ATP immunogenicity cohort.

The percentage of subjects initially seropositive for the H5N1 vaccine strain ranged from 0.0% to 4.1% across all vaccine groups (Appendix Table 2). Twenty one days after the first dose, SCR between 24.0% and 58.3% were observed in the adjuvanted vaccine groups, versus 0.0% to 26.5% in the unadjuvanted groups (Figure 1). The CHMP requirement for SCR (>40%) was reached after the first dose in all adjuvanted vaccine groups except 3.8µg HA/AS03. SCR after the second dose greatly exceeded the threshold required by CHMP in all adjuvanted vaccine groups, as illustrated by values ranging from 82.0% to 95.9%. At Day 42, the CHMP criterion was fulfilled with the non-adjuvanted vaccine containing 30µg HA (borderline value of 40.8%), but not with the other non-adjuvanted vaccine formulations (Table 15).

Prior to vaccination, only three subjects (1 in group 15µg HA, 1 in group 7.5µg HA/AS03 and 1 in group 3.8µg HA/AS03) had levels of antibodies ≥ 1:40. SPR ranged from 26.0% to 58.3% in the adjuvanted vaccine groups, as compared to 0.0% to 28.6% in the plain vaccine groups after the first dose (Figure 2). SPR did not reach the pre-defined CHMP requirement (>70%) in any of the vaccine groups at Day 21.

No group receiving non-adjuvanted formulations reached seroprotective levels above 70% after the second dose (Day 42) (values ranged from 4.0 % to 42.9%). At Day 42, seroprotective levels above 70% were obtained in all four adjuvanted D-Pan vaccine groups. SPR values in the latter groups ranged from 84.0% to 95.9% (Table 15), which is comparable to the homologous SPR results obtained with Q-Pan vaccine in studies Q-Pan-001 and Q-Pan-002 (Table 13 and Table 14).

The SCF after the second vaccination varied from 27.9 to 60.5 in the adjuvanted groups and from 1.2 to 3.9 in the non-adjuvanted groups (Figure 3). SCF in the adjuvanted groups were far superior to the 2.5 fold increase in GMT required by CHMP for annual relicensing of interpandemic vaccines in adults. Of note, all adjuvanted groups except the lowest antigen concentration (3.8µg HA/AS03) had already achieved a SCF of >2.5 after the first vaccination. Regarding the non-adjuvanted formulations, the two groups

receiving the highest antigen doses (15µg HA and 30 µg HA) reached the CHMP requirement at Day 42, and at Day 21 for 30 µg HA only.

At both time points (Day 21 and Day 42), SCR, SPR and SCF were higher in the adjuvanted vaccine groups as compared to the non-adjuvanted groups.

Pre-vaccination GMTs were within the same range in all vaccine groups. Following the first dose, a minor increase in anti-HA antibody levels was seen in all non-adjuvanted groups in a dose dependent manner (Figure 4). In the adjuvanted groups, a more prominent increase in anti-HA antibody levels was observed after the first dose, with the highest GMT obtained in the group receiving the highest antigen dose (30µg HA/AS03). Post second vaccination, GMTs in the non-adjuvanted groups increased slightly. Significantly higher GMTs were observed after the second vaccination in all adjuvanted groups, with a dose dependent increase in GMTs observed from 3.8 µg to 15 µg HA/AS03. There was no overlap of 95% CI between either of the adjuvanted groups with either of the non-adjuvanted groups at day 42 (Table 15).

Of note, the GMT of the adjuvanted group receiving the lowest antigen dose tested (3.8µg HA/AS03) was still 7.5 fold higher than the highest GMT achieved in the non-adjuvanted groups (i.e. following 30 µg HA).

Immunogenicity results obtained in initially seronegative subjects in study H5N1-007 were consistent with those reported in the ATP cohort for immunogenicity (Table 16).

Table 13 HI responses against vaccine strain H5N1 A/Indonesia/05/2005 of the Q-Pan and D-Pan monovalent pandemic influenza A vaccines (H5N1) in study Q-Pan-001 (ATP immunogenicity cohort)

Study (Age of vaccination)	Time-point	Strain	Manuf. site‡	HA (µg / dos	AS03	N	GMT			SCF			SCR			SPR		
							Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	Pre	H5N1 Indonesia	Quebec	3.8	AS03	144	**5.0**	5.0	5.0	-	-	-	-	-	-	**0.0**	0.0	2.5
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	**5.0**	5.0	5.0	-	-	-	-	-	-	**0.0**	0.0	2.5
		H5N1 Indonesia	Quebec	3.8	-	75	**5.0**	5.0	5.0	-	-	-	-	-	-	**0.0**	0.0	4.8
		H5N1 Indonesia	Dresden	3.8	AS03	140	**5.0**	5.0	5.1	-	-	-	-	-	-	**0.0**	0.0	2.6
		H5N1 Indonesia	Dresden	3.8	AS03/2	143	**5.0**	5.0	5.1	-	-	-	-	-	-	**0.0**	0.0	2.5
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	144	**22.5**	17.8	28.6	**4.5**	3.6	5.7	**41.7**	33.5	50.2	**41.7**	33.5	50.2
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	**19.9**	15.7	25.3	**4.0**	3.1	5.1	**41.1**	33.0	49.5	**41.1**	33.0	49.5
		H5N1 Indonesia	Quebec	3.8	-	75	**6.1**	5.2	7.1	**1.2**	1.0	1.4	**6.7**	2.2	14.9	**6.7**	2.2	14.9
		H5N1 Indonesia	Dresden	3.8	AS03	140	**23.5**	18.3	30.3	**4.7**	3.6	6.0	**45.7**	37.3	54.3	**45.7**	37.3	54.3
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	**16.8**	13.5	20.9	**3.3**	2.7	4.1	**38.0**	30.0	46.5	**38.0**	30.0	46.5
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	144	**464.7**	383.4	563.4	**92.9**	76.7	112.7	**97.2**	93.0	99.2	**97.2**	93.0	99.2
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	**320.7**	246.9	416.6	**64.1**	49.4	83.3	**89.7**	83.6	94.1	**89.7**	83.6	94.1
		H5N1 Indonesia	Quebec	3.8	-	75	**10.5**	8.2	13.5	**2.1**	1.6	2.7	**17.3**	9.6	27.8	**17.3**	9.6	27.8
		H5N1 Indonesia	Dresden	3.8	AS03	140	**480.3**	390.5	590.7	**95.3**	77.3	117.5	**96.4**	91.9	98.8	**96.4**	91.9	98.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	**347.7**	272.0	444.5	**69.0**	54.0	88.3	**92.3**	86.6	96.1	**92.3**	86.6	96.1

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); GMR = Geometric Mean Ratio; SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

Table 14 HI responses against vaccine strain H5N1 A/Indonesia/05/2005 of the AS03 adjuvanted Q-Pan H5N1 pandemic influenza vaccine in study Q-Pan-002 (ATP immunogenicity cohort)

Study (Age of vaccination)	Age group	Time-point	Study group	N	GMT			SCF			SCR			SPR		
					Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	1488	**5.0**	5.0	5.0	-	-	-	-	-	-	**0.0**	0.0	0.2
			Placebo	68	**5.0**	5.0	5.0	-	-	-	-	-	-	**0.0**	0.0	5.3
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	1488	**258.0**	239.7	277.7	**51.4**	47.8	55.3	**91.0**	89.4	92.4	**91.0**	89.4	92.4
			Placebo	68	**5.2**	4.9	5.5	**1.0**	1.0	1.1	**1.5**	0.0	7.9	**1.5**	0.0	7.9
	>60 years	Pre	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	479	**5.2**	5.0	5.3	**-**	-	-	**-**	-	-	**0.4**	0.1	1.5
			Placebo	48	**5.0**	5.0	5.0	**-**	-	-	**-**	-	-	**0.0**	0.0	7.4
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	479	**89.0**	77.1	102.7	**17.2**	14.9	19.9	**76.4**	72.3	80.1	**76.8**	72.8	80.5
			Placebo	48	**5.5**	4.6	6.5	**1.1**	0.9	1.3	**2.1**	0.1	11.1	**2.1**	0.1	11.1

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); GMR = Geometric Mean Ratio; SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

Table 15 HI responses against vaccine strain H5N1 A/Vietnam/1194/2004 of the D-Pan monovalent pandemic influenza A vaccine (H5N1) in adults from study H5N1-007 (ATP immunogenicity cohort)

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	GMT			SCF			SCR			SPR		
						Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
							LL	UL		LL	UL		LL	UL		LL	UL
H5N1-007	Pre	H5N1 split	30	-	49	5.2	4.8	5.6	-	-	-	-	-	-	0.0	0.0	7.3
18-60 yrs		H5N1 split	15	-	49	5.3	4.8	5.9	-	-	-	-	-	-	2.0	0.1	10.9
		H5N1 split	7.5	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	3.8	-	50	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.1
		H5N1 split	30	AS03	48	5.1	4.9	5.5	-	-	-	-	-	-	0.0	0.0	7.4
		H5N1 split	15	AS03	49	5.1	4.9	5.2	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	7.5	AS03	50	5.4	4.8	6.0	-	-	-	-	-	-	2.0	0.1	10.7
		H5N1 split	3.8	AS03	50	5.4	4.8	6.0	-	-	-	-	-	-	2.0	0.1	10.7
	Post I (D21)	H5N1 split	30	-	49	14.1	8.9	22.6	2.7	1.7	4.3	26.5	14.9	41.1	28.6	16.6	43.3
		H5N1 split	15	-	49	10.4	6.9	15.6	1.9	1.3	2.8	20.4	10.2	34.3	20.4	10.2	34.3
		H5N1 split	7.5	-	49	6.8	5.4	8.7	1.4	1.1	1.7	8.2	2.3	19.6	8.2	2.3	19.6
		H5N1 split	3.8	-	50	5.1	4.9	5.4	1.0	1.0	1.1	0.0	0.0	7.1	0.0	0.0	7.1
		H5N1 split	30	AS03	48	36.7	22.7	59.3	7.1	4.3	11.7	58.3	43.2	72.4	58.3	43.2	72.4
		H5N1 split	15	AS03	49	24.7	14.8	41.4	4.9	2.9	8.1	49.0	34.4	63.7	49.0	34.4	63.7
		H5N1 split	7.5	AS03	50	24.6	15.8	38.4	4.6	3.0	7.0	50.0	35.5	64.5	50.0	35.5	64.5
		H5N1 split	3.8	AS03	50	12.9	8.9	18.7	2.4	1.7	3.5	24.0	13.1	38.2	26.0	14.6	40.3
	Post II (D42)	H5N1 split	30	-	49	20.0	12.5	32.1	3.9	2.4	6.2	40.8	27.0	55.8	42.9	28.8	57.8
		H5N1 split	15	-	49	14.7	9.6	22.4	2.8	1.9	4.1	34.7	21.7	49.6	34.7	21.7	49.6
		H5N1 split	7.5	-	49	8.5	6.3	11.5	1.7	1.3	2.3	16.3	7.3	29.7	16.3	7.3	29.7
		H5N1 split	3.8	-	50	6.2	5.3	7.4	1.2	1.1	1.5	4.0	0.5	13.7	4.0	0.5	13.7
		H5N1 split	30	AS03	48	187.5	116.2	302.7	36.4	22.7	58.5	85.4	72.2	93.9	85.4	72.2	93.9
		H5N1 split	15	AS03	49	306.7	218.4	430.8	60.5	42.8	85.5	95.9	86.0	99.5	95.9	86.0	99.5
		H5N1 split	7.5	AS03	50	205.3	135.1	312.0	38.1	24.8	58.4	90.0	78.2	96.7	90.0	78.2	96.7
		H5N1 split	3.8	AS03	50	149.3	93.2	239.1	27.9	17.2	45.2	82.0	68.6	91.4	84.0	70.9	92.8

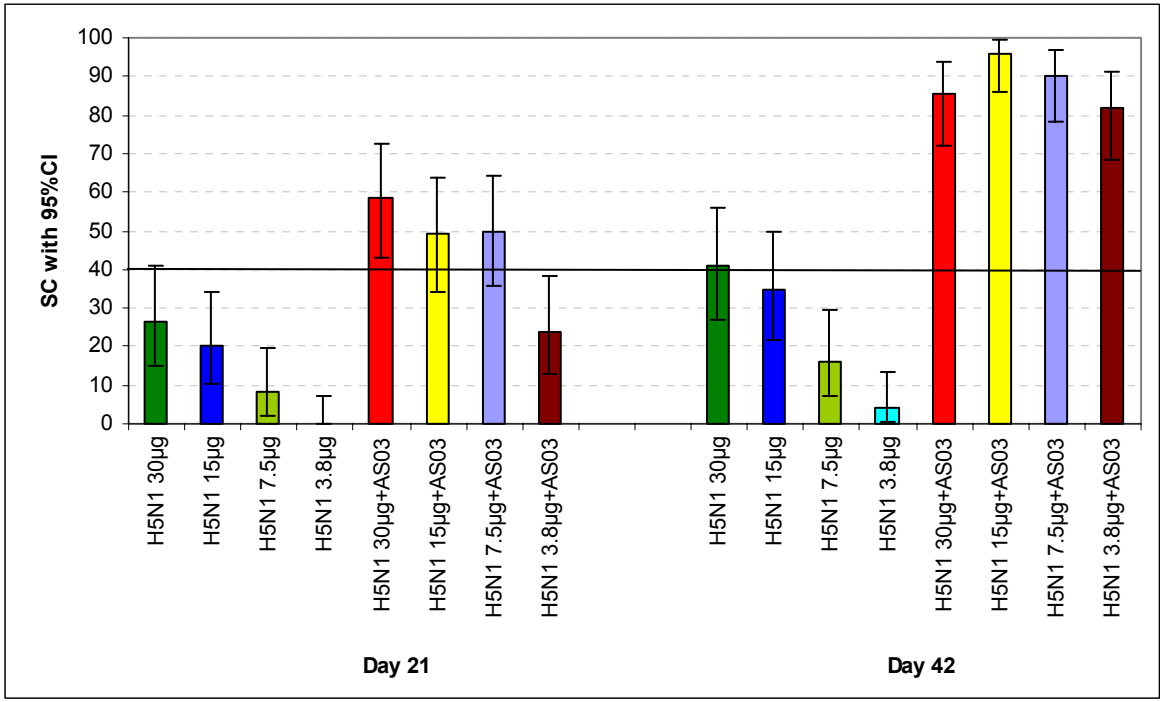
SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); GMR = Geometric Mean Ratio; SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

Table 16 HI responses against vaccine strain H5N1 A/Vietnam/1194/2004 of the D-Pan monovalent pandemic influenza A vaccine (H5N1) in adults from study H5N1-007 (initially seronegative subjects from the ATP immunogenicity cohort)

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	GMT			SCF			SCR			SPR		
						Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
							LL	UL		LL	UL		LL	UL		LL	UL
H5N1-007 18-60 yrs	Pre	H5N1 split	30	-	48	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.4
		H5N1 split	15	-	47	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.5
		H5N1 split	7.5	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.2
		H5N1 split	3.8	-	50	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.1
		H5N1 split	30	AS03	47	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.5
		H5N1 split	15	AS03	48	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.4
		H5N1 split	7.5	AS03	48	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.4
		H5N1 split	3.8	AS03	48	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.4
	Post I (D21)	H5N1 split	30	-	48	13.6	8.5	21.9	2.7	1.7	4.4	27.1	15.3	41.8	27.1	15.3	41.8
		H5N1 split	15	-	47	9.2	6.3	13.4	1.8	1.3	2.7	17.0	7.6	30.8	17.0	7.6	30.8
		H5N1 split	7.5	-	49	6.8	5.4	8.7	1.4	1.1	1.7	8.2	2.3	19.6	8.2	2.3	19.6
		H5N1 split	3.8	-	50	5.1	4.9	5.4	1.0	1.0	1.1	0.0	0.0	7.1	0.0	0.0	7.1
		H5N1 split	30	AS03	47	38.3	23.6	62.1	7.7	4.7	12.4	59.6	44.3	73.6	59.6	44.3	73.6
		H5N1 split	15	AS03	48	24.1	14.3	40.8	4.8	2.9	8.2	47.9	33.3	62.8	47.9	33.3	62.8
		H5N1 split	7.5	AS03	48	22.8	14.5	35.7	4.6	2.9	7.1	47.9	33.3	62.8	47.9	33.3	62.8
		H5N1 split	3.8	AS03	48	12.0	8.3	17.3	2.4	1.7	3.5	22.9	12.0	37.3	22.9	12.0	37.3
	Post II (D42)	H5N1 split	30	-	48	19.6	12.1	31.7	3.9	2.4	6.3	41.7	27.6	56.8	41.7	27.6	56.8
		H5N1 split	15	-	47	13.1	8.8	19.7	2.6	1.8	3.9	31.9	19.1	47.1	31.9	19.1	47.1
		H5N1 split	7.5	-	49	8.5	6.3	11.5	1.7	1.3	2.3	16.3	7.3	29.7	16.3	7.3	29.7
		H5N1 split	3.8	-	50	6.2	5.3	7.4	1.2	1.1	1.5	4.0	0.5	13.7	4.0	0.5	13.7
		H5N1 split	30	AS03	47	181.3	111.7	294.4	36.3	22.3	58.9	85.1	71.7	93.8	85.1	71.7	93.8
		H5N1 split	15	AS03	48	315.4	224.0	444.2	63.1	44.8	88.8	95.8	85.7	99.5	95.8	85.7	99.5
		H5N1 split	7.5	AS03	48	203.0	131.3	314.0	40.6	26.3	62.8	89.6	77.3	96.5	89.6	77.3	96.5
		H5N1 split	3.8	AS03	48	148.9	91.1	243.3	29.8	18.2	48.7	83.3	69.8	92.5	83.3	69.8	92.5

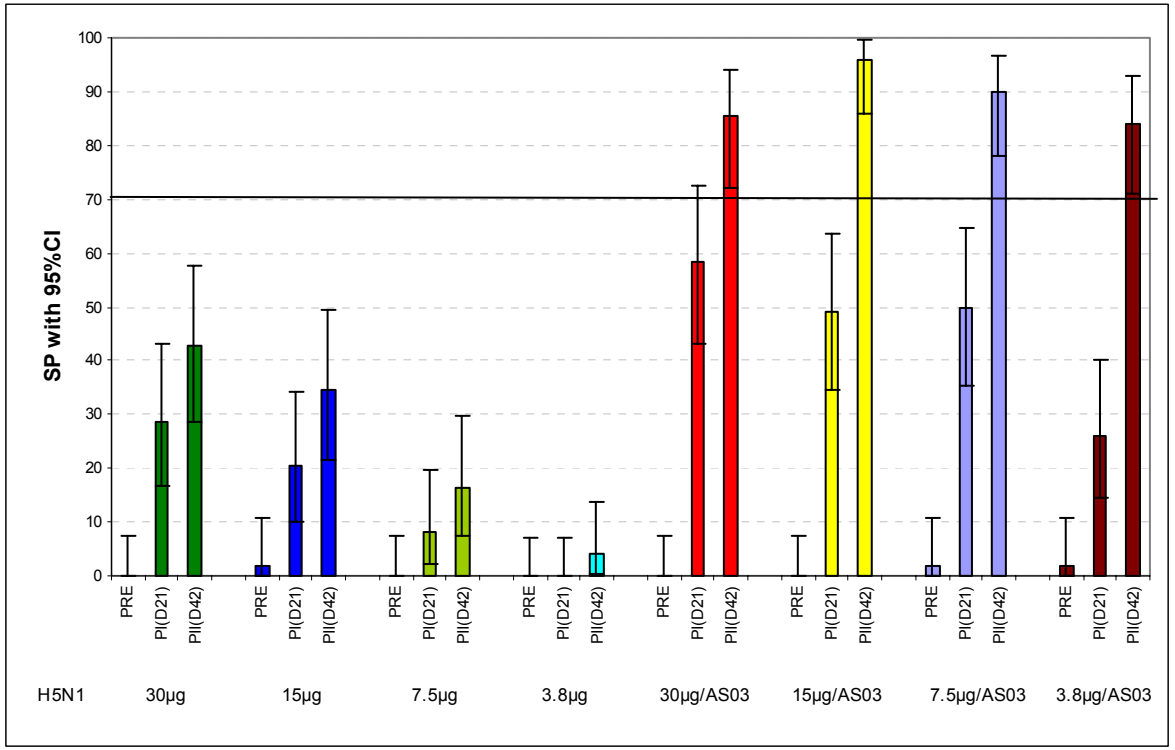
SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); SCR: seroconversion rate (i.e proportion of subjects who have a protective post-vaccination titre of ≥ 1:40); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

Figure 1 Seroconversion rates with 95% CI of serum anti-HA, day 0, 21, 42 in H5N1-007 (ATP immunogenicity cohort)



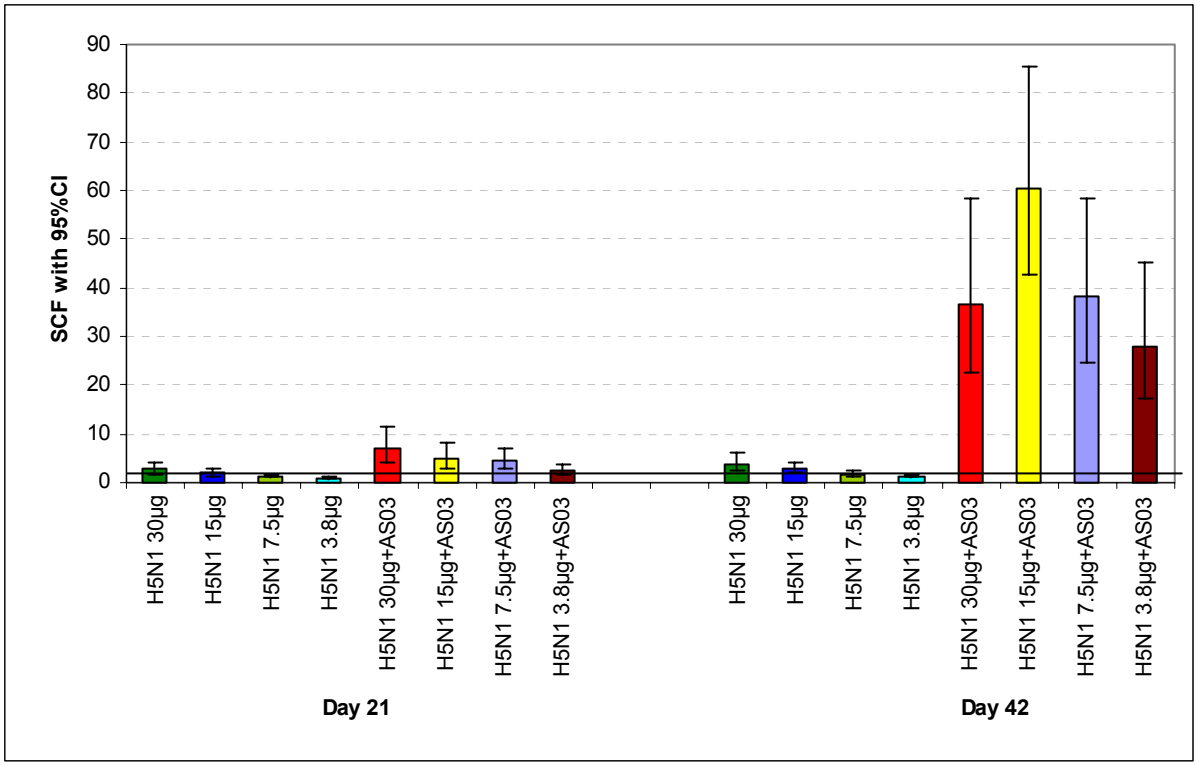
The horizontal line corresponds to the pre-defined CHMP criterion for seroconversion rates (>40%) in adults (18-60 years).

Figure 2 Seroprotection rates with 95% CI of serum anti-HA, day 0, 21, 42 in H5N1-007 (ATP immunogenicity cohort)



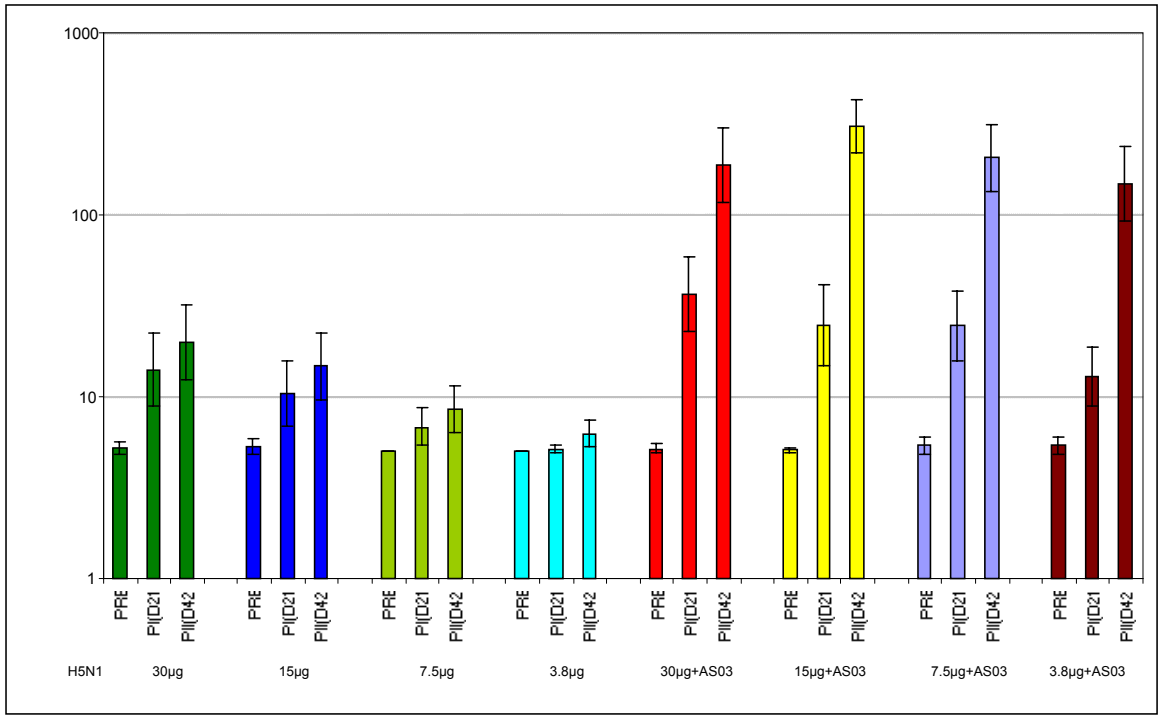
The horizontal line corresponds to the pre-defined CHMP criterion for seroprotection rates (>70%) in adults (18-60 years).

Figure 3 **Seroconversion factor (with 95%CI) for anti-HA antibody at post-vaccination (day 21 and 42) in H5N1-007 (ATP immunogenicity cohort)**



The horizontal line corresponds to the pre-defined CHMP criterion for seroconversion factors (>2.5) in adults.

Figure 4 GMT's with 95% CI of serum HA, day 0, 21, 42 in H5N1-007 (ATP immunogenicity cohort)



2.7.3.3.2.2 Heterologous HI antibody response (cross-reactive immunity)

In order to evaluate the ability of the pandemic H5N1 vaccine (containing strain A/Indonesia/05/2005) to induce cross-reactive immunity, anti-HA antibody titres were measured against heterologous strain (A/Vietnam/1194/2004) in study Q-Pan-001. Of note, A/Indonesia/05/2005 (H5N1) is a representative of Clade 2 and is the first pandemic vaccine prototype strain from this genetic group released by WHO in May 2006, whereas A/Vietnam/1194/2004 (H5N1), the vaccine strain, belongs to Clade 1.

Likewise, the cross-reactive immunity of the D-Pan pandemic vaccine in study H5N1-007 (performed with the vaccine strain A/Vietnam/1194/2004) was evaluated by measuring anti-HA antibody titres against heterologous strain A/Indonesia/05/2005. In addition, cross reactivity data against two other drifted clade 2 strains (derived from A/Anhui/01/2005/subclade 3 and A/turkey/Turkey/1/2005 -NIBRG23/subclade 2) have been obtained in a subset of subjects from study H5N1-007 who received 3.8µg HA, adjuvanted or not with AS03 (20 subjects per group).

Immunogenicity results (GMTs of HI antibodies, SCF, SCR and SPR) against heterologous H5N1 strain A/Vietnam/1194/2004 in the ATP immunogenicity cohort of study Q-Pan-001 are presented in Table 17.

Immunogenicity results (GMTs of HI antibodies, SCF, SCR and SPR) against heterologous H5N1 strain A/Indonesia/05/2005 in D-Pan study H5N1-007 are presented in Table 18 (ATP immunogenicity cohort). HI antibody responses at Days 0, 21, and 42 against strains A/Anhui/01/2005 and A/turkey/Turkey/1/2005 are presented in Table 19. Seropositivity rates for HI antibodies at pre-vaccination are presented in Appendix Table 3.

Study Q-Pan-001 with the candidate Q-Pan pandemic influenza vaccine

At Day 42, a significant increase in GMTs against the heterologous strain is observed in all four adjuvanted groups, whereas virtually no effect of vaccination on the heterologous titres is observed in the non-adjuvanted group (Table 17).

SCR and SCF for the heterologous HI response increased significantly following vaccination with all adjuvanted formulations, reaching levels of 53.5% to 61.8% (SCR), and of 5.7 to 7.6 (SCF). Results obtained in the non-adjuvanted group remained close to baseline for these parameters.

Importantly, results obtained in the groups vaccinated either with D-Pan or Q-Pan vaccines showed, for all parameters tested, widely overlapping 95% CIs, and further support the equivalence of the two vaccines.

Supportive study H5N1-007 with D-Pan H5N1 pandemic influenza vaccine

In study H5N1-007, no subjects were initially seropositive for A/Indonesia/05/2005. For all non-adjuvanted formulations, protective levels of antibodies were not reached at any time point (Day 21 or Day 42). In the adjuvanted vaccine groups, a significant increase in SPR was observed between Day 0 and Day 42. SPR after the second dose ranged from 20.0% (obtained with 3.8µg HA/AS03) to 32.0% (Table 18). These findings also apply to SCR as all subjects were initially seronegative for A/Indonesia/05/2005 (Appendix Table 3).

A SCF of 1.0 was obtained with all non-adjuvanted formulations after the first and second doses, which demonstrates that no immune response to vaccination was observed. In the adjuvanted vaccine groups, values ranged from 1.0 to 1.2 after the first dose, and from 2.0 to 2.8 after the second dose.

In the non-adjuvanted groups, only one subject from the highest dose group (30µg HA) had a GMT above the detection limit (1:10) after the first and second dose. With the adjuvanted formulations, GMTs ranged from 5.1 to 5.9 after the first dose, and increased significantly after the second dose to values ranging from 9.9 to 13.9 (Table 18).

In terms of HI antibody production against strains A/Anhui/01/2005 and A/Turkey/Turkey/1/2005, virtually no effect of vaccination against either strain was detected with the non-adjuvanted formulation. On the contrary, the adjuvanted vaccine mediated a significant increase in GMTs after the second vaccination against both strains, although the absolute titres were low. At Day 42, SCR and SPR in the adjuvanted group were both 35.0% against A/Anhui/01/2005, and 60.0% against A/turkey/Turkey/1/2005, with SCF of 3.4 and 4.7 respectively (Table 19).

Overall, although lower titres were obtained, these results are indicative of the induction of a cross-reactive immune response against heterologous strains following immunisation with the pandemic vaccine adjuvanted with AS03. This conclusion is further reinforced when considering that the H5N1 vaccine strain (A/Vietnam/1194/2004) and the heterologous strain (A/Indonesia/05/2005) pertain to two different clades (clade 1 and 2 respectively).

The data confirm the ability of the Q-Pan and D-Pan H5N1 pandemic vaccines to induce a cross-reactive immune response against strains from other clades/subclades than the vaccine strain.

Table 17 HI responses against heterologous strain H5N1 A/Vietnam/1194/2004 of the Q-Pan and D-Pan monovalent pandemic influenza A vaccine (H5N1) in study Q-Pan-001 (ATP immunogenicity cohort)

Study (Age of vaccination)	Time-point	Strain	Manuf. site‡	HA (µg /dose)	AS03	N	GMT			SCF			SCR			SPR		
							Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	Pre	H5N1 Indonesia	Quebec	3.8	AS03	144	**5.3**	5.0	5.6	-	-	-	-	-	-	**2.1**	0.4	6.0
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	**5.3**	5.0	5.6	-	-	-	-	-	-	**1.4**	0.2	4.9
		H5N1 Indonesia	Quebec	3.8	-	75	**5.4**	5.0	5.8	-	-	-	-	-	-	**0.0**	0.0	4.8
		H5N1 Indonesia	Dresden	3.8	AS03	140	**5.5**	5.1	5.9	-	-	-	-	-	-	**2.1**	0.4	6.1
		H5N1 Indonesia	Dresden	3.8	AS03/2	143	**5.4**	5.1	5.7	-	-	-	-	-	-	**1.4**	0.2	5.0
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	144	**9.9**	8.4	11.7	**1.9**	1.6	2.2	**13.2**	8.1	19.8	**15.3**	9.8	22.2
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	**8.5**	7.3	10.0	**1.6**	1.4	1.9	**9.6**	5.3	15.6	**12.3**	7.5	18.8
		H5N1 Indonesia	Quebec	3.8	-	75	**5.8**	5.1	6.6	**1.1**	1.0	1.2	**1.3**	0.0	7.2	**4.0**	0.8	11.2
		H5N1 Indonesia	Dresden	3.8	AS03	140	**9.1**	7.6	10.8	**1.7**	1.4	1.9	**12.1**	7.2	18.7	**15.0**	9.5	22.0
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	**8.9**	7.6	10.3	**1.6**	1.4	1.9	**10.6**	6.0	16.8	**14.8**	9.4	21.7
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	144	**39.9**	32.2	49.5	**7.6**	6.1	9.4	**61.8**	53.3	69.8	**63.9**	55.5	71.7
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	**33.4**	26.6	41.9	**6.3**	5.0	7.9	**58.9**	50.5	67.0	**60.3**	51.9	68.3
		H5N1 Indonesia	Quebec	3.8	-	75	**5.8**	5.1	6.5	**1.1**	1.0	1.2	**1.3**	0.0	7.2	**4.0**	0.8	11.2
		H5N1 Indonesia	Dresden	3.8	AS03	140	**33.3**	26.0	42.7	**6.1**	4.7	7.8	**56.4**	47.8	64.8	**59.3**	50.7	67.5
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	**30.6**	24.3	38.5	**5.7**	4.5	7.1	**53.5**	45.0	61.9	**56.3**	47.8	64.6

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); GMR = Geometric Mean Ratio; SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

Table 18 HI responses against H5N1 A/Indonesia/05/2005 of the D-Pan pandemic influenza A vaccine (H5N1) in adults from study H5N1-007 (ATP immunogenicity cohort)

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	GMT			SCF			SCR			SPR		
						Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
							LL	UL		LL	UL		LL	UL		LL	UL
H5N1-007 18-60 yrs	Pre	H5N1 split	30	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	15	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	7.5	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	3.8	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	30	AS03	48	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.4
		H5N1 split	15	AS03	48	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.4
		H5N1 split	7.5	AS03	50	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.1
		H5N1 split	3.8	AS03	50	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.1
	Post I (D21)	H5N1 split	30	-	49	5.1	4.9	5.4	1.0	1.0	1.1	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	15	-	49	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	7.5	-	49	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	3.8	-	49	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.4	0.0	0.0	7.3
		H5N1 split	30	AS03	48	5.9	4.9	7.1	1.2	1.0	1.4	4.2	0.5	14.3	4.2	0.5	14.3
		H5N1 split	15	AS03	49	5.4	4.8	6.0	1.1	1.0	1.2	2.1	0.1	11.1	2.0	0.1	10.9
		H5N1 split	7.5	AS03	50	5.7	5.0	6.4	1.1	1.0	1.3	2.0	0.1	10.6	2.0	0.1	10.7
		H5N1 split	3.8	AS03	50	5.1	4.9	5.4	1.0	1.0	1.1	0.0	0.0	7.1	0.0	0.0	7.1
	Post II (D42)	H5N1 split	30	-	49	5.1	4.9	5.2	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	15	-	49	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	7.5	-	49	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	3.8	-	50	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.1
		H5N1 split	30	AS03	48	11.7	8.0	17.2	2.3	1.6	3.4	29.2	17.0	44.1	29.2	17.0	44.1
		H5N1 split	15	AS03	49	10.2	7.1	14.7	2.1	1.4	3.0	20.8	10.5	35.0	20.4	10.2	34.3
		H5N1 split	7.5	AS03	50	13.9	9.7	20.1	2.8	1.9	4.0	32.0	19.5	46.7	32.0	19.5	46.7
		H5N1 split	3.8	AS03	50	9.9	7.0	14.0	2.0	1.4	2.8	20.0	10.0	33.7	20.0	10.0	33.7

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

Table 19 HI responses against H5N1 A/Anhui and A/Turkey strains of the D-Pan pandemic influenza A vaccine (H5N1) in adults from study H5N1-007 (ATP immunogenicity cohort, subset of 40 subjects)

Strain		Timepoint	HA (µg per dose)	AS03	N	GMT			SCF			SCR			SPR		
						Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
							LL	UL		LL	UL		LL	UL		LL	UL
A/ANHUI/05	**H5N1** split	**Pre**	3.8	AS03	20	**5.0**	5.0	5.0	**-**	-	-	**-**	-	-	**0.0**	0.0	16.8
	H5N1 split		3.8	-	20	**5.0**	5.0	5.0	**-**	-	-	**-**	-	-	**0.0**	0.0	16.8
	H5N1 split	**Post I (D21)**	3.8	AS03	20	**5.0**	5.0	5.0	**1.0**	1.0	1.0	**0.0**	0.0	16.8	**0.0**	0.0	16.8
	H5N1 split		3.8	-	20	**5.0**	5.0	5.0	**1.0**	1.0	1.0	**0.0**	0.0	16.8	**0.0**	0.0	16.8
	H5N1 split	**Post II (D42)**	3.8	AS03	20	**17.1**	9.6	30.5	**3.4**	1.9	6.1	**35.0**	15.4	59.2	**35.0**	15.4	59.2
	H5N1 split		3.8	-	20	**5.0**	5.0	5.0	**1.0**	1.0	1.0	**0.0**	0.0	16.8	**0.0**	0.0	16.8
A/ TURK/05	**H5N1** split	**Pre**	3.8	AS03	20	**5.0**	5.0	5.0	**-**	-	-	**-**	-	-	**0.0**	0.0	16.8
	H5N1 split		3.8	-	20	**5.0**	5.0	5.0	**-**	-	-	**-**	-	-	**0.0**	0.0	16.8
	H5N1 split	**Post I (D21)**	3.8	AS03	20	**7.6**	4.9	11.8	**1.5**	1.0	2.4	**10.0**	1.2	31.7	**10.0**	1.2	31.7
	H5N1 split		3.8	-	20	**5.7**	4.3	7.7	**1.1**	0.9	1.2	**5.0**	0.1	24.9	**5.0**	0.1	24.9
	H5N1 split	**Post II (D42)**	3.8	AS03	20	**23.4**	12.9	42.4	**4.7**	2.6	8.5	**60.0**	36.1	80.9	**60.0**	36.1	80.9
	H5N1 split		3.8	-	20	**5.7**	4.3	7.7	**1.1**	0.9	1.2	**5.0**	0.1	24.9	**5.0**	0.1	24.9

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

2.7.3.3.2.3 Comparison between Q-Pan and D-Pan vaccines in terms of HI antibody response

A secondary objective of study Q-Pan-001 was to assess the equivalence of the vaccine antigen manufactured in Quebec and the antigen manufactured in Dresden, both administered with AS03. For this analysis, subjects in Q-Pan groups with full and half dose AS03 were pooled together to form the Q-Pan with adjuvant group. Similarly, D-Pan groups with full and half dose AS03 were pooled to form the D-Pan with adjuvant group. GMTs for each group were adjusted for age and baseline antibody titre, and then a ratio of the group GMTs was calculated. For the groups to be considered equivalent, the limit of the 95% confidence interval on the ratio was to be between 0.67 and 1.5.

Table 20 presents the comparison between Quebec- and Dresden-manufactured vaccines, as assessed by HI antibody GMT. The actual GMT ratio was 0.94 (95% CI 0.75-1.17) for the homologous response and 1.16 (95% CI 0.92-1.46) for the heterologous anti-Vietnam strain response. The criterion was met for both the homologous and heterologous response since both ratios were within the pre-specified limits. Therefore, the vaccines containing Quebec- or Dresden-derived antigen may be considered equivalent.

Table 20 Adjusted GMT ratios for subjects receiving Quebec antigen with full or half dose adjuvant compared with subjects receiving Dresden antigen with full or half dose adjuvant at Day 42 in study Q-Pan-001 (ATP cohort for immunogenicity)

Antibody	Treatment Group				Adjusted GMT ratio (Q-Pan / D-Pan)		
	Q-Pan with adjuvant		D-Pan with adjuvant		Value	95% CI	
	N	Adjusted GMT	N	Adjusted GMT		LL	UL
HI antibody against A/Indonesia/05/2005	290	371.2	282	396.9	**0.94**	0.75	1.17
HI antibody against A/Vietnam/1194/2004	290	36.6	282	31.6	**1.16**	0.92	1.46

D-Pan with adjuvant = D-Pan with full dose and half dose AS03
Q-Pan with adjuvant = Q- Pan with full dose and half dose AS03
Adjusted GMT = geometric mean antibody titre adjusted for age strata, baseline titre
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 titre - pooled variance); LL = lower limit, UL = upper limit

2.7.3.3.2.4 Lot-to-lot consistency in terms of HI antibodies against vaccine strain H5N1 A/Indonesia/05/2005

A primary objective of study Q-Pan-002 was to demonstrate the immunogenic equivalence, based on Day 42 vaccine-homologous virus HI GMTs, of 3 consecutive lots of H5N1 antigen manufactured in Quebec combined with 3 consecutive lots of AS03 (manufactured in Rixensart), in subjects 18 to 49 years of age. The criterion for success was that the 2-sided 95% confidence bounds for all the pairwise ratios of GMT values were to be entirely within the interval [0.67;1.5]. The pairwise Day 42 GMT ratios of HI antibodies at against A/Indonesia/05/2005 are presented for the 18 to 49 years age group in Table 21.

Table 21 Adjusted GMT ratios of HI antibodies against vaccine strain A/Indonesia/05/2005 at Day 42 for all Q-Pan vaccine lots in subjects 18-49 years of age, study Q-Pan-002 (ATP cohort for immunogenicity)

Adjusted GMT	Q-Pan Lot A		Q-Pan Lot B		Q-Pan Lot C	
	N	GMT	N	GMT	N	GMT
	394	275.8	379	291.7	394	333.5
Adjusted GMT Ratio (95% CI)						
Q-Pan Lot A and Q-Pan Lot B	0.95 (0.78, 1.15)					
Q-Pan Lot A and Q-Pan Lot C	0.83 (0.68, 1.00)					
Q-Pan Lot B and Q-Pan Lot C	0.87 (0.72, 1.06)					

Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
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 - pooled variance with the 3 lots groups); LL = lower limit, UL = upper limit

As shown in Table 21, consistency between the three Q-Pan vaccine lots at the Day 42 post-vaccination time point was demonstrated as the 2-sided 95% CIs for the ratio of HI antibody GMT between each pair of lots were within the pre-specified interval of [0.67;1.5].

2.7.3.3.2.5 Homologous neutralizing antibody response

As a preliminary remark, it should be noted that the neutralization assay is a method which allows for the quantification of antibodies that inhibit the attachment, penetration and propagation of influenza virus into cells.

As no seroprotection threshold has been established for the neutralizing assay, a simple four-fold increase (seroconversion or “vaccine response”) in neutralizing titre at post-vaccination is used to evaluate whether vaccinated individuals have responded against the vaccination strain. Since the assay has a high sensitivity, a higher background prior to vaccination can be detected as seen from the relatively high levels of initial seropositivity rates.

By calculating the post vaccination seroconversion or vaccine response (defined as a 4-fold or greater increase in reciprocal neutralizing titer), the influence of such higher percentage of titres at prevaccination is mitigated.

Pivotal studies with the candidate Q-Pan pandemic influenza vaccine (Q-Pan-001 and Q-Pan-002)

Neutralizing antibody responses against vaccine strain H5N1 A/Indonesia/05/2005 in terms of GMTs, vaccine response and the percentage of subjects with serum neutralization titres (SNT) ≥1:28, ≥1:40 and ≥1:80 are presented for the ATP immunogenicity cohort of study Q-Pan-001 in Table 22 and Table 23.

Neutralizing antibody responses in study Q-Pan-002 against vaccine strain A/Indonesia/05/2005 are presented by age strata (18-60 years; >60 years) for Q-Pan vaccine recipients included in the ATP immunogenicity cohort, in Table 24 and Table 25.

Study Q-Pan-001

In study Q-Pan-001, at pre-vaccination, approximately two-thirds of subjects in all treatment groups were seronegative for neutralizing antibodies (titers < 1:28). However, neutralizing titers ≥1:80 before vaccination were not uncommon. The percentage of subjects seropositive at baseline (titres ≥1:28, ≥1:40 or ≥1:80) as well as the GMTs were generally similar between the different vaccine groups (Table 22 and Table 23).

At Day 21, all vaccine regimens demonstrated neutralizing antibody responses to the A/Indonesia/05/2005 vaccine strain, with a further increase at Day 42.

Following the first vaccine dose, an increase in seropositivity rates for neutralizing antibodies was observed in adjuvanted Q-Pan and D-Pan vaccine groups. Among subjects who received any adjuvanted vaccine regimen, all but 2 were seropositive (titer ≥1:28) at Day 21; and 100% became seropositive at Day 42. The shift to higher titers occurred more rapidly among recipients of adjuvanted vaccines, with 80.9 to 96.0% having titers ≥1:80 by Day 21. At 21 days after the second dose (Day 42), 100% of subjects receiving adjuvanted Q-Pan or D-Pan vaccines demonstrated A/Indonesia/05/2005 neutralizing antibody titers ≥ 1:80.

All treatment groups receiving adjuvanted vaccine demonstrated a much sharper increase in neutralizing GMTs against A/Indonesia/05/2005 than the group receiving non-adjuvanted Q-Pan vaccine, attaining values of 199 to 260.5 by Day 21. At Day 42, the recipients of Q-Pan antigen with full dose AS03 attained a GMT of 1566.8, a 70-fold increase over baseline, and recipients of D-Pan antigen with full dose AS03 attained a GMT of 1497.2, a 63-fold increase over baseline. Groups which received half dose AS03 in association demonstrated marginally lower Day 42 GMT values relative to full dose AS03 recipients, but with substantially overlapping 95% CIs.

At 21 days after completion of a 2-dose vaccine regimen (Day 42), a neutralizing antibody vaccine response (defined as titre at Day 42 ≥ 4-fold the pre-vaccination titre) against A/Indonesia/05/2005 could be detected in 91.3% to 97.9% of subjects in vaccinated with adjuvanted vaccine (Table 22). The rate of vaccine response was

somewhat greater among subjects with undetectable neutralizing antibodies to A/Indonesia/05/2005 at pre-vaccination (Appendix Table 4). Among subjects with detectable neutralizing antibodies at baseline, 77.8% to 92.3% showed a vaccine response after two doses of the adjuvanted Q-Pan or D-Pan vaccine, whereas in these groups all subjects who were seronegative at baseline were vaccine responders.

In the absence of adjuvant, the 95% confidence interval for vaccine response rate at Day 42 was 58.9 to 85.1%; whereas in all groups receiving adjuvanted vaccine the 95% confidence lower limit for vaccine response was ≥79%.

Reverse cumulative curves (RCCs) for titers of neutralizing antibodies against strain A/Indonesia/05/2005 at the Day 42 time point are presented in Figure 5. As illustrated by the RCC, all subjects vaccinated with AS03 adjuvanted Q-Pan or D-Pan vaccine with H5N1 strain A/Indonesia/05/2005 reached neutralizing antibody titres against A/Indonesia/05/2005 above the cut-off of 1:80 at Day 42 post-vaccination.

Study Q-Pan-002

In study Q-Pan-002, almost one-fourth (24.2%) of subjects in the 18 to 60 years age group were seropositive at baseline for neutralizing antibodies against A/Indonesia/ (titre ≥ 1:28). Following vaccination with the AS03 adjuvanted Q-Pan vaccine, seroneutralization antibodies specific for the vaccine-homologous virus were induced.

Similar to the neutralization antibody response in adult recipients of adjuvanted Q-Pan or D-Pan vaccine in study Q-Pan-001, all subjects 18 to 60 years of age in study Q-Pan-002 had become seropositive for neutralizing antibodies against A/Indonesia/05/2005 after two Q-Pan vaccine doses (at Day 42) and all subjects tested attained titers ≥1:80 (Table 24 and Table 25).

Fewer subjects in the > 60 years age group compared with the younger age group in study Q-Pan-002 were seronegative at baseline for neutralizing antibodies against the A/Indonesia/05/2005 (25%). Nevertheless, immunization with Q-Pan vaccine resulted in a clear upward shift in titer distributions. At Day 42, 98.2% of subjects were seropositive for neutralizing antibodies against A/Indonesia/05/2005. After immunization, the proportion of subjects with neutralizing titers of ≥ 1:80 against A/Indonesia/05/2005 increased from 44.6% at baseline to 96.4% at Day 42.

RCCs for titers of neutralizing antibodies against strain A/Indonesia/05/2005 at the Day 42 time point are presented by age strata (18-60 years; >60 years) in Figure 6.

Although an important proportion of subjects had measurable neutralizing antibody titers at baseline, this figure demonstrates that there is a marked and uniform upward shift in the population distribution of titres following Q-Pan vaccination.

Supportive study H5N1-007 with D-Pan H5N1 pandemic influenza vaccine

Neutralizing antibody responses against vaccine strain H5N1 A/Vietnam/1194/2004 in terms of the percentage of subjects with serum neutralization titres ≥1:28 (SNT), SCR and GMTs were evaluated in D-Pan study H5N1-007 at Days 0, 21 and 42. Results are presented for the ATP immunogenicity cohort in Table 26.

Seropositivity rates for neutralizing antibodies (i.e. titres ≥1:28) were generally similar between all D-Pan vaccine formulation groups prior to vaccination (i.e 24.5% to 34.7% in the non-adjuvanted groups, and 18.8% to 34.0% in the adjuvanted groups). An increase in seropositivity rates was observed in all vaccine groups after the first dose, which ranged from 62.0% to 89.8% with the non-adjuvanted formulations and from 95.7% to 100.0% with the adjuvanted formulations. After the second dose, all subjects from the adjuvanted groups except two (who received 7.5µg HA/AS03 and 3.8µg HA/AS03 respectively) were seropositive for neutralizing antibodies. In the non-adjuvanted groups, 72.0% to 95.8% of subjects were seropositive at this timepoint.

At both timepoints (Day 21 and Day 42), SCR were higher in the adjuvanted groups as compared to the respective non-adjuvanted formulations. SCR ranged from 14.0% to 57.1% in the non-adjuvanted groups after the first dose, versus 63.3% to 83.7% in the adjuvanted groups. After the second dose, SCR were generally stable or only slightly increased with the non-adjuvanted formulations. In the adjuvanted groups, SCR between 85.7% and 97.9% were observed at this timepoint.

At pre-vaccination, similar GMTs were observed in all vaccine groups. The GMTs increased significantly after the first dose in all groups, with higher GMTs obtained with the adjuvanted formulations. There was a further increase in GMTs after the second dose in all groups, with statistically significant increases as compared to Day 21 in all adjuvanted vaccine groups.

In conclusion, a high neutralizing antibody response was induced with all adjuvanted D-Pan vaccine formulations. In the lowest dose group (3.8µg HA/AS03), all subjects except one were seropositive after the second dose, with a SCR of 85.7%.

Neutralizing antibody responses against vaccine strain H5N1 A/Vietnam/1194/2004 in study H5N1-007 were also calculated in terms of the percentage of subjects with serum neutralization titre ≥1:40 and 1:80 at Days 0, 21 and 42 (Table 27). Reverse cumulative curves (RCCs) for the Day 21 and Day 42 time points in study H5N1-007 are presented in Figure 7 and Figure 8, respectively.

The percentage of subjects with pre-vaccination titres ≥1:40 or 1:80 was generally similar between all vaccine formulations. This percentage ranged from 10.4% to 24.5% based on the 1:40 cut off and from 2.1% to 10.2% based on the 1:80 cut off.

The adjuvanted formulations demonstrated their ability to induce neutralizing antibody responses after already one vaccine dose, independently of their antigen content (i.e. 87.8%-100% and 71.4%-83.7% of subjects had SNT ≥1:40 and ≥1:80 respectively at Day 21). At this time point, the percentage of subjects with SNT ≥1:40 and ≥1:80 ranged from

46.0% to 77.6%, and from 22.0% to 55.1% respectively in the non-adjuvanted groups. As shown by the RCC, no significant differences were shown between adjuvanted groups at Day 21 as the curves crossed between groups. Regarding the non-adjuvanted groups, a statistical difference was observed between the 30µg HA and 3.8µg HA dose groups.

As illustrated by the RCC, the majority of subjects from the adjuvanted groups had titres above the two cut-offs at Day 42 (i.e. 97.9%-100% and 91.5%-100% for the 1:40 and 1:80 cut offs, respectively). At Day 42, the percentage of subjects with SNT ≥1:40 and ≥1:80 ranged from 58.0% to 87.5% and from 20.0% to 64.6% in the non-adjuvanted groups.

Thus, a high neutralizing antibody response was observed with all adjuvanted formulations irrespective of the defined threshold (≥1:40 or 1:80), which was substantially higher as compared to that seen in the non-adjuvanted groups. Among adjuvanted formulations, no antigen-dose effect was detected on the neutralizing antibody production. With respect to the selected dosage (3.8µg HA/AS03), the percentage of subjects with SNT ≥1:40 and 1:80 was 98.0% and 93.9% respectively at Day 42. These percentages were statistically higher as compared to those obtained with the non-adjuvanted formulation of the same antigen content.

Table 22 Neutralizing antibody responses (GMT, titre ≥1:28, vaccine response) against vaccine strain H5N1 A/Indonesia/05/2005 of the H5N1 (A/Indonesia) influenza vaccine in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site‡	HA (µg per dose)	AS03	N	GMT			≥1:28			Vaccine Response		
							Value	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**Pre**	H5N1 Indonesia	Quebec	3.8	AS03	47	**22.3**	17.4	28.5	**27.7**	15.6	42.6	**-**	**-**	**-**
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	**31.8**	23.0	43.8	**40.4**	26.4	55.7	**-**	**-**	**-**
		H5N1 Indonesia	Quebec	3.8	-	49	**25.7**	19.9	33.1	**36.7**	23.4	51.7	**-**	**-**	**-**
		H5N1 Indonesia	Dresden	3.8	AS03	48	**23.7**	18.3	30.8	**31.3**	18.7	46.3	-	-	-
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**25.7**	19.6	33.7	**34.0**	21.2	48.8	-	-	-
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	**199.0**	148.9	266.1	**100**	92.5	100	**76.6**	62.0	87.7
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	**240.1**	191.4	301.3	**96.0**	86.3	99.5	**68.1**	52.9	80.9
		H5N1 Indonesia	Quebec	3.8	-	49	**78.6**	57.7	107.1	**81.6**	68.0	91.2	**42.9**	28.8	57.8
		H5N1 Indonesia	Dresden	3.8	AS03	49	**260.5**	208.1	326.0	**100**	92.7	100	**79.2**	65.0	89.5
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	**248.7**	202.0	306.3	**100**	92.7	100	**71.4**	56.7	83.4
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	**1566.8**	1227.3	2000.2	**100**	92.5	100	**97.9**	88.7	99.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	48	**1242.1**	902.2	1710.0	**100**	92.6	100	**91.3**	79.2	97.6
		H5N1 Indonesia	Quebec	3.8	-	49	**183.8**	138.4	244.2	**93.9**	83.1	98.7	**73.5**	58.9	85.1
		H5N1 Indonesia	Dresden	3.8	AS03	49	**1497.2**	1192.0	1880.5	**100**	92.7	100	**95.8**	85.7	99.5
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**1352.8**	1075.5	1701.6	**100**	92.9	100	**96.0**	86.3	99.5

N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Vaccine response defined as antibody titer ≥ 4-fold the pre-vaccination titer (samples seronegative at pre-vaccination were assigned a reciprocal titer of 14)
‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

Table 23 Neutralizing antibody responses (titre ≥1:40 ≥1:80) against strain vaccine H5N1 A/Indonesia/05/2005 of the H5N1 (A/Indonesia) influenza vaccine in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site‡	HA (µg per dose)	AS03	N	≥1:40			≥1:80		
							%	95% CI		%	95% CI	
								LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**Pre**	H5N1 Indonesia	Quebec	3.8	AS03	47	**21.3**	10.7	35.7	**12.8**	4,8	25.7
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	**36.2**	22.7	51.5	**23.4**	12.3	38.0
		H5N1 Indonesia	Quebec	3.8	-	49	**28.6**	16.6	43.3	**16.3**	7.3	29.7
		H5N1 Indonesia	Dresden	3.8	AS03	48	**22.9**	12.0	37.3	**14.6**	6.1	27.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**26.0**	14.6	40.3	**20.0**	10.0	33.7
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	**93.6**	82.5	98.7	**80.9**	66.7	90.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	**96.0**	86.3	99.5	**96.0**	86.3	99.5
		H5N1 Indonesia	Quebec	3.8	-	49	**75.5**	61.1	86.7	**53.1**	38.3	67.5
		H5N1 Indonesia	Dresden	3.8	AS03	49	**98.0**	89.1	99.9	**93.9**	83.1	98.7
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	**98.0**	89.1	99.9	**95.9**	86.0	99.5
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	**100**	92.5	100	**100**	92.5	100
		H5N1 Indonesia	Quebec	3.8	AS03/2	48	**100**	92.6	100	**100**	92.6	100
		H5N1 Indonesia	Quebec	3.8	-	49	**91.8**	80.4	97.7	**81.6**	68.0	91.2
		H5N1 Indonesia	Dresden	3.8	AS03	49	**100**	92.7	100	**100**	92.7	100
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**100**	92.9	100	**100**	92.9	100

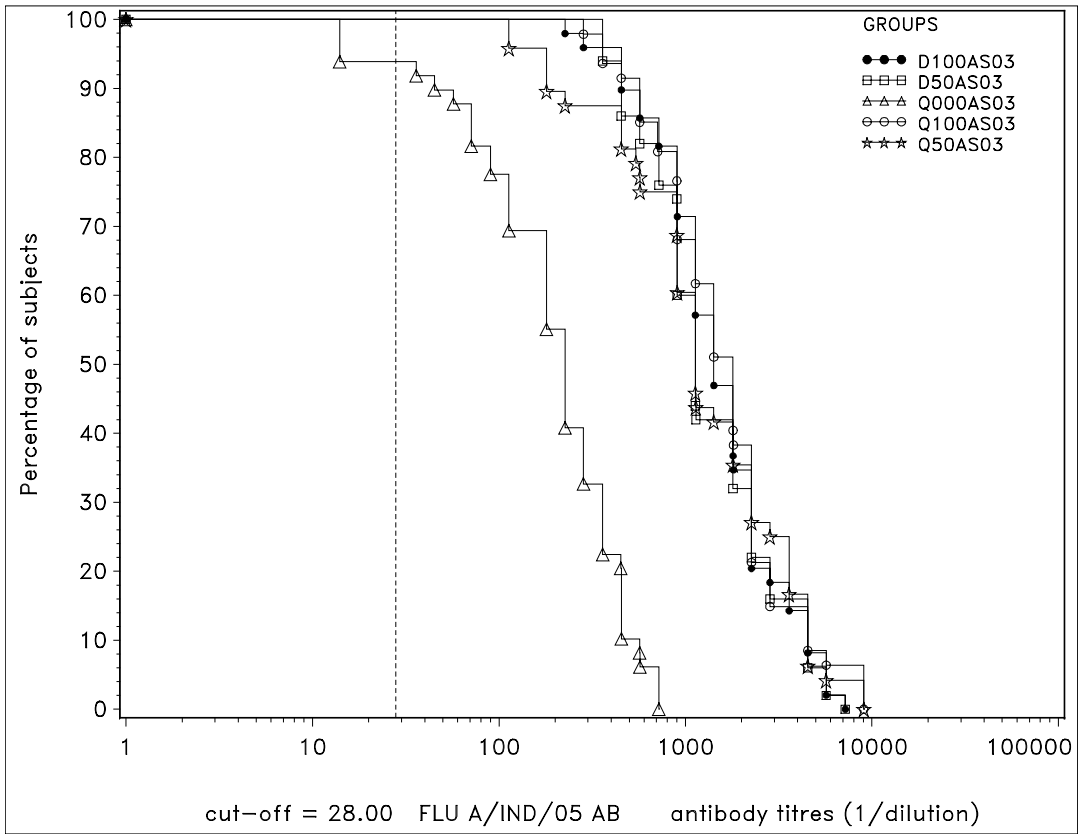
N = number of subjects with available results

% = percentage of subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

Figure 5 Reverse cumulative curves of neutralising antibody titres against vaccine A/Indonesia/05/2005 strain at Day 42 in study Q-Pan-001 (ATP cohort for immunogenicity)



Q000AS03 = Q000AS03: 3.8 ug Quebec A/Indo No AS03
Q100AS03 = Q100AS03: 3.8 ug Quebec A/Indo Full AS03
Q50AS03 = Q50AS03: 3.8 ug Quebec A/Indo Half AS03
D100AS03 = D100AS03: 3.8 ug Dresden A/Indo Full AS03
D50AS03 = D50AS03: 3.8 ug Dresden A/Indo Half AS03

Table 24 Neutralizing antibody responses (GMT, GMFR, titre ≥1:28, vaccine response) against vaccine strain H5N1 A/Indonesia/05/2005 of the AS03 adjuvanted Q-Pan H5N1 pandemic influenza vaccine in study Q-Pan-002 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Age group	Time-point	Study group	N	GMT			GMFR			≥1:28			Vaccine response		
					Value	95% CI		Value	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	178	**21.2**	18.8	23.9	**-**	-	-	**24.2**	18.1	31.1	**-**	-	-
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	178	**1529.0**	1332.0	1755.1	**72.1**	58.5	88.9	**100**	97.9	100	**94.4**	89.9	97.3
	>60 years	Pre	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	56	**54.0**	42.0	69.3	**-**	-	-	**75.0**	63.7	84.2	**-**	-	-
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	56	**619.4**	462.7	829.1	**11.5**	8.1	16.3	**98.2**	91.8	99.9	**80.4**	67.6	89.8

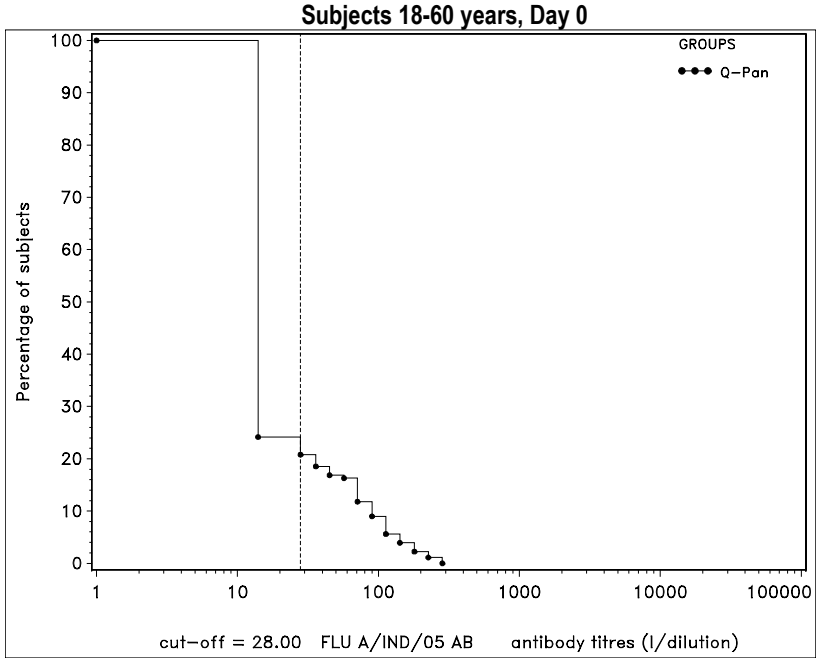
N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
GMFR = Geometric mean fold rise
Vaccine response defined as antibody titer ≥ 4-fold the pre-vaccination titer (samples seronegative at pre-vaccination were assigned a reciprocal titer of 14)

Table 25 Neutralizing antibody responses (titre ≥1:40, ≥1:80) against vaccine strain H5N1 A/Indonesia/05/2005 of the AS03 adjuvanted Q-Pan H5N1 pandemic influenza vaccine in study Q-Pan-002 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Age group	Time-point	Study group	N	≥1:40			≥1:80		
					%	95% CI		%	95% CI	
						LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	178	**18.5**	13.9	24.0	**11.8**	8.0	16.5
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	178	**100**	98.3	100	**100**	98.3	100
	>60 years	Pre	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	56	**62.5**	50.7	73.3	**44.6**	33.3	56.5
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	56	**98.2**	91.8	99.9	**96.4**	89.2	99.4

N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Figure 6 **Reverse cumulative curves for neutralizing antibody titres against vaccine strain H5N1 A/Indonesia/05/2005 following AS03 adjuvanted Q-Pan H5N1 pandemic influenza vaccine in study Q-Pan-002 (ATP cohort for immunogenicity, subset)**



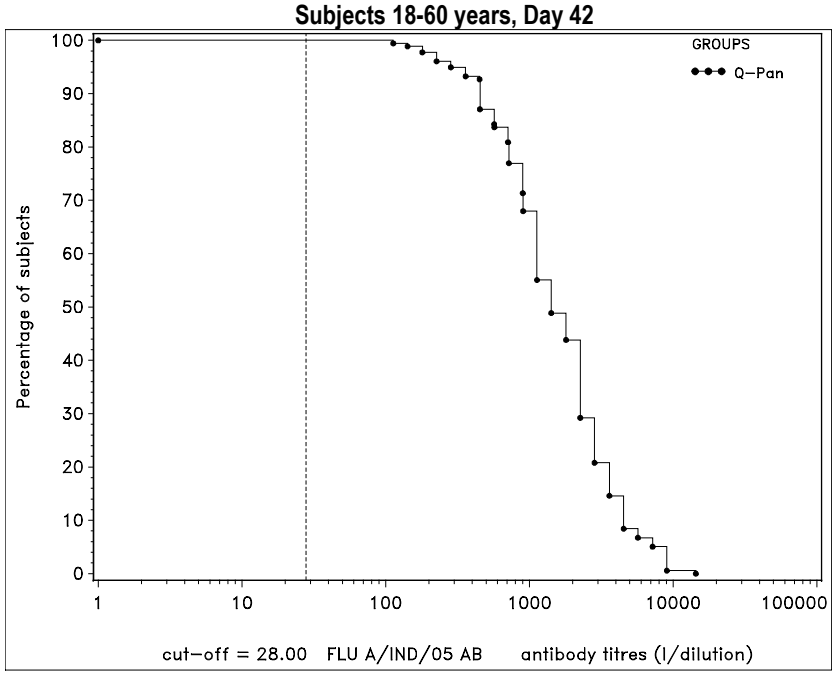
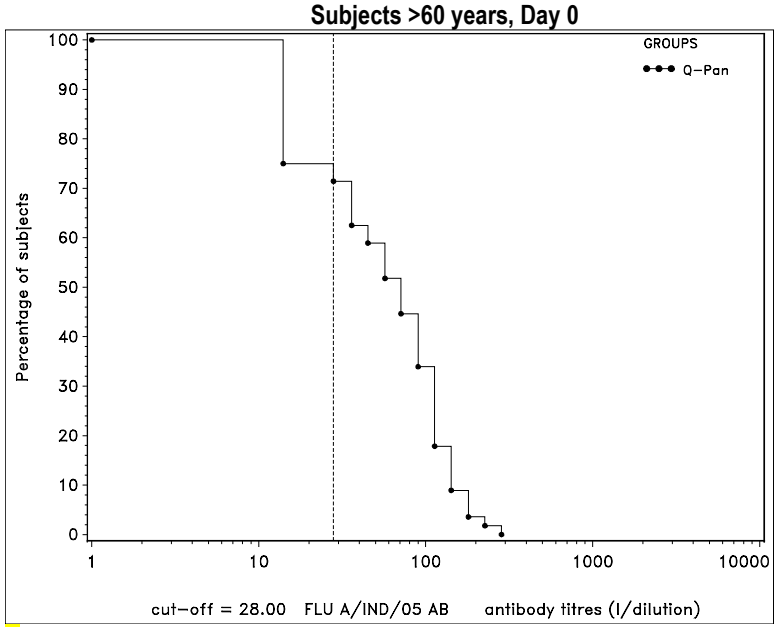


Figure 6 (cont'd) Reverse cumulative curves for neutralizing antibody titres against vaccine strain H5N1 A/Indonesia/05/2005 following AS03 adjuvanted Q-Pan H5N1 pandemic influenza vaccine in study Q-Pan-002 (ATP cohort for immunogenicity, subset)



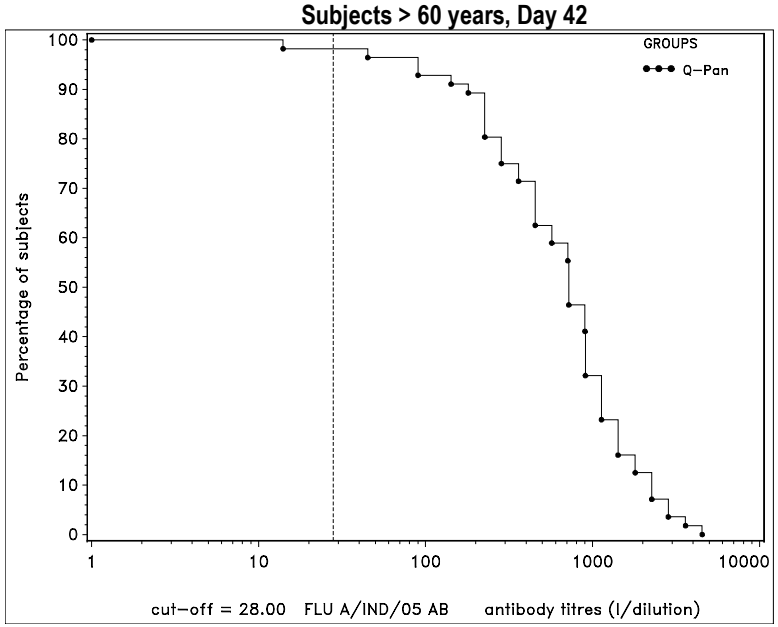


Table 26 Neutralizing antibody responses against vaccine strain H5N1 A/Vietnam/1194/2004 of the D-Pan H5N1 pandemic influenza vaccine in adults from study H5N1-007 (ATP immunogenicity cohort)

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	≥1:28			SCR			GMT		
						%	95% CI		%	95% CI		Value	95% CI	
							LL	UL		LL	UL		LL	UL
H5N1-007 18-60 yrs	**Pre**	H5N1 split	30	-	49	**24.5**	13.3	38.9	**-**	-	-	**18.9**	16.0	22.3
		H5N1 split	15	-	49	**34.7**	21.7	49.6	**-**	-	-	**22.6**	18.2	28.2
		H5N1 split	7.5	-	49	**30.6**	18.3	45.4	**-**	-	-	**20.9**	17.2	25.2
		H5N1 split	3.8	-	50	**28.0**	16.2	42.5	**-**	-	-	**20.2**	16.8	24.3
		H5N1 split	30	AS03	48	**18.8**	8.9	32.6	**-**	-	-	**17.3**	15.1	20.0
		H5N1 split	15	AS03	49	**32.7**	19.9	47.5	**-**	-	-	**22.0**	17.9	27.0
		H5N1 split	7.5	AS03	50	**34.0**	21.2	48.8	**-**	-	-	**23.3**	18.4	29.4
		H5N1 split	3.8	AS03	50	**32.0**	19.5	46.7	**-**	-	-	**21.7**	17.8	26.4
	Post I (D21)	H5N1 split	30	-	49	**89.8**	77.8	96.6	**57.1**	42.2	71.2	**80.1**	61.0	105.3
		H5N1 split	15	-	48	**79.2**	65.0	89.5	**47.9**	33.3	62.8	**66.9**	47.9	93.4
		H5N1 split	7.5	-	49	**67.3**	52.5	80.1	**22.4**	11.8	36.6	**40.3**	31.2	52.1
		H5N1 split	3.8	-	50	**62.0**	47.2	75.3	**14.0**	5.8	26.7	**35.5**	27.8	45.4
		H5N1 split	30	AS03	47	**95.7**	85.5	99.5	**83.0**	69.2	92.4	**146.6**	113.3	189.8
		H5N1 split	15	AS03	49	**100.0**	92.7	100.0	**83.7**	70.3	92.7	**181.3**	144.6	227.3
		H5N1 split	7.5	AS03	49	**95.9**	86.0	99.5	**63.3**	48.3	76.6	**134.6**	101.3	178.7
		H5N1 split	3.8	AS03	50	**96.0**	86.3	99.5	**66.0**	51.2	78.8	**117.9**	93.7	148.3
	Post II (D42)	H5N1 split	30	-	48	**95.8**	85.7	99.5	**64.6**	49.5	77.8	**113.6**	85.5	150.9
		H5N1 split	15	-	49	**87.8**	75.2	95.4	**53.1**	38.3	67.5	**80.1**	60.1	107.0
		H5N1 split	7.5	-	49	**77.6**	63.4	88.2	**36.7**	23.4	51.7	**53.4**	41.6	68.6
		H5N1 split	3.8	-	50	**72.0**	57.5	83.8	**22.0**	11.5	36.0	**40.7**	32.4	51.0
		H5N1 split	30	AS03	47	**100.0**	92.5	100.0	**97.9**	88.7	99.9	**258.2**	205.5	324.5
		H5N1 split	15	AS03	49	**100.0**	92.7	100.0	**85.7**	72.8	94.1	**400.1**	319.3	501.4
		H5N1 split	7.5	AS03	50	**98.0**	89.4	99.9	**86.0**	73.3	94.2	**343.0**	260.5	451.5
		H5N1 split	3.8	AS03	49	**98.0**	89.1	99.9	**85.7**	72.8	94.1	**314.7**	243.1	407.3

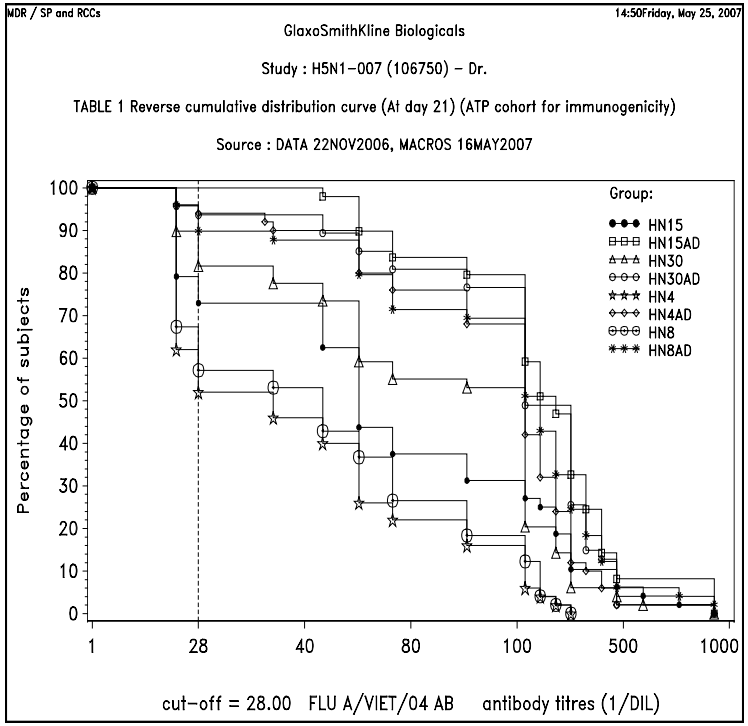
SCR: seroconversion rate defined as the percentage of vaccinees with a minimum 4-fold increase in titre at post-vaccination
N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 27 Percentage of subjects that reached neutralizing antibody titres ≥1:40 and ≥1:80 at each time point against vaccine strain H5N1 A/Vietnam/1194/2004 in H5N1-007 (ATP cohort for Immunogenicity)

Group	Timing	N	≥40 1/DIL				≥80 1/DIL			
			n	%	95% CI		n	%	95% CI	
					LL	UL			LL	LL
HN30	PRE	49	8	**16.3**	7.3	29.7	2	**4.1**	0.5	14.0
	PI(D21)	49	38	**77.6**	63.4	88.2	27	**55.1**	40.2	69.3
	PII(D42)	48	42	**87.5**	74.8	95.3	31	**64.6**	49.5	77.8
HN15	PRE	49	11	**22.4**	11.8	36.6	5	**10.2**	3.4	22.2
	PI(D21)	48	35	**72.9**	58.2	84.7	18	**37.5**	24.0	52.6
	PII(D42)	49	39	**79.6**	65.7	89.8	25	**51.0**	36.3	65.6
HN8	PRE	49	11	**22.4**	11.8	36.6	4	**8.2**	2.3	19.6
	PI(D21)	49	26	**53.1**	38.3	67.5	13	**26.5**	14.9	41.1
	PII(D42)	49	36	**73.5**	58.9	85.1	17	**34.7**	21.7	49.6
HN4	PRE	50	9	**18.0**	8.6	31.4	3	**6.0**	1.3	16.5
	PI(D21)	50	23	**46.0**	31.8	60.7	11	**22.0**	11.5	36.0
	PII(D42)	50	29	**58.0**	43.2	71.8	10	**20.0**	10.0	33.7
HN30AD	PRE	48	5	**10.4**	3.5	22.7	1	**2.1**	0.1	11.1
	PI(D21)	47	44	**93.6**	82.5	98.7	38	**80.9**	66.7	90.9
	PII(D42)	47	46	**97.9**	88.7	99.9	43	**91.5**	79.6	97.6
HN15AD	PRE	49	12	**24.5**	13.3	38.9	3	**6.1**	1.3	16.9
	PI(D21)	49	49	**100**	92.7	100.0	41	**83.7**	70.3	92.7
	PII(D42)	49	49	**100**	92.7	100.0	49	**100**	92.7	100.0
HN8AD	PRE	50	12	**24.0**	13.1	38.2	4	**8.0**	2.2	19.2
	PI(D21)	49	43	**87.8**	75.2	95.4	35	**71.4**	56.7	83.4
	PII(D42)	50	49	**98.0**	89.4	99.9	47	**94.0**	83.5	98.7
HN4AD	PRE	50	12	**24.0**	13.1	38.2	3	**6.0**	1.3	16.5
	PI(D21)	50	45	**90.0**	78.2	96.7	38	**76.0**	61.8	86.9
	PII(D42)	49	48	**98.0**	89.1	99.9	46	**93.9**	83.1	98.7

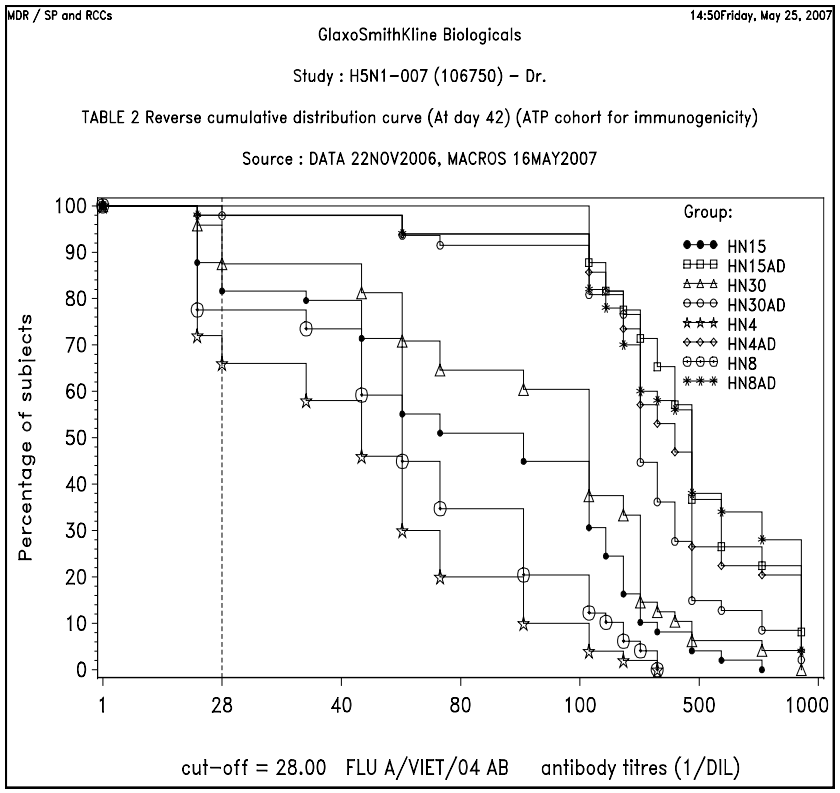
HN30= H5N1 30µg, HN15= H5N1 15µg, HN8= H5N1 7.5µg, HN4= H5N1 3.8µg
HN30AD= H5N1 30µg + AS03, HN15AD= H5N1 15µg + AS03
HN8AD= H5N1 7.5µg + AS03, HN4AD= H5N1 3.8µg + AS03
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
PRE = Pre-vaccination dose 1, PI(D21) = 21 days after vaccination, PII(D42) = 42 days after vaccination

Figure 7 Reverse cumulative Curve for neutralizing antibody titres (SNT) against vaccine strain H5N1 A/Vietnam/1194/2004 at Day 21 in study H5N1-007 (ATP cohort for immunogenicity)



HN30= H5N1 30µg, HN15= H5N1 15µg, HN8= H5N1 7.5µg, HN4= H5N1 3.8µg
HN30AD= H5N1 30µg + AS03, HN15AD= H5N1 15µg + AS03
HN8AD= H5N1 7.5µg + AS03, HN4AD= H5N1 3.8µg + AS03

Figure 8 Reverse cumulative Curve for neutralizing antibody titres (SNT) against vaccine strain H5N1 A/Vietnam/1194/2004 at Day 42 in study H5N1-007 (ATP cohort for immunogenicity)



HN30= H5N1 30µg, HN15= H5N1 15µg, HN8= H5N1 7.5µg, HN4= H5N1 3.8µg
HN30AD= H5N1 30µg + AS03, HN15AD= H5N1 15µg + AS03
HN8AD= H5N1 7.5µg + AS03, HN4AD= H5N1 3.8µg + AS03

2.7.3.3.2.6 Heterologous neutralizing antibody response (cross-reactive immunity)

Pivotal studies with the candidate Q-Pan pandemic influenza vaccine (Q-Pan-001 and Q-Pan-002)

Neutralizing antibody responses against H5N1 drift-variant strain A/Vietnam/1194/2004 in terms of GMTs, vaccine response and the percentage of subjects with serum neutralization titres (SNT) ≥1:28, ≥1:40 and ≥1:80 in study Q-Pan-001 are presented for subsets of the ATP immunogenicity cohort in Table 28 and Table 29.

In order to explore the potential of the adjuvanted H5N1 vaccine to evoke neutralizing antibody responses to additional virus strains, and to assess the heterogeneity of heterologous strain neutralization, induction of neutralizing antibodies against the drifted clade 2 strains A/turkey/Turkey/1/05 (a clade 2.2 virus) and A/Anhui/1/05 (a clade 2.3 virus) was tested in study Q-Pan-001. Of note, these clade 2 strains used for assessing the potential for cross-reactivity of antibodies elicited by the candidate Q-Pan H5N1 vaccine are considered by WHO as representatives of the clade 2 strains, but represent subclades different from A/Indonesia/5/05 (which is a clade 2.1 virus). This exploration was carried out with sera from the subset of recipients of Q-Pan A/Indonesia/05/2005 vaccine with full dose AS03 only.

Neutralizing antibody responses in study Q-Pan-001 against drift-variant virus strains H5N1 A/Anhui/1/05 and A/turkey/Turkey/1/05 (GMTs, vaccine response, percentage of subjects with titers ≥1:28, ≥1:40 and ≥1:80) are presented in Table 30 and Table 31.

Neutralizing antibody responses in study Q-Pan-002 against drift-variant H5N1 strain A/Vietnam/1194/2004, in terms of GMTs, GMT ratio's, vaccine response and the percentage of subjects with serum neutralization titres (SNT) ≥1:28, ≥1:40 and ≥1:80 are presented by age strata (18-60 years; >60 years) in Table 32 and Table 33.

Study Q-Pan-001

At the pre-vaccination observation, the majority of subjects were seropositive for A/Vietnam/1194/2004 neutralizing antibodies (titers ≥ 1:28). Similar to HI antibodies, the prevaccination neutralizing antibody seropositivity rates against strain A/Vietnam/1194/2004 were higher than those against homologous strain A/Indonesia. Neutralizing antibody titers against A/Vietnam/1194/2004 ≥1:80 before immunization were noted in 32.7% to 58.7% of subjects in the various treatment groups.

Among subjects studied who received any adjuvanted vaccine regimen, all but 2 were seropositive (titer ≥ 1:28) at Day 21; and 100% became seropositive at Day 42 (Table 28). At Day 42, 94.0% to 100% of recipients of adjuvanted Q-Pan or D-Pan vaccines had titers ≥ 1:80, versus 77.6% of subjects in the non-adjuvanted Q-Pan vaccine group (Table 29).

Baseline GMTs of neutralizing antibodies against A/Vietnam/1194/2004 were approximately twice those observed for A/Indonesia/05/2005. GMTs at prevaccination

were similar among the various vaccine groups. The GMTs increased significantly after the first dose in the adjuvanted Q-Pan or D-Pan vaccine groups. After the second dose, there was a further increase in GMTs in these groups to values between 254.0 and 327.1 (Table 28). In the group that received non-adjuvanted vaccine, the rise in GMT at Day 21 was less pronounced (almost 3-fold), but there was no further increase by Day 42. Groups which received half dose AS03 vaccine, demonstrated Day 42 GMT values which were not systematically different from those in full dose AS03 recipients, with overlapping 95% CIs.

At Day 42, after two doses of vaccine, a neutralizing antibody vaccine response against strain A/Vietnam/1194/2004 could be detected in 30.6% of subjects in the non-adjuvanted group and 42.0% to 67.3% of subjects in adjuvanted vaccine groups (Table 28). In contrast to A/Indonesia, the majority of subjects in all groups were seropositive for A/Vietnam/1194/2004 at baseline. The vaccine response rate was substantially greater among subjects with undetectable neutralizing antibodies to A/Vietnam/1194/2004 at pre-vaccination (Appendix Table 5). While the rate of vaccine response in the baseline-seropositive subset did not improve with a second dose of unadjuvanted vaccine, there was a consistent increase in vaccine response among the important and vulnerable group of baseline seronegatives who received adjuvanted vaccine. After two doses of vaccine, all baseline-seronegatives demonstrated a vaccine response in the adjuvanted Q-Pan or D-Pan vaccine groups.

Reverse cumulative curves (RCCs) for titers of neutralizing antibodies against strain A/Vietnam/1194/2004 at the Day 42 time point are presented in Figure 9. Neutralizing antibody RCC for Q-Pan and D-Pan vaccines were largely overlapping for vaccines formulated with the same amount of AS03.

The subject population was largely seronegative for neutralizing antibodies to strain A/Anhui, with no subject having any detectable neutralizing antibody at a 1:28 serum dilution prior to immunization. At Day 42, after 2 vaccine doses, 78.9% of subjects had a ≥ 4-fold rise in neutralizing antibody titer against A/Anhui and GMT rose from 14 (or undetectable) to 91.3. Furthermore, 80.3% of Q-Pan vaccinees had A/Anhui neutralizing titers ≥ 40 and 60.6% had titers ≥ 80 (Table 30 and Table 31).

In contrast, 35.7% of subjects were seropositive to A/turkey at baseline and approximately 25% of subjects had pre-vaccination neutralizing titers ≥40. At Day 42, after 2 vaccine doses, 88.8% of subjects had a ≥ 4-fold rise in neutralizing antibody titer and GMT rose from 25.6 to 594.4. At Day 42, all subjects were seropositive for A/turkey neutralizing antibodies and 98.6% had titers ≥ 80 (Table 30 and Table 31).

Study Q-Pan-002

In study Q-Pan-002, 37.4% of subjects in the 18 to 60 years age group were seropositive (titer ≥ 1:28) for neutralizing antibodies against A/Vietnam/1194/2004 at baseline. Additional serum neutralizing antibodies specific for the drift-variant virus A/Vietnam/1194/2004 were induced by the AS03 adjuvanted Q-Pan vaccine. At Day 42, 96.5% of subjects were seropositive and 84.2% of subjects attained antibody titers ≥ 1:80 against A/Vietnam/1194/2004 (Table 32 and Table 33), which is a slightly smaller

proportion compared to the 100% homologous response against A/Indonesia/05/2005 in this age group (Table 24 and Table 25).

Fewer subjects in the > 60 years age group (17%) compared with the younger age group were seronegative at baseline for neutralizing antibodies against A/Vietnam/1194/2004 viruses. Nevertheless, immunization with Q-Pan vaccine still resulted in a clear upward shift in titer distributions. At Day 42, 96.3% of subjects were seropositive for neutralizing antibodies against A/Vietnam/1194/2004. After immunization, the proportion of subjects with neutralizing titers of ≥ 1:80 increased from 70.4% to 92.6% for A/Vietnam/1194/2004.

RCCs for titers of neutralizing antibodies at the Day 42 time point are presented by age strata (18-60 years; >60 years) in Figure 10 for responses against strain A/Vietnam/1194/2004.

Although an important proportion of subjects had measurable neutralizing antibody titers at baseline, especially in the case of antibodies against A/Vietnam/1194/2004 in the older age group, these figures demonstrate that there is a marked and broad-based upward shift in the population distribution of titers following Q-Pan vaccination.

In conclusion, these data obtained in studies Q-Pan-001 and Q-Pan-002 indicate that the AS03 adjuvanted H5N1 vaccine with strain A/Indonesia/05/2005 was able to induce high neutralizing antibody responses to both the vaccine virus and to drift-variant virus A/Vietnam/1194/2004, irrespective of the defined threshold (≥1:28, ≥1:40 or ≥1:80).

The neutralizing antibody responses with the Q-Pan vaccine and the D-Pan vaccine when formulated with the same amount of AS03 were similar; titers induced with half dose AS03 were slightly lower than those resulting from immunizations with either Q- or D-antigens with the full dose of AS03. The data confirm the ability of the candidate Q-Pan pandemic vaccine to induce a cross-reactive immune response against strain variation.

Supportive study H5N1-007 with D-Pan H5N1 pandemic influenza vaccine

Neutralizing antibody titres were measured against H5N1 heterologous strain (A/Indonesia/05/2005) in all vaccine groups from study H5N1-007 (Table 34 and Table 35). Cross reactivity data to drifted clade 2 strains (RG derived from A/Anhui/01/2005/subclade 3; A/turkey/Turkey/1/2005 -NIBRG23/subclade 2) have been obtained in a subset of subjects from study H5N1-007 who received 3.8µg HA, adjuvanted or not with AS03 (20 per group) (Table 36).

In study H5N1-007, as shown in Table 34, seropositivity rates at prevaccination ranged from 0.0% to 4.1% in the non-adjuvanted groups, and from 0.0% to 21.3% in the adjuvanted groups. After the first dose, significantly higher values were observed in the adjuvanted groups (between 66.7% and 82.6%) as compared to non-adjuvanted formulations (between 2.3% and 41.7%). After the second dose, seropositivity rates further increased in the adjuvanted groups (ranging from 87.5% to 97.8%) and remained stable in the non-adjuvanted groups (2.3% to 31.3%).

After both doses, SCR were significantly higher in the adjuvanted groups as compared to the non-adjuvanted formulations. SCR with the adjuvanted formulations ranged from 27.3% to 54.3% after the first dose and from 63.0% to 77.1% after the second dose (versus 0.0%-18.8% and 0.0%-8.3% respectively after the two injections in the non-adjuvanted groups).

GMTs were similar in all vaccine groups prior to vaccination, and were significantly higher after both doses in the adjuvanted groups.

The higher neutralizing antibody response after the first dose as compared to after the second dose in the non-adjuvanted 30 µg HA vaccine group is most likely related to the fact that the observed post vaccination GMTs in this group are in the low titre range (close to the assay cut-off) which introduces more variability in the assay results.

Neutralizing antibody responses against H5N1 A/Indonesia/05/2005 in study H5N1-007 in terms of the percentage of subjects with serum neutralization titre ≥1:40 and 1:80 at Days 0, 21 and 42 are included in Table 35. Reverse cumulative curves (RCCs) for the Day 21 and Day 42 time points in study H5N1-007 are presented in Figure 11 and Figure 12 respectively.

For adjuvanted H5N1 vaccine groups, the percentage of subjects who had titres ≥1:40 and 1:80 at Day 21 ranged from 31.8% to 60.9%, and 15.9% to 45.7% respectively. As shown by the RCC, no significant differences were shown between adjuvanted groups as the curves crossed between groups.

The majority of subjects from the adjuvanted groups had titres above the cut-offs of 1:40 and 1:80 at Day 42 (i.e. 79.2%-82.6% and 45.7%-58.3% respectively). Significantly lower antibody titres ≥1:40 and 1:80 were observed in the non-adjuvanted groups as compared to the adjuvanted groups as illustrated by the RCC.

In terms of neutralizing antibody production after the first and second dose, almost no effect of vaccination was detected with non-adjuvanted formulations according to either threshold (≥1:40 and 1:80).

In terms of neutralizing antibody production against strains A/Anhui/01/2005 and A/turkey/Turkey/1/2005, almost no effect of vaccination was observed in the non-adjuvanted group. Indeed, similar GMTs were observed at pre-vaccination and post vaccination time points, and no subjects seroconverted against either strain after the first or second dose (Table 36).

There was a significant increase in GMTs after the first and second vaccination with the adjuvanted formulations. At Day 42, 75.0% and 85.0% of vaccinees from the adjuvanted groups had seroconverted against strains A/Anhui/01/2005 and A/turkey/Turkey/1/2005 respectively.

These data further confirm the ability of the pandemic vaccine to induce a cross-reactive immune response against strain variation.

Table 28 Neutralizing antibody responses (GMT, titre ≥1:28 and vaccine response) against strain H5N1 A/Vietnam/1194/2004 of the H5N1 (A/Indonesia) influenza vaccine in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site‡	HA (µg per dose)	AS03	N	GMT			≥1:28			Vaccine response		
							Value	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**Pre**	H5N1 Indonesia	Quebec	3.8	AS03	47	**57.0**	41.3	78.6	**70.2**	55.1	82.7	**-**	**-**	**-**
		H5N1 Indonesia	Quebec	3.8	AS03/2	46	**82.3**	59.0	114.7	**80.4**	66.1	90.6	**-**	**-**	**-**
		H5N1 Indonesia	Quebec	3.8	-	49	**55.7**	38.7	80.2	**67.3**	52.5	80.1	**-**	**-**	**-**
		H5N1 Indonesia	Dresden	3.8	AS03	49	**51.3**	34.6	76.2	**55.1**	40.2	69.3	-	-	-
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**59.6**	44.2	80.5	**72.0**	57.5	83.8	-	-	-
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	**250.9**	203.6	309.2	**100**	92.5	100	**44.7**	30.2	59.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	**260.9**	205.1	331.9	**96.0**	86.3	99.5	**30.4**	17.7	45.8
		H5N1 Indonesia	Quebec	3.8	-	49	**145.2**	108.0	195.3	**91.8**	80.4	97.7	**34.7**	21.7	49.6
		H5N1 Indonesia	Dresden	3.8	AS03	49	**201.9**	151.9	268.4	**98.0**	89.1	99.9	**49.0**	34.4	63.7
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	**215.0**	174.3	265.3	**100**	92.7	100	**40.8**	27.0	55.8
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	**264.8**	216.7	323.6	**100**	92.5	100	**53.2**	38.1	67.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	**327.1**	269.8	396.6	**100**	92.5	100	**45.5**	30.4	61.2
		H5N1 Indonesia	Quebec	3.8	-	49	**143.9**	111.2	186.2	**98.0**	89.1	99.9	**30.6**	18.3	45.4
		H5N1 Indonesia	Dresden	3.8	AS03	49	**319.2**	261.6	389.4	**100**	92.7	100	**67.3**	52.5	80.1
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**254.0**	213.0	302.9	**100**	92.9	100	**42.0**	28.2	56.8

N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Vaccine response defined as antibody titer ≥ 4-fold the pre-vaccination titer (samples seronegative at pre-vaccination were assigned a reciprocal titer of 14)
‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

Table 29 Neutralizing antibody responses (titre ≥1:40 ≥1:80) against strain H5N1 A/Vietnam/1194/2004 of the H5N1 (A/Indonesia) influenza vaccine in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site‡	HA (µg per dose)	AS03	N	≥1:40			≥1:80		
							%	95% CI		%	95% CI	
								LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**Pre**	H5N1 Indonesia	Quebec	3.8	AS03	47	**61.7**	46.4	75.5	**51.1**	36.1	65.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	46	**71.7**	56.5	84.0	**58.7**	43.2	73.0
		H5N1 Indonesia	Quebec	3.8	-	49	**57.1**	42.2	71.2	**32.7**	19.9	47.5
		H5N1 Indonesia	Dresden	3.8	AS03	49	**55.1**	40.2	69.3	**42.9**	28.8	57.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**66.0**	51.2	78.8	**48.0**	33.7	62.6
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	**97.9**	88.7	99.9	**95.7**	85.5	99.5
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	**96.0**	86.3	99.5	**96.0**	86.3	99.5
		H5N1 Indonesia	Quebec	3.8	-	49	**91.8**	80.4	97.7	**77.6**	63.4	88.2
		H5N1 Indonesia	Dresden	3.8	AS03	49	**93.9**	83.1	98.7	**85.7**	72.8	94.1
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	**98.0**	89.1	99.9	**89.8**	77.8	96.6
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	**100**	92.5	100	**95.7**	85.5	99.5
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	**100**	92.5	100	**97.9**	88.7	99.9
		H5N1 Indonesia	Quebec	3.8	-	49	**89.8**	77.8	96.6	**77.6**	63.4	88.2
		H5N1 Indonesia	Dresden	3.8	AS03	49	**100**	92.7	100	**100**	92.7	100
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**100**	92.9	100	**94.0**	83.5	98.7

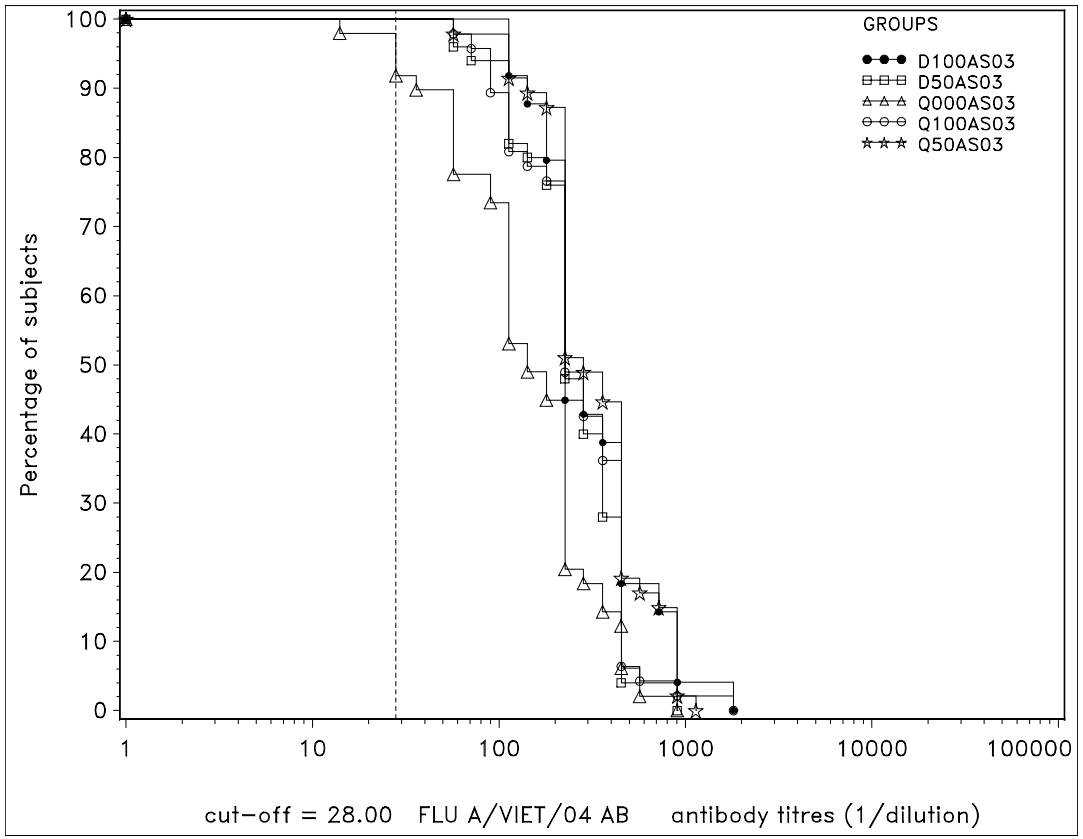
N = number of subjects with available results

% = percentage of subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

Figure 9 Reverse cumulative curves of neutralising antibody titres against A/Vietnam/1194/2004 strain at Day 42 in study Q-Pan-001 (ATP cohort for immunogenicity)



Q000AS03 = Q000AS03: 3.8 ug Quebec A/Indo No AS03
Q100AS03 = Q100AS03: 3.8 ug Quebec A/Indo Full AS03
Q50AS03 = Q50AS03: 3.8 ug Quebec A/Indo Half AS03
D100AS03 = D100AS03: 3.8 ug Dresden A/Indo Full AS03
D50AS03 = D50AS03: 3.8 ug Dresden A/Indo Half AS03

Table 30 Neutralizing antibody responses (GMT, titre ≥1:28 and vaccine response) against strains H5N1 A/Anhui/05 and A/Turkey/05 of the H5N1 (A/Indonesia) influenza vaccine in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Antibody	Vaccine strain and adjuvant	Timepoint	N	GMT			≥1:28			Vaccine Response		
					Value	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**A/Anhuil/05**	H5N1 3.8µg (Quebec) Indonesia + full AS03	**Pre**	143	**14.0**	14.0	14.0	**0.0**	0.0	2.5	**-**	**-**	**-**
			Post II (D42)	142	**91.3**	78.4	106.4	**95.1**	90.1	98.0	**78.9**	71.2	85.3
	A/Turkey/05	H5N1 3.8µg (Quebec) Indonesia + full AS03	**Pre**	143	**25.6**	21.9	29.9	**35.7**	27.8	44.1	**-**	-	-
			Post II (D42)	143	**594.4**	523.6	674.7	**100.0**	97.5	100.0	**88.8**	82.5	93.5

N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Vaccine response defined as antibody titer ≥ 4-fold the pre-vaccination titer (samples seronegative at pre-vaccination were assigned a reciprocal titer of 14)

Table 31 Neutralizing antibody responses (titre ≥1:40 ≥1:80) against strains H5N1 A/Anhui/05 and A/Turkey/05 of the H5N1 (A/Indonesia) influenza vaccine in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Antibody	Vaccine strain and adjuvant	Timepoint	N	≥1:40			≥1:80		
					%	95% CI		%	95% CI	
						LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**A/Anhuil/05**	H5N1 3.8µg (Quebec) Indonesia + full AS03	**Pre**	143	**0.0**	0.0	2.5	**0.0**	0.0	2.5
			Post II (D42)	142	**80.3**	72.8	86.5	**60.6**	52.0	68.7
	A/Turkey/05	H5N1 3.8µg (Quebec) Indonesia + full AS03	**Pre**	143	**25.2**	18.3	33.1	**15.4**	9.9	22.4
			Post II (D42)	143	**98.6**	95.0	99.8	**98.6**	95.0	99.8

N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 32 Neutralizing antibody responses (GMT, GMFR, titre ≥1:28, vaccine response) against strain H5N1 A/Vietnam/1194/2004 of the AS03 adjuvanted Q-Pan H5N1 pandemic influenza vaccine in study Q-Pan-002 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Age group	Time-point	Study group	N	GMT			GMFR			≥1:28			Vaccine response		
					Value	95% CI		Value	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	**Pre**	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	171	**27.8**	23.9	32.4	**-**	-	-	**37.4**	30.2	45.1	**-**	-	-
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	171	**159.8**	142.1	179.8	**5.7**	4.9	6.7	**96.5**	92.5	98.7	**65.5**	57.9	72.6
	>60 years	**Pre**	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	54	**96.4**	72.6	128.0	**-**	-	-	**83.3**	72.7	91.0	**-**	-	-
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	54	**216.6**	174.1	269.4	**2.2**	1.7	2.9	**96.3**	88.8	99.3	**24.1**	13.5	37.6

N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
GMFR = Geometric mean fold rise
Vaccine response defined as antibody titer ≥ 4-fold the pre-vaccination titer (samples seronegative at pre-vaccination were assigned a reciprocal titer of 14)

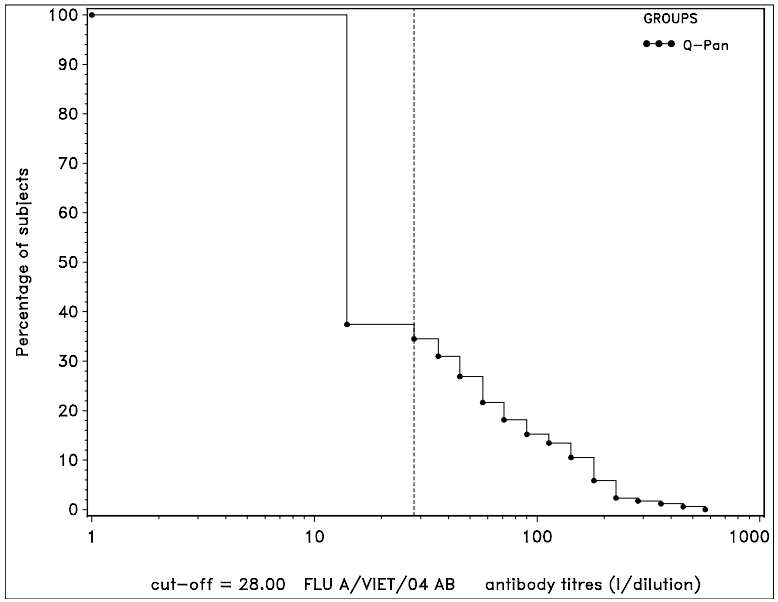
Table 33 Neutralizing antibody responses (titre ≥1:40, ≥1:80) against strain H5N1 A/Vietnam/1194/2004 of the AS03 adjuvanted Q-Pan pandemic influenza vaccine in study Q-Pan-002 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Age group	Time-point	Study group	N	≥1:40			≥1:80		
					%	95% CI		%	95% CI	
						LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	**Pre**	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	171	**31.0**	25.2	37.3	**18.1**	13.4	23.7
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	171	**95.9**	92.4	98.1	**84.2**	78.9	88.6
	>60 years	**Pre**	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	54	**81.5**	70.6	89.6	**70.4**	58.5	80.4
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	54	**96.3**	88.8	99.3	**92.6**	83.8	97.4

N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Figure 10 **Reverse cumulative curves for neutralizing antibody titres against strain H5N1 A/Vietnam/1194/2004 following AS03 adjuvanted Q-Pan H5N1 pandemic influenza vaccine in study Q-Pan-002 (ATP cohort for immunogenicity, subset)**

Subjects 18-60 years, Day 0



Subjects 18-60 years, Day 42

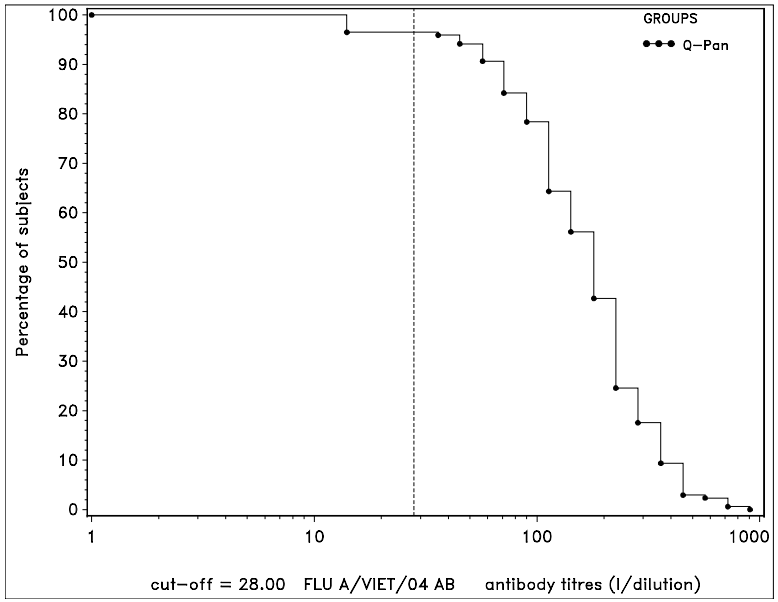
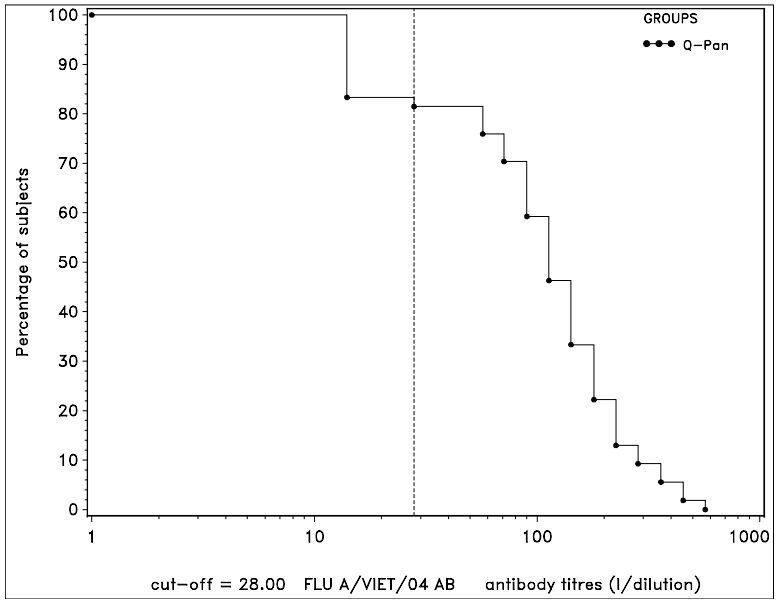


Figure 10 (cont'd) Reverse cumulative curves for neutralizing antibody titres against strain H5N1 A/Vietnam/1194/2004 following AS03 adjuvanted Q-Pan H5N1 pandemic influenza vaccine in study Q-Pan-002 (ATP cohort for immunogenicity, subset)

Subjects > 60 years, Day 0



Subjects > 60 years, Day 42

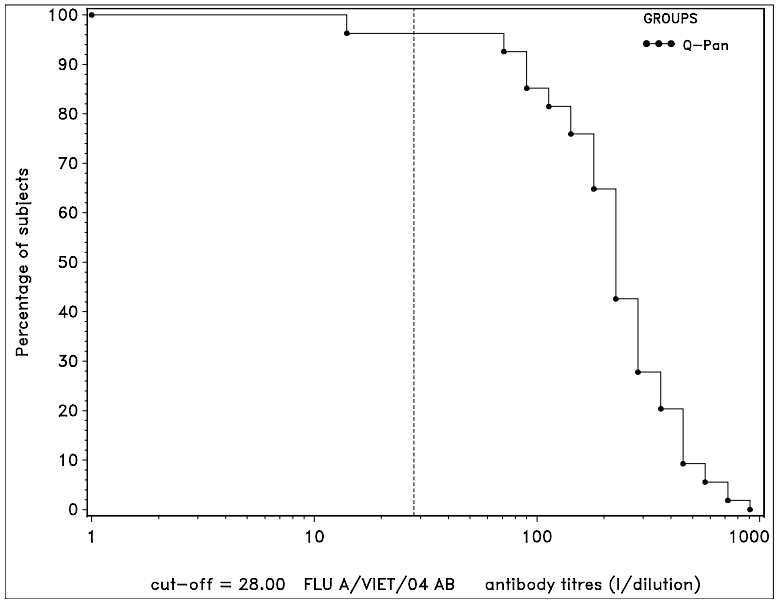


Table 34 Neutralizing antibody responses against H5N1 A/Indonesia/05/2005 of the D-Pan H5N1 pandemic influenza vaccine in adults from study H5N1-007 (ATP immunogenicity cohort)

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	≥1:28			SCR			GMT		
						%	95% CI		%	95% CI		Value	95% CI	
							LL	UL		LL	UL		LL	UL
H5N1-007	Pre	H5N1 split	30	-	49	4.1	0.5	14.0	-	-	-	14.5	13.8	15.2
18-60 yrs		H5N1 split	15	-	45	0.0	0.0	7.9	-	-	-	14.0	14.0	14.0
		H5N1 split	7.5	-	44	2.3	0.1	12.0	-	-	-	14.2	13.8	14.7
		H5N1 split	3.8	-	43	0.0	0.0	8.2	-	-	-	14.0	14.0	14.0
		H5N1 split	30	AS03	47	0.0	0.0	7.5	-	-	-	14.0	14.0	14.0
		H5N1 split	15	AS03	44	2.3	0.1	12.0	-	-	-	14.2	13.8	14.7
		H5N1 split	7.5	AS03	47	21.3	10.7	35.7	-	-	-	17.3	15.2	19.5
		H5N1 split	3.8	AS03	48	8.3	2.3	20.0	-	-	-	15.8	13.9	17.9
	Post I (D21)	H5N1 split	30	-	48	41.7	27.6	56.8	18.8	8.9	32.6	24.9	20.0	30.8
		H5N1 split	15	-	43	14.0	5.3	27.9	4.7	0.6	15.8	16.9	14.2	20.2
		H5N1 split	7.5	-	43	11.6	3.9	25.1	0.0	0.0	8.2	15.4	14.2	16.8
		H5N1 split	3.8	-	43	2.3	0.1	12.3	2.3	0.1	12.3	14.5	13.5	15.4
		H5N1 split	30	AS03	46	82.6	68.6	92.2	54.3	39.0	69.1	54.6	42.5	70.1
		H5N1 split	15	AS03	44	79.5	64.7	90.2	27.3	15.0	42.8	38.1	30.0	48.5
		H5N1 split	7.5	AS03	47	72.3	57.4	84.4	36.2	22.7	51.5	43.7	33.7	56.6
		H5N1 split	3.8	AS03	48	66.7	51.6	79.6	31.3	18.7	46.3	36.6	28.8	46.5
	Post II (D42)	H5N1 split	30	-	48	31.3	18.7	46.3	8.3	2.3	20.0	20.6	17.2	24.6
		H5N1 split	15	-	44	15.9	6.6	30.1	2.3	0.1	12.0	16.5	14.6	18.7
		H5N1 split	7.5	-	44	6.8	1.4	18.7	0.0	0.0	8.0	15.0	13.8	16.3
		H5N1 split	3.8	-	43	2.3	0.1	12.3	2.3	0.1	12.3	14.5	13.5	15.7
		H5N1 split	30	AS03	46	91.3	79.2	97.6	63.0	47.5	76.8	66.8	53.4	83.5
		H5N1 split	15	AS03	44	93.2	81.3	98.6	68.2	52.4	81.4	72.9	58.5	90.9
		H5N1 split	7.5	AS03	46	97.8	88.5	99.9	67.4	52.0	80.5	95.7	75.3	121.7
		H5N1 split	3.8	AS03	48	87.5	74.8	95.3	77.1	62.7	88.0	80.3	62.0	103.9

SCR: seroconversion rate defined as the percentage of vaccinees with a minimum 4-fold increase in titre at post-vaccination
N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 35 Percentage of subjects that reached neutralizing antibody titres ≥1:40 and ≥1:80 against H5N1 A/Indonesia/05/2005 at each time point in study H5N1-007 (ATP cohort for Immunogenicity)

Group	Timing	N	≥40 1/DIL				≥80 1/DIL			
			n	%	95%CI		n	%	95%CI	
					LL	UL			LL	UL
HN30	PRE	49	0	**0.0**	0.0	7.3	0	**0.0**	0.0	7.3
	PI(D21)	48	13	**27.1**	15.3	41.8	5	**10.4**	3.5	22.7
	PII(D42)	48	8	**16.7**	7.5	30.2	2	**4.2**	0.5	14.3
HN15	PRE	45	0	**0.0**	0.0	7.9	0	**0.0**	0.0	7.9
	PI(D21)	43	2	**4.7**	0.6	15.8	2	**4.7**	0.6	15.8
	PII(D42)	44	2	**4.5**	0.6	15.5	1	**2.3**	0.1	12.0
HN8	PRE	44	0	**0.0**	0.0	8.0	0	**0.0**	0.0	8.0
	PI(D21)	43	1	**2.3**	0.1	12.3	0	**0.0**	0.0	8.2
	PII(D42)	44	2	**4.5**	0.6	15.5	0	**0.0**	0.0	8.0
HN4	PRE	43	0	**0.0**	0.0	8.2	0	**0.0**	0.0	8.2
	PI(D21)	43	1	**2.3**	0.1	12.3	0	**0.0**	0.0	8.2
	PII(D42)	43	1	**2.3**	0.1	12.3	0	**0.0**	0.0	8.2
HN30AD	PRE	47	0	**0.0**	0.0	7.5	0	**0.0**	0.0	7.5
	PI(D21)	46	28	**60.9**	45.4	74.9	21	**45.7**	30.9	61.0
	PII(D42)	46	37	**80.4**	66.1	90.6	21	**45.7**	30.9	61.0
HN15AD	PRE	44	0	**0.0**	0.0	8.0	0	**0.0**	0.0	8.0
	PI(D21)	44	14	**31.8**	18.6	47.6	7	**15.9**	6.6	30.1
	PII(D42)	44	36	**81.8**	67.3	91.8	21	**47.7**	32.5	63.3
HN8AD	PRE	47	4	**8.5**	2.4	20.4	0	**0.0**	0.0	7.5
	PI(D21)	47	27	**57.4**	42.2	71.7	11	**23.4**	12.3	38.0
	PII(D42)	46	38	**82.6**	68.6	92.2	26	**56.5**	41.1	71.1
HN4AD	PRE	48	3	**6.3**	1.3	17.2	2	**4.2**	0.5	14.3
	PI(D21)	48	25	**52.1**	37.2	66.7	9	**18.8**	8.9	32.6
	PII(D42)	48	38	**79.2**	65.0	89.5	28	**58.3**	43.2	72.4

HN4 = H5N1 3.8µg;HN4AD = H5N1 3.8µg + AS03; HN8 = H5N1 7.5µg; HN8AD = H5N1 7.5µg + AS03
HN15 = H5N1 15µg; HN15AD = H5N1 15µg + AS03 ;HN30 = H5N1 30µg; HN30AD = H5N1 30µg + AS03
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
PRE = pre-vaccination dose 1
PI(D21) = 21 days after the fisrt vaccination
PII(D42) = 42 after the first vaccination

Figure 11 Reverse cumulative Curve for neutralizing antibody titres (SNT) against vaccine strain H5N1 A/Indonesia/05/2005 at Day 21 in study H5N1-007 (ATP cohort for immunogenicity)

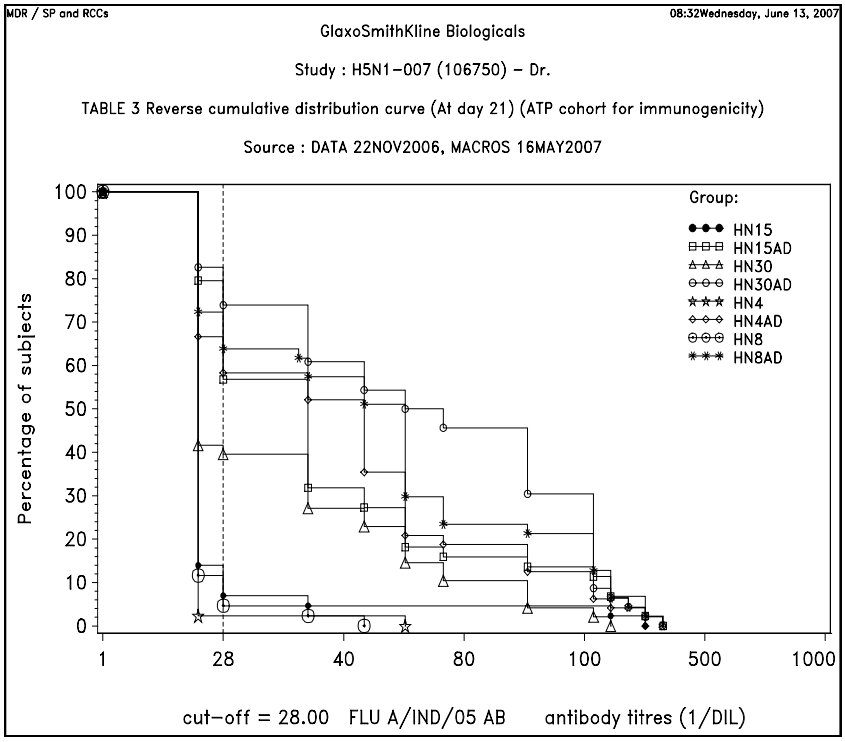


Figure 12 Reverse cumulative Curve for neutralizing antibody titres (SNT) against vaccine strain H5N1 A/Indonesia/05/2005 at Day 42 in study H5N1-007 (ATP cohort for immunogenicity)

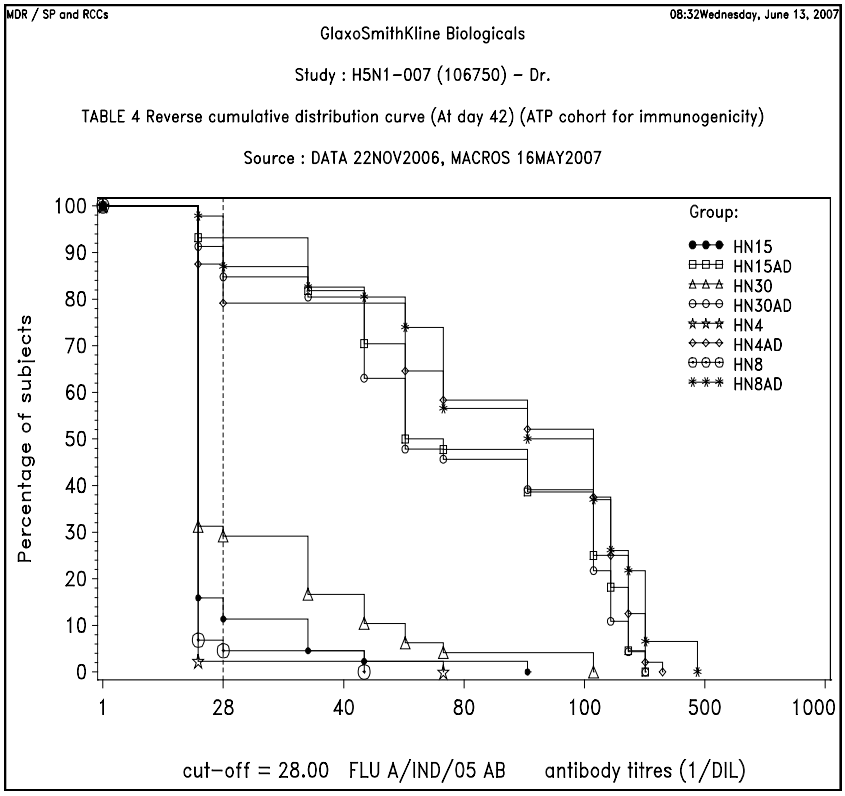


Table 36 Neutralizing antibody responses of the D-Pan H5N1 pandemic influenza vaccine against H5N1 A/Anhui and A/Turkey strains in adults from study H5N1-007 (ATP immunogenicity cohort)

Strain		Timepoint	HA (µg per dose)	AS03	N	≥1:28			SCR			GMT		
						Value	95% CI		%	95% CI		Value	95% CI	
							LL	UL		LL	UL		LL	UL
A/ANHUI/05	H5N1 split	Pre	3.8	AS03	20	**20.0**	5.7	43.7	**-**	-	-	**17.9**	13.7	23.3
	H5N1 split		3.8	-	20	**5.0**	0.1	24.9	**-**	-	-	**14.5**	13.5	15.6
	H5N1 split	Post I (D21)	3.8	AS03	20	**75.0**	50.9	91.3	**35.0**	15.4	59.2	**37.7**	26.8	53.1
	H5N1 split		3.8	-	20	**20.0**	5.7	43.7	**0.0**	0.0	16.8	**16.3**	14.1	18.9
	H5N1 split	Post II (D42)	3.8	AS03	20	**100**	83.2	100	**75.0**	50.9	91.3	**97.3**	72.5	130.6
	H5N1 split		3.8	-	20	**15.0**	3.2	37.9	**0.0**	0.0	16.8	**16.1**	13.6	19.1
A/ TURK/05	H5N1 split	Pre	3.8	AS03	20	**0.0**	0.0	16.8	**-**	-	-	**14.0**	14.0	14.0
	H5N1 split		3.8	-	17	**5.9**	0.1	28.7	**-**	-	-	**14.8**	13.2	16.6
	H5N1 split	Post I (D21)	3.8	AS03	20	**75.0**	50.9	91.3	**45.0**	23.1	68.5	**42.3**	27.7	64.5
	H5N1 split		3.8	-	17	**17.6**	3.8	43.4	**0.0**	0.0	19.5	**17.2**	13.3	22.3
	H5N1 split	Post II (D42)	3.8	AS03	20	**100**	83.2	100	**85.0**	62.1	96.8	**113.2**	80.7	158.9
	H5N1 split		3.8	-	17	**11.8**	1.5	36.4	**0.0**	0.0	19.5	**16.7**	12.4	22.5

GMT = geometric mean antibody titre calculated on all subjects
Seroconversion defined as: antibody titre after vaccination ≥ 4 fold the pre-vaccination antibody titre
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = pre-vaccination dose 1 ; PI(D21) = Post vaccination at day 21
PII(D42) = Post vaccination at day 42

2.7.3.3.3 Comparison of Results in Subpopulations

2.7.3.3.3.1 Effect of age at vaccination

The immunogenicity of the AS03 adjuvanted candidate vaccine containing H5N1 antigen manufactured in Quebec (3.8µg HA) has been evaluated in healthy adults (18-60 or 18-64 years old) from studies Q-Pan-001, Q-Pan-002 and H5N1-007 and in a subset of 436 elderly subjects (>60 years old) included in study Q-Pan-002. The effect of age at vaccination, i.e. adults versus elderly, is further discussed in below.

In 18-60 (or 64 for Q-Pan-001) year old subjects, results from pivotal studies Q-Pan-001 and Q-Pan-002 with Q-Pan vaccine and supportive study H5N1-007 with D-Pan vaccine showed that all three immunological criteria defined by CHMP for annual relicensing of interpandemic influenza vaccines were met or exceeded after two doses of AS03 adjuvanted vaccine (administered at 0 and 21 days) containing antigen concentrations as low as 3.8 µg HA. In study Q-Pan-001, SCR and SPR following two doses of Q-Pan vaccine adjuvanted with full dose AS03 were both 97.2%, with a SCF of 92.9. In study Q-Pan-002, a 2-dose vaccination schedule with AS03 adjuvanted Q-Pan vaccine resulted in SCR and SPR of 91.0%, with a SCF of 51.4. In supportive study H5N1-007, SCR and SPR of 83.3% were obtained at Day 42 in initially seronegative subjects who received 3.8 µg HA of D-Pan H5N1 antigen adjuvanted with AS03, with a SCF of 29.8. With respect to the neutralizing antibody response, all subjects from studies Q-Pan-001 and Q-Pan-002 were seropositive following a 2-dose schedule with AS03 adjuvanted Q-Pan vaccine. Vaccine response rates (defined as neutralizing antibody titre ≥ 4-fold the pre-vaccination titre) after the second dose were 97.9% and 94.4% for study Q-Pan-001 and Q-Pan-002, respectively. Likewise, in study H5N1-007, all subjects from the 3.8 µg HA/AS03 vaccine group were seropositive after the second dose of D-Pan vaccine and vaccine response after the second dose was 86.0%. Notably, a meaningful humoral response (in terms of both anti-HA and neutralizing antibodies) against an H5N1 strain heterologous to the vaccine strain was also observed with adjuvanted formulations after the second dose. In particular, SPR of 63.9% for HI antibodies in studies Q-Pan-001 and vaccine response rate of 53.2% and 65.5% for neutralizing antibodies in studies Q-Pan-001 and Q-Pan-002, respectively, were obtained against the heterologous strain A/Vietnam/1194/2004 after two doses of the (full dose) AS03 adjuvanted Q-Pan vaccine containing 3.8 µg HA of strain A/Indonesia. In supportive study H5N1-007 with adjuvanted D-Pan H5N1 vaccine formulated with strain A/Vietnam/1194/2004 (at 3.8 µg HA), SPR of 20.0% for HI antibodies and SCR of 77.1% for neutralizing antibodies were obtained against the heterologous strain A/Indonesia.

Considering the limited manufacturing capacities in case of a pandemic, the formulation containing the minimal amount of antigen that fulfilled all three CHMP criteria was selected for the adult population (18-60 years old). The safety and reactogenicity profile of the selected dosage (3.8 µg HA/AS03) was also proven to be satisfactory, as described in Section 2.7.4.

An assessment of the immune response **in elderly subjects (>60 years old)** was performed in study Q-Pan-002 following administration of the AS03 adjuvanted Q-Pan vaccine containing H5N1 A/Indonesia/05/2005 (3.8µg HA/dose). A total of 1489 elderly subjects were enrolled in this study, of which 436 were included in the ATP immunogenicity subset. After the second dose, homologous HI antibody SCR and SPR were 76.4% and 76.8% respectively, with a SCF of 17.2. All three immunological criteria defined by CHMP for the elderly population were fulfilled after the second dose. The vaccine response rate for neutralizing antibodies against vaccine strain following vaccination with 2 doses of AS03-adjuvanted Q-Pan vaccine in elderly subjects was 80.4%. Of note, AS03 adjuvanted Q-Pan vaccine was also proven to be safe and well-tolerated in elderly subjects. These results obtained in study Q-Pan-002 demonstrate that a very high immune response was elicited in elderly subjects aged 60 years or older by the AS03 adjuvanted Q-Pan H5N1 A/Indonesia/05/2005 vaccine containing the same dosage (3.8 µg HA) as recommended for the adult population aged 18 to 60 years.

Based on the data obtained in pivotal studies Q-Pan-001 and Q-Pan-002, the age indication will therefore be adults aged 18 years or older (including elderly).

Of note, none of the various formulations tested met all three CHMP requirements after the first dose, therefore indicating the need for a 2 dose schedule in the elderly.

2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

2.7.3.4.1 Effect of antigen dose

In study H5N1-007, the effect of HA antigen dose on the response was evaluated in terms of SPR against the vaccine strain H5N1 A/Vietnam/1194/2004. To this end, the difference in SPR between groups has been calculated at Day 21 (i.e. 21 days after the first dose) and Day 42 (i.e. 21 days after the second dose), with the corresponding p-values using 2-sided Fisher exact test. Results of this inferential analysis are presented in Table 37 (Day 21) and Table 38 (Day 42). Differences between adjuvanted groups have been highlighted in the tables.

Among adjuvanted formulations, statistically significant differences in SPR were observed at Day 21 between each of the highest dose groups (30µg HA, 15µg HA, 7.5µg HA) and 3.8 µg HA. SPR obtained in adjuvanted vaccine groups containing 30µg HA, 15µg HA and 7.5µg HA were similar (i.e. 58.3%, 49.0% and 50.0% respectively). At Day 42, no statistically significant differences were observed among adjuvanted formulations. No antigen dose effect was therefore observed after the second dose among adjuvanted vaccine groups.

Among non-adjuvanted formulations, a statistically significant difference was seen between each of the two highest dose groups (30µg HA, 15µg HA) and 3.8µg HA, and between the 30µg HA and 7.5µg HA dose groups at Day 21 and Day 42.

For each dose of HA, a statistically significant difference was observed between adjuvanted and non-adjuvanted formulations at both timepoints.

Additional inferential analyses were performed to evaluate the interaction between the two factors "HA antigen dose" and "adjuvantation" in study H5N1-007. To this end, the HI antibody response against the vaccine strain A/Vietnam observed 21 days after the first vaccination was compared between groups using a two-way analysis of co-variance (ANCOVA) model on the logarithm10 transformed titres. The ANCOVA model included the "HA antigen dose" and the "adjuvantation" as fixed effects and the pre-vaccination titre (baseline) as regressor.

According to the inferential analysis, the interaction between the two factors "HA dose" and "adjuvantation" after the first vaccination was not statistically significant (p-value =0.7186) allowing to assess the two fixed effects globally. A highly significant "adjuvant" ($p<0.0001$) and "HA dose" ($p<0.0001$) effect on the GMTs was observed after the first dose.

Adjusted GMT ratio for the "adjuvantation" effect after the first dose is presented in Table 39 and clearly demonstrates that adjuvantation with AS03 improved the humoral response in terms of anti-HA antibody production. The anti-HA titres were at least two-fold superior in formulations containing AS03.

For the antigen dose effect after the first dose, pairwise comparisons were performed using a Tukey adjustment (Table 39). Formulations containing 15 and 30 µg HA induced a significantly higher immune response as compared to formulations containing 3.8 µg HA. Similarly, formulations containing 30 µg HA induced a significantly greater immune response than formulations containing 7.5 µg HA.

After the second vaccination, the interaction between the two factors "HA antigen dose" and "adjuvantation" was not significant using a significance level of 5% (p-value=0.0517). This borderline value is however indicative of a difference in the response curve of "HA-doses" adjuvanted or not with AS03 which is mainly related to the GMTs induced by the 30 µg AS03-adjuvanted formulation (Figure 13).

For this reason, one-way analyses of variance were performed in order to test the effect of HA antigen dose for the adjuvanted and non-adjuvanted groups separately, and to compare for each HA-dose the effect of adjuvantation. Results showed no significant difference in the post-vaccination anti-HA antibody titre between the four groups who received adjuvanted formulations, therefore excluding an HA antigen dose response effect. A significant difference in the post-vaccination anti-HA antibody titre was observed between the four non-adjuvanted groups.

For each dose of HA antigen, a significant difference is evidenced between the adjuvanted and non-adjuvanted groups, as shown in Table 40. The lower limit of the 95% CI on the GMT ratio demonstrated that for all HA doses, there is a minimum 12-fold increase in GMT in favour of the adjuvanted group except for the 30 µg dose for which there is only a 4 fold increase.

Results of this inferential analysis are further detailed in the clinical study report for H5N1-007 located in Module 5, Section 5.3.5.

The above results indicate that the stimulatory effect of the adjuvant on the immune system compensates for the limiting effect of antigen concentration and serve as a basis for the decision to develop a dose as low as 3.8 µg in the context of an antigen sparing approach for a pandemic situation.

Table 37 Difference between groups for seroprotection rate in anti-HA antibody titres against vaccine strain H5N1 A/Vietnam/1194/2004 of the D-Pan monovalent pandemic influenza A vaccine (H5N1) at post-vaccination time point Day 21 (ATP cohort for immunogenicity)

						Difference in seroprotection rate (Group 2 minus Group 1)				P-value
Group 1	N	%	Group 2	N	%	Difference	%	95 % CI		
								LL	UL	
HN4	50	0.0	HN4AD	50	26.0	HN4AD - HN4	26.0	15.9	39.6	<0.001
HN4	50	0.0	HN8	49	8.2	HN8 - HN4	8.2	0.7	19.2	0.056
HN4	50	0.0	HN8AD	50	50.0	HN8AD - HN4	50.0	36.6	63.4	<0.001
HN4	50	0.0	HN15	49	20.4	HN15 - HN4	20.4	11.5	33.6	<0.001
HN4	50	0.0	HN15AD	49	49.0	HN15AD - HN4	49.0	35.6	62.5	<0.001
HN4	50	0.0	HN30	49	28.6	HN30 - HN4	28.6	17.9	42.4	<0.001
HN4	50	0.0	HN30AD	48	58.3	HN30AD - HN4	58.3	44.3	71.2	<0.001
HN8	49	8.2	HN4AD	50	26.0	HN4AD - HN8	17.8	3.2	32.7	0.031
HN4AD	50	26.0	HN8AD	50	50.0	HN8AD - HN4AD	24.0	5.0	41.4	0.023
HN15	49	20.4	HN4AD	50	26.0	HN4AD - HN15	5.6	-11.3	22.2	0.635
HN4AD	50	26.0	HN15AD	49	49.0	HN15AD - HN4AD	23.0	4.0	40.5	0.023
HN4AD	50	26.0	HN30	49	28.6	HN30 - HN4AD	2.3	-15.0	20.1	0.824
HN4AD	50	26.0	HN30AD	48	58.3	HN30AD - HN4AD	32.3	13.0	49.4	0.002
HN8	49	8.2	HN8AD	50	50.0	HN8AD - HN8	41.8	25.2	56.7	<0.001
HN8	49	8.2	HN15	49	20.4	HN15 - HN8	12.2	-1.8	26.8	0.147
HN8	49	8.2	HN15AD	49	49.0	HN15AD - HN8	40.8	24.2	55.9	<0.001
HN8	49	8.2	HN30	49	28.6	HN30 - HN8	20.4	5.4	35.6	0.017
HN8	49	8.2	HN30AD	48	58.3	HN30AD - HN8	50.2	33.1	64.6	<0.001
HN15	49	20.4	HN8AD	50	50.0	HN8AD - HN15	29.6	11.0	46.3	0.003
HN15AD	49	49.0	HN8AD	50	50.0	HN8AD - HN15AD	1.0	-18.3	20.3	1.000
HN30	49	28.6	HN8AD	50	50.0	HN8AD - HN30	21.4	2.2	39.2	0.040
HN8AD	50	50.0	HN30AD	48	58.3	HN30AD - HN8AD	8.3	-11.3	27.3	0.426
HN15	49	20.4	HN15AD	49	49.0	HN15AD - HN15	28.6	9.9	45.5	0.005
HN15	49	20.4	HN30	49	28.6	HN30 - HN15	8.2	-9.020	25.1	0.482
HN15	49	20.4	HN30AD	48	58.3	HN30AD - HN15	37.9	18.9	54.3	<0.001
HN30	49	28.6	HN15AD	49	49.0	HN15AD - HN30	20.4	1.1	38.3	0.061
HN15AD	49	49.0	HN30AD	48	58.3	HN30AD - HN15AD	9.4	-10.4	28.4	0.418
HN30	49	28.6	HN30AD	48	58.3	HN30AD - HN30	29.8	10.2	47.2	0.004

Differences between adjuvanted groups have been highlighted in the table
HN4 = H5N1 3.8µg; HN4AD = H5N1 3.8µg + AS03
HN8 = H5N1 7.5µg; HN8AD = H5N1 7.5µg + AS03
HN15 = H5N1 15µg; HN15AD = H5N1 15µg + AS03
HN30 = H5N1 30µg; HN30AD = H5N1 30µg + AS03
N = number of subjects with available results
% = percentage of subjects with titre >= 40 1/DIL
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
P-value = 2-sided Fisher Exact Test

Table 38 Difference between groups for seroprotection rate in anti-HA antibody titres against vaccine strain H5N1 A/Vietnam/1194/2004 of the D-Pan monovalent pandemic influenza A vaccine (H5N1) at post-vaccination time point Day 42 (ATP cohort for immunogenicity)

						Difference in seroprotection rate (Group 2 minus Group 1)				P-value
Group 1	N	%	Group 2	N	%	Difference	%	95 % CI		
								LL	UL	
HN4	50	4.0	HN4AD	50	84.0	HN4AD - HN4	80.0	65.7	88.9	<0.001
HN4	50	4.0	HN8	49	16.3	HN8 - HN4	12.3	0.5	25.7	0.051
HN4	50	4.0	HN8AD	50	90.0	HN8AD - HN4	86.0	72.7	93.1	<0.001
HN4	50	4.0	HN15	49	34.7	HN15 - HN4	30.7	16.5	45.4	<0.001
HN4	50	4.0	HN15AD	49	95.9	HN15AD - HN4	91.9	80.1	96.8	<0.001
HN4	50	4.0	HN30	49	42.9	HN30 - HN4	38.9	23.9	53.5	<0.001
HN4	50	4.0	HN30AD	48	85.4	HN30AD - HN4	81.4	67.1	90.0	<0.001
HN8	49	16.3	HN4AD	50	84.0	HN4AD - HN8	67.7	50.7	79.6	<0.001
HN4AD	50	84.0	HN8AD	50	90.0	HN8AD - HN4AD	6.0	-7.7	20.1	0.554
HN15	49	34.7	HN4AD	50	84.0	HN4AD - HN15	49.3	31.1	64.2	<0.001
HN4AD	50	84.0	HN15AD	49	95.9	HN15AD - HN4AD	11.9	0.1	25.1	0.092
HN30	49	42.9	HN4AD	50	84.0	HN4AD - HN30	41.1	22.9	56.9	<0.001
HN4AD	50	84.0	HN30AD	48	85.4	HN30AD - HN4AD	1.4	-13.5	16.2	1.000
HN8	49	16.3	HN8AD	50	90.0	HN8AD - HN8	73.7	57.7	84.3	<0.001
HN8	49	16.3	HN15	49	34.7	HN15 - HN8	18.4	1.2	35.0	0.063
HN8	49	16.3	HN15AD	49	95.9	HN15AD - HN8	79.6	65.0	88.7	<0.001
HN8	49	16.3	HN30	49	42.9	HN30 - HN8	26.5	8.7	43.1	0.007
HN8	49	16.3	HN30AD	48	85.4	HN30AD - HN8	69.1	52.1	80.8	<0.001
HN15	49	34.7	HN8AD	50	90.0	HN8AD - HN15	55.3	38.1	69.1	<0.001
HN8AD	50	90.0	HN15AD	49	95.9	HN15AD - HN8AD	5.9	-5.1	17.9	0.436
HN30	49	42.9	HN8AD	50	90.0	HN8AD - HN30	47.1	29.9	61.9	<0.001
HN30AD	48	85.4	HN8AD	50	90.0	HN8AD - HN30AD	4.6	-9.0	18.7	0.549
HN15	49	34.7	HN15AD	49	95.9	HN15AD - HN15	61.2	45.4	73.9	<0.001
HN15	49	34.7	HN30	49	42.9	HN30 - HN15	8.2	-11.1	26.8	0.534
HN15	49	34.7	HN30AD	48	85.4	HN30AD - HN15	50.7	32.5	65.4	<0.001
HN30	49	42.9	HN15AD	49	95.9	HN15AD - HN30	53.1	37.3	66.7	<0.001
HN30AD	48	85.4	HN15AD	49	95.9	HN15AD - HN30AD	10.5	-1.2	23.7	0.091
HN30	49	42.9	HN30AD	48	85.4	HN30AD - HN30	42.6	24.3	58.1	<0.001

Differences between adjuvanted groups have been highlighted in the table
HN4 = H5N1 3.8µg ; HN4AD = H5N1 3.8µg + AS03
HN8 = H5N1 7.5µg; HN8AD = H5N1 7.5µg + AS03
HN15 = H5N1 15µg; HN15AD = H5N1 15µg + AS03
HN30 = H5N1 30µg; HN30AD = H5N1 30µg + AS03
N = number of subjects with available results
% = percentage of subjects with titre >= 40 1/DIL
95% CI = 95% Standardized asymptotic confidence interval; LL = lower limit, UL = upper limit
P-value = 2-sided Fisher Exact Test

Table 39 First vaccination: Adjusted GMT ratio between HA dose and adjuvantation in study H5N1-007 (ATP cohort for immunogenicity)

Adjuvant A	Adjuvant B	Adjusted GMT ratio (B/A)	95% CI		
			LL	UL	p-value
No adjuvant	AS03	2.74	2.08	3.61	<0.0001
Dose A	Dose B	Adjusted GMT ratio (B/A)	Tukey adjustment		
			LL	UL	p-value
3.8 µg	7.5 µg	1.59	0.96	2.65	0.0875
3.8 µg	15 µg	1.96	1.18	3.27	0.0039
3.8 µg	30 µg	2.79	1.68	4.66	<0.0001
7.5 µg	15 µg	1.23	0.74	2.06	0.7116
7.5 µg	30 µg	1.76	1.05	2.93	0.0247
15 µg	30 µg	1.42	0.85	2.38	0.2895

Figure 13 "Adjuvantation" over 'HA-dose effect" after the second vaccination (Day 42) in study H5N1-007 (ATP cohort for immunogenicity)

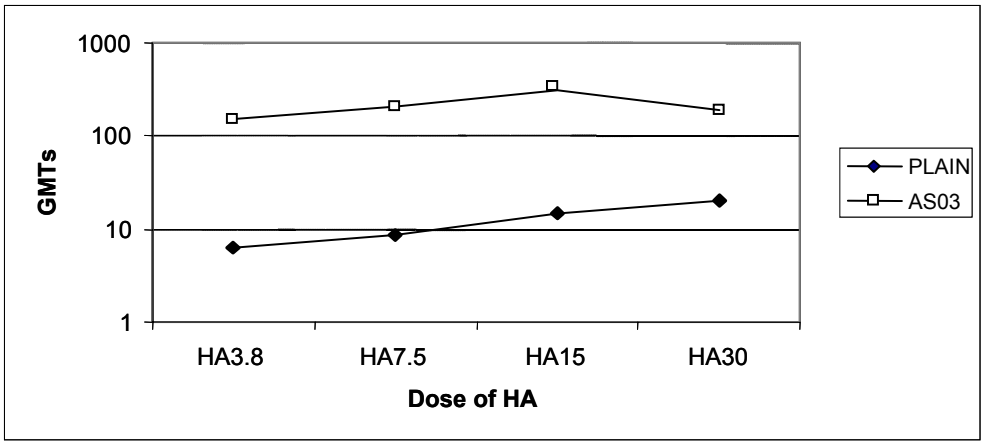


Table 40 Second vaccination: Adjusted GMT ratio for each HA-dose with or without adjuvant in study H5N1-007 (ATP cohort for immunogenicity)

Dose	Adjuvant A	Adjuvant B	Adjusted GMT ratio (B/A)	95% CI		
				LL	UL	p-value
3.8 µg	No adjuvant	AS03	23.92	14.60	39.18	<0.0001
7.5 µg	No adjuvant	AS03	24.16	14.46	40.36	<0.0001
15 µg	No adjuvant	AS03	20.93	12.23	35.80	<0.0001
30 µg	No adjuvant	AS03	9.37	4.82	18.20	<0.0001

2.7.3.4.2 Effect of AS03 adjuvant dose

The AS03 adjuvant activity for the Quebec-manufactured antigen, as determined by SCR and GMT after receiving two doses of vaccine was evaluated in pivotal study Q-Pan-001. Immunogenicity results of study Q-Pan-001 have been presented in detail in Section 2.7.3.3.2.

A primary objective of study Q-Pan-001 was to demonstrate the AS03 adjuvant activity for the Quebec-manufactured antigen, as determined by SCR and GMT at Day 42, after receiving two doses of vaccine. A comparison of the Day 42 SCR among subjects receiving Quebec antigen with full dose AS03, and Quebec antigen without adjuvant, is presented in Table 41 for the vaccine strain A/Indonesia/05/2005 and for the heterologous strain A/Vietnam/1194/2004. A comparison of the Day 42 GMTs for subjects receiving Quebec antigen with full adjuvant, or Quebec antigen without adjuvant, is presented in Table 42 for the vaccine strain A/Indonesia/05/2005 and for the heterologous strain A/Vietnam/1194/2004.

In order to claim that the Quebec antigen with full dose adjuvant was superior to the Quebec antigen without adjuvant, the lower bound of the 95% confidence interval on the difference in SCR between the two groups needed to be greater than 15%. As shown in Table 41, the difference between the group with full dose AS03 and the non-adjuvanted group was 79.9% (95% CI: 69.4 - 87.3%) for the vaccine strain A/Indonesia/05/2005 and 60.5% (95% CI: 51.5 - 68.3%) for the heterologous strain A/Vietnam/1194/2004, respectively, well exceeding the minimum difference required to claim superiority of the adjuvanted vaccine.

Table 41 Comparison of seroconversion rates at Day 42 in subjects receiving Quebec antigen with full dose adjuvant and Quebec antigen with no adjuvant in study Q-Pan-001 (ATP cohort for immunogenicity)

	Treatment Group						Difference in SCR (Q-Pan AS03 full dose minus Q-Pan without AS03)		
Antibody	Q-Pan AS03 full dose			Q-Pan withoutAS03				95% CI	
	N	n	%	N	n	%	%	LL	UL
A/indonesia/05/2005	144	140	97.2	75	13	17.3	79.89	69.36	87.27
A/Vietnam/1194/2004	144	89	61.8	75	1	1.3	60.47	51.45	68.30

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response
95% CI = Unstand. asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

A second criterion for demonstrating the superiority of the group with full dose AS03 over the non-adjuvanted group was GMT; a 2-fold increase in titre was required to claim superiority of the adjuvanted vaccine. As shown in Table 42, this criterion was again exceeded for both antibodies against homologous and heterologous strain. The adjusted GMT ratio was 43.4 (95% CI 29.9-62.9) for the vaccine strain A/Indonesia/05/2005 and 7.0 (95% CI 4.8-10.1) for the heterologous strain A/Vietnam/1194/2004, respectively.

Table 42 Comparison of adjusted ratios of GMTs at Day 42 in subjects receiving Quebec antigen with full dose adjuvant and Quebec antigen with no adjuvant in study Q-Pan-001 (ATP cohort for immunogenicity)

Antibody	Treatment Group				Adjusted GMT ratio (Q-Pan AS03 full dose minus Q-Pan without AS03)		
	Q-Pan AS03 full dose		Q-Pan withoutAS03		Value	95% CI	
	N	Adjusted GMT	N	Adjusted GMT		LL	UL
A/indonesia/05/2005	144	450.8	75	10.4	43.40	29.93	62.94
A/Vietnam/1194/2004	144	40.2	75	5.8	6.98	4.84	10.07

Adjusted GMT = geometric mean antibody titre adjusted for age stratum, baseline titre
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 age stratum, baseline titre - pooled variance); LL = lower limit, UL = upper limit

As the effect of full dose AS03 versus no AS03 was significant when assessed by SCR and GMT, a comparison also was done to describe the effect of Q-Pan vaccine with half dose AS03 versus the non-adjuvanted vaccine, to demonstrate the activity of half dose adjuvant.

As with the full dose adjuvant, the Quebec antigen with half dose adjuvant provided significantly higher SCRs for both antibodies as compared to the Quebec antigen without adjuvant. A comparison of the Day 42 SCR in these groups is presented in Table 43.The difference between the group with half dose AS03 and the non-adjuvanted group was 72.4% (95% CI 61.0-80.8%) for the vaccine strain A/Indonesia/05/2005 and 57.6% (95% CI 48.6-65.5%) for the heterologous strain A/Vietnam/1194/2004, well exceeding the minimum difference (15%) required to claim superiority of the formulation with half dose adjuvant.

Table 43 Comparison of seroconversion rates at Day 42 in subjects receiving Quebec antigen with half dose adjuvant and Quebec antigen with no adjuvant in study Q-Pan-001 (ATP cohort for immunogenicity)

	Treatment Group						Difference in SCR (Q-Pan AS03 half dose minus Q-Pan without AS03)		
Antibody	Q-Pan AS03 half dose			Q-Pan withoutAS03				95% CI	
	N	n	%	N	n	%	%	LL	UL
A/indonesia/05/2005	146	131	89.7	75	13	17.3	72.39	61.04	80.80
A/Vietnam/1194/2004	146	86	58.9	75	1	1.3	57.57	48.57	65.52

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a vaccine response
95% CI = Unstand. asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

The Quebec antigen with half dose adjuvant also induced significantly higher GMTs for both antibodies as compared to the Quebec antigen without adjuvant. As shown in Table 44, the adjusted GMT ratio was 30.0 (95% CI 20.7-43.4) for the vaccine strain A/Indonesia/05/2005 and 5.8 (95% CI 4.0-8.8) for the heterologous strain A/Vietnam/1194/2004. Thus, the vaccine with half dose adjuvant exceeded the 2-fold increase in titre at the lower bound of the 95% confidence interval needed to satisfy this criterion of superiority.

Table 44 Comparison of adjusted ratios of GMTs at Day 42 in subjects receiving Quebec antigen with half dose adjuvant and Quebec antigen with no adjuvant in study Q-Pan-001 (ATP cohort for immunogenicity)

Antibody	Treatment Group				Adjusted GMT ratio (Q-Pan AS03 half dose minus Q-Pan without AS03)		
	Q-Pan AS03 half dose		Q-Pan withoutAS03		Value	95% CI	
	N	Adjusted GMT	N	Adjusted GMT		LL	UL
A/indonesia/05/2005	146	311.2	75	10.4	29.96	20.68	43.41
A/Vietnam/1194/2004	146	33.5	75	5.8	5.83	4.04	8.84

Adjusted GMT = geometric mean antibody titre adjusted for age stratum, baseline titre
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 age stratum, baseline titre pooled variance); LL = lower limit, UL = upper limit

While slightly higher SCRs and GMTs were seen with full dose adjuvant, the differences were not large enough to definitively indicate superiority of the full dose adjuvant over half dose adjuvant in the entire 18 to 64 year-old age group (Table 45 and Table 46).

Table 45 Comparison of seroconversion rates at Day 42 in subjects receiving Quebec antigen with full dose adjuvant and Quebec antigen with subjects receiving Quebec antigen with half dose adjuvant and Quebec antigen in study Q-Pan-001 (ATP cohort for immunogenicity)

Antibody							Difference in SCR (Q-Pan AS03 full dose minus Q-Pan half dose AS03)		
	Q-Pan AS03 full dose			Q-Pan AS03 half dose				95% CI	
	N	n	%	N	n	%	%	LL	UL
A/indonesia/05/2005	144	140	97.2	146	131	89.7	7.50	1.97	13.84
A/Vietnam/1194/2004	144	89	61.8	146	86	58.9	2.90	-8.35	14.08

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

Table 46 Comparison of adjusted ratios of GMTs at Day 42 in subjects receiving Quebec antigen with full dose adjuvant and Quebec antigen with subjects receiving Quebec antigen with half dose adjuvant and Quebec antigen, by antibody (ATP cohort for immunogenicity)

Antibody	Treatment Group				Adjusted GMT ratio (Q-Pan AS03 full dose minus Q-Pan half dose AS03)		
	Q-Pan AS03 full dose		Q-Pan AS03 half dose		Value	95% CI	
	N	Adjusted GMT	N	Adjusted GMT		LL	UL
A/indonesia/05/2005	144	450.8	146	311.2	1.45	1.07	1.97
A/Vietnam/1194/2004	144	40.2	146	33.5	1.20	0.89	1.62

Adjusted GMT = geometric mean antibody titre adjusted for age strata, baseline titre
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 age stratum, baseline titre pooled variance); LL = lower limit, UL = upper limit

In order to further assess the AS03 adjuvant activity, a *post hoc* analysis of the HI antibody response in study Q-Pan-001 was performed wherein subjects who received full dose AS03 adjuvant with Q-Pan and D-Pan antigen were pooled together to form a "full dose" adjuvant group. Similarly, half dose AS03 groups with Q-Pan and D-Pan antigen were pooled to form a "half dose" AS03 adjuvant group.

When the above contrasts are examined separately in the two age strata (18 to 40 and 41 to 64 years old), the criteria for adjuvant effect are fulfilled in both strata, but the results for the older age stratum were generally not as positive as those for the younger age stratum (see Appendix Table 6 through Appendix Table 9). Notably, whereas the homologous virus (A/Indonesia) SCR in the younger age group dropped only by 4% when the adjuvant dose was halved, the impact in the older age group was a 14% drop. Similarly, whereas the improvement in post-vaccination GMT versus antigen without adjuvant was only slightly affected in the younger age group when the adjuvant dose was halved, the effect was a nearly two-fold reduction in this parameter in the older age group. Similar effects were apparent, although less marked, in the responses to the drift virus A/Vietnam.

The results indicate that the impact of halving the adjuvant dose in the older age stratum results in a reduced homologous and heterologous HI antibody response; whereas in the younger age group the effect of decreasing adjuvant dose is less pronounced. These results argue caution in the application of reduced AS03 doses for a vaccine intended to provide protection to the entire adult population.

2.7.3.5 Persistence of Efficacy and/or Tolerance Effects

The persistence of antibodies (HI and serum neutralizing antibodies) against the vaccine strain and heterologous strains has been evaluated at six months after first vaccination in studies Q-Pan-001, Q-Pan-002 and H5N1-007.

These persistence data are presented below and are further detailed in the individual clinical study reports located in Module 5.3.5.

A total of 680 subjects were enrolled and vaccinated in study Q-Pan-001. The number of subjects remaining for evaluation at 6 months (Day 182) post-vaccination in the ATP cohort for immunogenicity was 648.

In study Q-Pan-002, the persistence of HI antibodies against the vaccine strain and heterologous strains has been evaluated at six months after first vaccination in a subset of subjects. The number of subjects in the ATP cohort for immunogenicity with Day 182 results available was 382 in the age group 18-60 years and 131 in age group >60 years.

A total of 400 subjects were enrolled and vaccinated in study H5N1-007. The number of subjects remaining for evaluation at 6 months (Day 180) post-vaccination (ATP persistence cohort) following exclusion from the Total Vaccinated cohort was 392.

2.7.3.5.1 Persistence of homologous HI antibody response (against vaccine strain)

Persistence of homologous antibody response following Q-Pan vaccine in study Q-Pan-001

HI antibody responses against vaccine strain H5N1 A/Indonesia/05/2005 (in terms of GMTs, SCF, SCR and SPR) up to Day 182 in the ATP immunogenicity cohort of study Q-Pan-001 are presented in Table 47. Of note, SPR and GMT are the two key parameters for assessing antibody persistence.

Seroconversion rates of HI antibodies against vaccine strain A/Indonesia/05/2005 at Day 182 ranged from 44.9% to 54.6% in the AS03 adjuvanted Q-Pan and D-Pan vaccine groups, thereby still exceeding the 40% CHMP threshold in all adjuvanted vaccine groups.

While all AS03 adjuvanted Q-Pan and D-Pan vaccine groups fulfilled the 70% SPR CHMP criterion at Day 42, no treatment group maintained this level at Day 182. However, SPR values in adjuvanted vaccine groups at Day 182 were still between 45.5% and 54.6%.

On Day 182, GMTs remained notably higher in the adjuvanted Q-Pan and D-Pan vaccine groups (22.6 to 27.8) than in the unadjuvanted group. Although this represented a substantial decline in GMT between Day 42 and Day 182, the GMTs at Day 182 were similar to those seen at Day 21 following one dose of vaccine and still approximately 4-5 fold in excess of baseline values.

As with GMT, SCF relative to Day 0 decreased substantially from Day 42 to Day 182. Nonetheless, SCF were still between 4.5 and 5.6 in AS03 adjuvanted vaccine groups and were similar to those at Day 21 following one dose of vaccine. Therefore, SCFs in adjuvanted groups continued to exceed the 2.5 CHMP threshold at Day 182.

In conclusion, while HI titers against H5N1 viruses at Day 182 were not as high as at Day 42 (21 days following the second vaccine dose), a persistent HI antibody response against A/Indonesia/05/2005 vaccine strain was still present after 6 months in the groups that had received AS03 adjuvanted Q-Pan or D-Pan vaccine, but not in the non-adjuvanted Q-Pan vaccine group.

Persistence of homologous antibody response following Q-Pan vaccine in study Q-Pan-002

HI antibody responses against vaccine strain H5N1 A/Indonesia/05/2005 (in terms of GMTs, SCF, SCR and SPR) up to Day 182 in the ATP immunogenicity cohort of study Q-Pan-002 are presented in Table 48.

Seroconversion rates of HI antibodies against vaccine strain A/Indonesia/05/2005 at Day 182 after vaccination with Q-Pan vaccine were 62.0% in the group aged 18-60 years and 62.5% in the group aged >60 years, thereby still exceeding the respective 40% and 30% CHMP threshold.

At Day 182, Q-Pan recipients in the 18-60 years age stratum no longer fulfilled the 70% SPR CHMP criterion, with an SPR of 62.0%. However, SPR values were maintained above the CHMP threshold of 60% SPR among subjects in the older, >60 years age stratum, with an SPR of 63.5%.

At Day 42, Q-Pan vaccinees in the 18-60 years group had GMTs that were approximately 3 times higher than GMTs for Q-Pan subjects for the > 60 years age group. As expected, at Day 182, Q-Pan recipients had significantly lower GMTs regardless of age, with a GMT of 37.2 for the 18-60 years age stratum and 39.6 for the >60 years age stratum. The GMTs for the placebo group remained low and unchanged from Day 42.

As expected, the SCFs at Day 182 were lower than the values obtained at Day 42. However, the SCR in the Q-Pan groups continued to largely exceed the CHMP target values with 7.4 for the 18-60 years age group and 7.8 for the >60 years age group.

In conclusion, Day 182 HI antibody titers in study Q-Pan-002 confirm the Day 182 results obtained in study Q-Pan-001: a persistent HI antibody response against A/Indonesia/05/2005 vaccine strain was still present 6 months after vaccination with Q-Pan vaccine. In study Q-Pan-002 this was observed in the adult group aged 18-60 years as well as in the older group aged >60 years.

Persistence of homologous antibody response following D-Pan vaccine in supportive study H5N1-007

Immunogenicity results (GMTs of HI antibodies, SCF, SCR and SPR) up to Day 180 against vaccine strain H5N1 A/Vietnam/1194/2004 in the ATP immunogenicity cohort are presented for study H5N1-007 in Table 49.

At Day 180, SCR were statistically higher in the adjuvanted groups (52.0% to 62.0%) as compared to the respective non-adjuvanted groups (4.0% to 35.4%), except for the highest antigen dose (30µg HA) where 95% confidence intervals (CIs) were slightly overlapping. At six months following the first vaccination, the CHMP criterion for SCR (>40%) was only fulfilled with the adjuvanted formulations.

Similarly, SPR for the adjuvanted groups were statistically higher at Day 180 (54.0% to 64.0%), as compared to the non-adjuvanted groups (4.0% to 37.5%) except for the highest antigen dose. None of the vaccine groups reached the CHMP criterion for SPR (>70%) at Day 180. The decline in SPR from Day 42 to Day 180 was between 22.9% and 34.7% in the adjuvanted groups.

SCF for all adjuvanted formulations substantially exceeded the CHMP criterion (>2.5) six months following initial vaccination. With respect to the non-adjuvanted groups, the CHMP requirement was only reached in the 30µg HA dose group. Statistically higher SCF were observed in the adjuvanted groups as compared to the non-adjuvanted groups except for the highest antigen dose.

SCR, SPR and SCF were 52.0%, 54.0% and 4.4 respectively at Day 180 with the adjuvanted vaccine containing 3.8 µg HA.

GMTs of HI antibodies at Day 180 were in the same magnitude as those reached 21 days after the first dose in all groups.

No antigen dose effect was observed in the adjuvanted groups for the humoral response in terms of SCR or SPR, SCF and GMTs.

2.7.3.5.2 Persistence of heterologous HI antibody response (cross-reactive immunity)

Persistence of heterologous HI antibody response following Q-Pan vaccine in study Q-Pan-001

HI antibody responses against strain H5N1 A/Vietnam/1194/2004 (in terms of GMTs, SCF, SCR and SPR) up to Day 182 in the ATP immunogenicity cohort of study Q-Pan-001 are presented in Table 50.

Overall, SCR of HI antibodies against strain A/Vietnam/1194/2004 at Day 182 were notably lower than for the A/Indonesia/05/2005 antibody. SCR against A/Vietnam/1194/2004 at Day 182 in the adjuvanted vaccine groups were in the same range as those seen at Day 21 after the first vaccine dose (8.7% to 10.9%, and no longer exceeded the 40% SCR CHMP threshold.

SPR values with AS03 adjuvanted Q-Pan and D-Pan vaccine had decreased after Day 42 to 10.6-13.1% at Day 182.

GMTs declined between Day 42 and Day 182. The pattern observed relative to adjuvant effects was similar to that seen with antibodies against vaccine-homologous virus, although less pronounced, as overall GMTs were lower for the clade 1 A/Vietnam/1194/2004 strain. At Day 182 GMTs were 7.9 to 8.9 in the adjuvanted vaccine groups, which is in the same range as the GMTs seen at Day 21 following one dose of vaccine but still higher than the Day 182 GMT in the non-adjuvanted group (5.4).

The SCF also decreased after Day 42 to values of 1.5-1.7 at Day 182 in adjuvanted vaccine groups.

Persistence of heterologous HI antibody response following D-Pan vaccine in study H5N1-007

Immunogenicity results (GMTs of HI antibodies, SCF, SCR and SPR) against heterologous H5N1 strain A/Indonesia/05/2005 at Day 180 in study H5N1-007 are presented in Table 51 (ATP immunogenicity cohort).

No effect of vaccination was detected with non-adjuvanted formulations at Day 180 or at previous time points. Some degree of protection against the heterologous strain remained in all adjuvanted groups except with the lowest antigen dose (3.8µg HA) at Day 180 (SPR ranged from 4.1% to 6.0%).

HI antibody responses up to Day 180 against two other heterologous strains A/Anhui/01/2005 and A/turkey/Turkey/1/2005 are presented in Table 52.

In terms of anti-HA antibody production, the adjuvanted vaccine mediated a significant increase in GMTs after the second vaccination against both strains, although the absolute titres were low. At Day 180, the SPR had decreased to 5.0% or lower for both strains.

Table 47 HI responses against vaccine strain H5N1 A/Indonesia/05/2005 of the H5N1 (A/Indonesia) influenza vaccine up to Day 182 in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Time-point	Strain	Manuf. site‡	HA (µg / dose)	AS03	N	GMT			SCF			SCR			SPR		
							Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**Pre**	H5N1 Indonesia	Quebec	3.8	AS03	144	**5.0**	5.0	5.0	-	-	-	-	-	-	**0.0**	0.0	2.5
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	**5.0**	5.0	5.0	-	-	-	-	-	-	**0.0**	0.0	2.5
		H5N1 Indonesia	Quebec	3.8	-	75	**5.0**	5.0	5.0	-	-	-	-	-	-	**0.0**	0.0	4.8
		H5N1 Indonesia	Dresden	3.8	AS03	140	**5.0**	5.0	5.1	-	-	-	-	-	-	**0.0**	0.0	2.6
		H5N1 Indonesia	Dresden	3.8	AS03/2	143	**5.0**	5.0	5.1	-	-	-	-	-	-	**0.0**	0.0	2.5
	Post I	H5N1 Indonesia	Quebec	3.8	AS03	144	**22.5**	17.8	28.6	-	-	-	-	-	-	**41.7**	33.5	50.2
	(D21)	H5N1 Indonesia	Quebec	3.8	AS03/2	146	**19.9**	15.7	25.3	-	-	-	-	-	-	**41.1**	33.0	49.5
		H5N1 Indonesia	Quebec	3.8	-	75	**6.1**	5.2	7.1	-	-	-	-	-	-	**6.7**	2.2	14.9
		H5N1 Indonesia	Dresden	3.8	AS03	140	**23.5**	18.3	30.3	-	-	-	-	-	-	**45.7**	37.3	54.3
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	**16.8**	13.5	20.9	-	-	-	-	-	-	**38.0**	30.0	46.5
	Post II	H5N1 Indonesia	Quebec	3.8	AS03	144	**464.7**	383.4	563.4	-	-	-	-	-	-	**97.2**	93.0	99.2
	(D42)	H5N1 Indonesia	Quebec	3.8	AS03/2	146	**320.7**	246.9	416.6	-	-	-	-	-	-	**89.7**	83.6	94.1
		H5N1 Indonesia	Quebec	3.8	-	75	**10.5**	8.2	13.5	-	-	-	-	-	-	**17.3**	9.6	27.8
		H5N1 Indonesia	Dresden	3.8	AS03	140	**480.3**	390.5	590.7	-	-	-	-	-	-	**96.4**	91.9	98.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	**347.7**	272.0	444.5	-	-	-	-	-	-	**92.3**	86.6	96.1
	Post II	H5N1 Indonesia	Quebec	3.8	AS03	141	**27.8**	22.8	33.8	**5.6**	4.6	6.8	**54.6**	46.0	63.0	**54.6**	46.0	63.0
	(D182)	H5N1 Indonesia	Quebec	3.8	AS03/2	145	**22.6**	18.4	27.9	**4.5**	3.7	5.6	**45.5**	37.2	54.0	**45.5**	37.2	54.0
		H5N1 Indonesia	Quebec	3.8	-	74	**5.6**	5.1	6.2	**1.1**	1.0	1.2	**2.7**	0.3	9.4	**2.7**	0.3	9.4
		H5N1 Indonesia	Dresden	3.8	AS03	138	**26.1**	20.7	32.8	**5.2**	4.1	6.5	**48.6**	40.0	57.2	**49.3**	40.7	57.9
		H5N1 Indonesia	Dresden	3.8	AS03/2	138	**22.6**	18.3	28.0	**4.5**	3.6	5.6	**44.9**	36.5	53.6	**45.7**	37.2	54.3

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); GMR = Geometric Mean Ratio; SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

Table 48 HI responses against vaccine strain H5N1 A/Indonesia/05/2005 of the H5N1 (A/Indonesia) influenza vaccine up to Day 182 in study Q-Pan-002 (ATP immunogenicity cohort)

Study (Age of vaccination)	Age group	Time-point	Study group	N	GMT			SCF			SCR			SPR		
					Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-002 >18 yrs	18-60 years	Pre	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	1488	**5.0**	5.0	5.0	-	-	-	-	-	-	**0.0**	0.0	0.2
			Placebo	68	**5.0**	5.0	5.0	-	-	-	-	-	-	**0.0**	0.0	5.3
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	1488	**258.0**	239.7	277.7	**51.4**	47.8	55.3	**91.0**	89.4	92.4	**91.0**	89.4	92.4
			Placebo	68	**5.2**	4.9	5.5	**1.0**	1.0	1.1	**1.5**	0.0	7.9	**1.5**	0.0	7.9
		Post II (D182)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	353	**37.2**	31.8	43.6	**7.4**	6.3	8.7	**62.0**	56.8	67.1	**62.0**	56.8	67.1
			Placebo	29	**5.7**	4.7	6.9	**1.1**	0.9	1.4	**3.4**	0.1	17.8	**3.4**	0.1	17.8
	>60 years	Pre	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	479	**5.2**	5.0	5.3	**-**	-	-	**-**	-	-	**0.4**	0.1	1.5
			Placebo	48	**5.0**	5.0	5.0	**-**	-	-	**-**	-	-	**0.0**	0.0	7.4
		Post II (D42)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	479	**89.0**	77.1	102.7	**17.2**	14.9	19.9	**76.4**	72.3	80.1	**76.8**	72.8	80.5
			Placebo	48	**5.5**	4.6	6.5	**1.1**	0.9	1.3	**2.1**	0.1	11.1	**2.1**	0.1	11.1
		Post II (D182)	**Q-Pan H5N1 (3.8µg) Indonesia + AS03**	104	**39.6**	29.9	52.5	**7.8**	5.9	10.4	**62.5**	52.5	71.8	**63.5**	53.4	72.7
			Placebo	27	**5.3**	4.7	5.8	**1.1**	0.9	1.2	**0.0**	0.0	12.8	**0.0**	0.0	12.8

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); GMR = Geometric Mean Ratio; SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)
Day 182 immunogenicity was assessed in a subset of subjects.

Table 49 HI responses of the D-Pan H5N1 pandemic influenza vaccine against vaccine strain H5N1 A/Vietnam/1194/2004 up to Day 180 in adults from study H5N1-007 (ATP immunogenicity cohort)

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	GMT			SCF			SCR			SPR		
						Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
							LL	UL		LL	UL		LL	UL		LL	UL
H5N1-007	Pre	H5N1 split	30	-	49	5.2	4.8	5.6	-	-	-	-	-	-	0.0	0.0	7.3
18-60 yrs		H5N1 split	15	-	49	5.3	4.8	5.9	-	-	-	-	-	-	2.0	0.1	10.9
		H5N1 split	7.5	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	3.8	-	50	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.1
		H5N1 split	30	AS03	48	5.1	4.9	5.5	-	-	-	-	-	-	0.0	0.0	7.4
		H5N1 split	15	AS03	49	5.1	4.9	5.2	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	7.5	AS03	50	5.4	4.8	6.0	-	-	-	-	-	-	2.0	0.1	10.7
		H5N1 split	3.8	AS03	50	5.4	4.8	6.0	-	-	-	-	-	-	2.0	0.1	10.7
	Post I (D21)	H5N1 split	30	-	49	14.1	8.9	22.6	2.7	1.7	4.3	26.5	14.9	41.1	28.6	16.6	43.3
		H5N1 split	15	-	49	10.4	6.9	15.6	1.9	1.3	2.8	20.4	10.2	34.3	20.4	10.2	34.3
		H5N1 split	7.5	-	49	6.8	5.4	8.7	1.4	1.1	1.7	8.2	2.3	19.6	8.2	2.3	19.6
		H5N1 split	3.8	-	50	5.1	4.9	5.4	1.0	1.0	1.1	0.0	0.0	7.1	0.0	0.0	7.1
		H5N1 split	30	AS03	48	36.7	22.7	59.3	7.1	4.3	11.7	58.3	43.2	72.4	58.3	43.2	72.4
		H5N1 split	15	AS03	49	24.7	14.8	41.4	4.9	2.9	8.1	49.0	34.4	63.7	49.0	34.4	63.7
		H5N1 split	7.5	AS03	50	24.6	15.8	38.4	4.6	3.0	7.0	50.0	35.5	64.5	50.0	35.5	64.5
		H5N1 split	3.8	AS03	50	12.9	8.9	18.7	2.4	1.7	3.5	24.0	13.1	38.2	26.0	14.6	40.3
	Post II (D42)	H5N1 split	30	-	49	20.0	12.5	32.1	3.9	2.4	6.2	40.8	27.0	55.8	42.9	28.8	57.8
		H5N1 split	15	-	49	14.7	9.6	22.4	2.8	1.9	4.1	34.7	21.7	49.6	34.7	21.7	49.6
		H5N1 split	7.5	-	49	8.5	6.3	11.5	1.7	1.3	2.3	16.3	7.3	29.7	16.3	7.3	29.7
		H5N1 split	3.8	-	50	6.2	5.3	7.4	1.2	1.1	1.5	4.0	0.5	13.7	4.0	0.5	13.7
		H5N1 split	30	AS03	48	187.5	116.2	302.7	36.4	22.7	58.5	85.4	72.2	93.9	85.4	72.2	93.9
		H5N1 split	15	AS03	49	306.7	218.4	430.8	60.5	42.8	85.5	95.9	86.0	99.5	95.9	86.0	99.5
		H5N1 split	7.5	AS03	50	205.3	135.1	312.0	38.1	24.8	58.4	90.0	78.2	96.7	90.0	78.2	96.7
		H5N1 split	3.8	AS03	50	149.3	93.2	239.1	27.9	17.2	45.2	82.0	68.6	91.4	84.0	70.9	92.8

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	GMT			SCF			SCR			SPR		
						Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
							LL	UL		LL	UL		LL	UL		LL	UL
H5N1-007 18-60 yrs	Post II (D180)	H5N1 split	30	-	48	17.8	11.5	27.5	3.4	2.2	5.3	35.4	22.2	50.5	37.5	24.0	52.6
		H5N1 split	15	-	48	10.7	7.4	15.5	2.0	1.4	2.8	22.9	12.0	37.3	25.0	13.6	39.6
		H5N1 split	7.5	-	49	7.6	5.9	10.0	1.5	1.2	2.0	14.3	5.9	27.2	14.3	5.9	27.2
		H5N1 split	3.8	-	50	5.9	5.0	7.0	1.2	1.0	1.4	4.0	0.5	13.7	4.0	0.5	13.7
		H5N1 split	30	AS03	48	35.4	23.2	53.9	6.9	4.5	10.5	60.4	45.3	74.2	62.5	47.4	76.0
		H5N1 split	15	AS03	49	34.0	21.4	54.0	6.7	4.2	10.6	61.2	46.2	74.8	61.2	46.2	74.8
		H5N1 split	7.5	AS03	50	36.3	24.4	54.0	6.7	4.5	10.0	62.0	47.2	75.3	64.0	49.2	77.1
		H5N1 split	3.8	AS03	50	23.3	15.8	34.5	4.4	2.9	6.4	52.0	37.4	66.3	54.0	39.3	68.2

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

Table 50 HI responses against strain H5N1 A/Vietnam/1194/2004 of the H5N1 (A/Indonesia) influenza vaccine up to Day 182 in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Time-point	Strain	Manuf. site‡	HA (µg / dos	AS03	N	GMT			SCF			SCR			SPR		
							Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**Pre**	H5N1 Indonesia	Quebec	3.8	AS03	144	**5.3**	5.0	5.6	-	-	-	-	-	-	**2.1**	0.4	6.0
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	**5.3**	5.0	5.6	-	-	-	-	-	-	**1.4**	0.2	4.9
		H5N1 Indonesia	Quebec	3.8	-	75	**5.4**	5.0	5.8	-	-	-	-	-	-	**0.0**	0.0	4.8
		H5N1 Indonesia	Dresden	3.8	AS03	140	**5.5**	5.1	5.9	-	-	-	-	-	-	**2.1**	0.4	6.1
		H5N1 Indonesia	Dresden	3.8	AS03/2	143	**5.4**	5.1	5.7	-	-	-	-	-	-	**1.4**	0.2	5.0
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	144	**9.9**	8.4	11.7	-	-	-	-	-	-	**15.3**	9.8	22.2
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	**8.5**	7.3	10.0	-	-	-	-	-	-	**12.3**	7.5	18.8
		H5N1 Indonesia	Quebec	3.8	-	75	**5.8**	5.1	6.6	-	-	-	-	-	-	**4.0**	0.8	11.2
		H5N1 Indonesia	Dresden	3.8	AS03	140	**9.1**	7.6	10.8	-	-	-	-	-	-	**15.0**	9.5	22.0
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	**8.9**	7.6	10.3	-	-	-	-	-	-	**14.8**	9.4	21.7
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	144	**39.9**	32.2	49.5	-	-	-	-	-	-	**63.9**	55.5	71.7
		H5N1 Indonesia	Quebec	3.8	AS03/2	146	**33.4**	26.6	41.9	-	-	-	-	-	-	**60.3**	51.9	68.3
		H5N1 Indonesia	Quebec	3.8	-	75	**5.8**	5.1	6.5	-	-	-	-	-	-	**4.0**	0.8	11.2
		H5N1 Indonesia	Dresden	3.8	AS03	140	**33.3**	26.0	42.7	-	-	-	-	-	-	**59.3**	50.7	67.5
		H5N1 Indonesia	Dresden	3.8	AS03/2	142	**30.6**	24.3	38.5	-	-	-	-	-	-	**56.3**	47.8	64.6
	Post II (D182)	H5N1 Indonesia	Quebec	3.8	AS03	141	**8.9**	7.8	10.2	**1.7**	1.5	1.9	**9.2**	5.0	15.3	**10.6**	6.1	16.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	145	**7.9**	6.8	9.1	**1.5**	1.3	1.7	**10.3**	5.9	16.5	**13.1**	8.1	19.7
		H5N1 Indonesia	Quebec	3.8	-	74	**5.4**	4.9	5.9	**1.0**	0.9	1.1	**0.0**	0.0	4.9	**1.4**	0.0	7.3
		H5N1 Indonesia	Dresden	3.8	AS03	138	**8.7**	7.5	10.2	**1.6**	1.4	1.8	**10.9**	6.2	17.3	**13.0**	7.9	19.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	138	**8.6**	7.4	9.9	**1.6**	1.4	1.8	**8.7**	4.6	14.7	**10.9**	6.2	17.3

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); GMR = Geometric Mean Ratio; SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

N = number of subjects with available results; % = percentage of subjects with titre within the specified range; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 51 HI responses of the D-Pan H5N1 pandemic influenza vaccine against H5N1 A/Indonesia/05/2005 up to Day 180 in adults from study H5N1-007 (ATP immunogenicity cohort)

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	GMT			SCF			SCR			SPR		
						Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
							LL	UL		LL	UL		LL	UL		LL	UL
H5N1-007	Pre	H5N1 split	30	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.3
18-60 yrs		H5N1 split	15	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	7.5	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	3.8	-	49	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.3
		H5N1 split	30	AS03	48	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.4
		H5N1 split	15	AS03	48	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.4
		H5N1 split	7.5	AS03	50	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.1
		H5N1 split	3.8	AS03	50	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	7.1
	Post I (D21)	H5N1 split	30	-	49	5.1	4.9	5.4	1.0	1.0	1.1	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	15	-	49	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	7.5	-	49	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	3.8	-	49	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.4	0.0	0.0	7.3
		H5N1 split	30	AS03	48	5.9	4.9	7.1	1.2	1.0	1.4	4.2	0.5	14.3	4.2	0.5	14.3
		H5N1 split	15	AS03	49	5.4	4.8	6.0	1.1	1.0	1.2	2.1	0.1	11.1	2.0	0.1	10.9
		H5N1 split	7.5	AS03	50	5.7	5.0	6.4	1.1	1.0	1.3	2.0	0.1	10.6	2.0	0.1	10.7
		H5N1 split	3.8	AS03	50	5.1	4.9	5.4	1.0	1.0	1.1	0.0	0.0	7.1	0.0	0.0	7.1
	Post II (D42)	H5N1 split	30	-	49	5.1	4.9	5.2	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	15	-	49	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	7.5	-	49	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	3.8	-	50	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.1
		H5N1 split	30	AS03	48	11.7	8.0	17.2	2.3	1.6	3.4	29.2	17.0	44.1	29.2	17.0	44.1
		H5N1 split	15	AS03	49	10.2	7.1	14.7	2.1	1.4	3.0	20.8	10.5	35.0	20.4	10.2	34.3
		H5N1 split	7.5	AS03	50	13.9	9.7	20.1	2.8	1.9	4.0	32.0	19.5	46.7	32.0	19.5	46.7
		H5N1 split	3.8	AS03	50	9.9	7.0	14.0	2.0	1.4	2.8	20.0	10.0	33.7	20.0	10.0	33.7

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	GMT			SCF			SCR			SPR		
						Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
							LL	UL		LL	UL		LL	UL		LL	UL
	Post II (D180)	H5N1 split	30	-	48	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.4	0.0	0.0	7.4
		H5N1 split	15	-	48	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	7.4	0.0	0.0	7.4
		H5N1 split	7.5	-	49	5.1	4.9	5.2	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.3
		H5N1 split	3.8	-	50	5.1	4.9	5.2	1.0	1.0	1.0	0.0	0.0	7.3	0.0	0.0	7.1
		H5N1 split	30	AS03	48	5.8	5.0	6.7	1.2	1.0	1.3	4.2	0.5	14.3	4.2	0.5	14.3
		H5N1 split	15	AS03	49	6.0	5.1	7.0	1.2	1.0	1.4	4.2	0.5	14.3	4.1	0.5	14.0
		H5N1 split	7.5	AS03	50	5.9	5.0	6.9	1.2	1.0	1.4	6.0	1.3	16.5	6.0	1.3	16.5
		H5N1 split	3.8	AS03	50	5.4	4.9	6.0	1.1	1.0	1.2	0.0	0.0	7.1	0.0	0.0	7.1

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

Table 52 HI responses of the D-Pan H5N1 pandemic influenza vaccine against H5N1 A/Anhui and A/Turkey strains up to Day 180 in adults from study H5N1-007 (ATP immunogenicity cohort, subset of 40 subjects)

Strain		Timepoint	HA (µg per dose)	AS03	N	GMT			SCF			SCR			SPR		
						Value	95% CI		GMR	95% CI		%	95% CI		%	95% CI	
							LL	UL		LL	UL		LL	UL		LL	UL
A/ANHUI/05	H5N1 split	Pre	3.8	AS03	20	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	16.8
	H5N1 split		3.8	-	20	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	16.8
	H5N1 split	Post I (D21)	3.8	AS03	20	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	16.8	0.0	0.0	16.8
	H5N1 split		3.8	-	20	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	16.8	0.0	0.0	16.8
	H5N1 split	Post II (D42)	3.8	AS03	20	17.1	9.6	30.5	3.4	1.9	6.1	35.0	15.4	59.2	35.0	15.4	59.2
	H5N1 split		3.8	-	20	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	16.8	0.0	0.0	16.8
	H5N1 split	Post II (D180)	3.8	AS03	20	5.4	4.6	6.2	1.1	0.9	1.2	0.0	0.0	16.8	0.0	0.0	16.8
	H5N1 split		3.8	-	20	5.0	5.0	5.0	1.0	1.0	1.0	0.0	0.0	16.8	0.0	0.0	16.8
A/ TURK/05	H5N1 split	Pre	3.8	AS03	20	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	16.8
	H5N1 split		3.8	-	20	5.0	5.0	5.0	-	-	-	-	-	-	0.0	0.0	16.8
	H5N1 split	Post I (D21)	3.8	AS03	20	7.6	4.9	11.8	1.5	1.0	2.4	10.0	1.2	31.7	10.0	1.2	31.7
	H5N1 split		3.8	-	20	5.7	4.3	7.7	1.1	0.9	1.2	5.0	0.1	24.9	5.0	0.1	24.9
	H5N1 split	Post II (D42)	3.8	AS03	20	23.4	12.9	42.4	4.7	2.6	8.5	60.0	36.1	80.9	60.0	36.1	80.9
	H5N1 split		3.8	-	20	5.7	4.3	7.7	1.1	0.9	1.2	5.0	0.1	24.9	5.0	0.1	24.9
	H5N1 split	Post II (D180)	3.8	AS03	20	7.4	5.4	10.3	1.5	1.1	2.1	5.0	0.1	24.9	5.0	0.1	24.9
	H5N1 split		3.8	-	20	5.7	4.3	7.7	1.1	0.9	1.2	5.0	0.1	24.9	5.0	0.1	24.9

SCF: seroconversion factor (i.e ratio of the post-vaccination GMT and the pre-vaccination GMT); SCR: seroconversion rate (i.e proportion of subjects who were either seronegative at pre-vaccination and have a protective post-vaccination titre of ≥ 1:40, or who were seropositive at pre-vaccination and have a 4-fold increase in titre); SPR: seroprotection rate (i.e proportion of subjects with HI titre ≥ 1:40)

2.7.3.5.3 Persistence of homologous neutralizing antibody response

Persistence of homologous neutralizing antibody response following Q-Pan vaccine in study Q-Pan-001

Neutralizing antibody responses against vaccine strain A/Indonesia/05/2005 up to Day 182 in terms of the percentage of subjects with serum neutralization titre (SNT ≥1:28, ≥1:40 and ≥1:80) and GMTs are presented for study Q-Pan-001 in Table 53 and Table 54.

Neutralizing antibodies against vaccine-homologous virus persisted at levels well above baseline values through Day 182 in adjuvanted Q-Pan and D-Pan vaccine groups. By Day 182, six months after immunization, all subjects receiving AS03 adjuvanted Q-Pan or D-Pan vaccine remained seropositive for neutralizing antibody titers (≥ 1:28) against A/Indonesia, with all but one subject maintaining titers ≥ 1:80.

At Day 182, vaccine response rates against A/Indonesia/05/2005 had declined in all treatment groups; however, adjuvanted treatment groups retained 25-38% advantage over the treatment group that did not receive adjuvant.

GMTs in all adjuvanted vaccine recipients declined to levels between 414.0 and 456.2 by Day 182, but these levels remained 13 to 19-fold elevated relative to baseline values and approximately 4-fold above the GMT value at Day 182 in vaccinees with non-adjuvanted antigen.

Reverse cumulative curves (RCCs) for titers of neutralizing antibodies against strain A/Indonesia/05/2005 at the Day 182 time point are presented in Figure 14.

Persistence of homologous neutralizing antibody response following D-Pan vaccine in study H5N1-007

Neutralizing antibody responses against vaccine strain H5N1 A/Vietnam/1194/2004 in terms of the percentage of subjects with serum neutralization titre (SNT) ≥1:28, SCR and GMTs are presented in Table 55 for the ATP immunogenicity cohort of supportive study H5N1-007.

Six months after the first dose, all subjects from the adjuvanted groups except for one from the lowest dose group (3.8µg HA) were seropositive for neutralizing antibodies. In the non-adjuvanted groups, 42.0% to 91.8% of subjects were seropositive at this time point.

SCR and GMTs were statistically higher in the adjuvanted groups as compared to the respective non-adjuvanted formulations at Day 180. SCR ranged from 8.0% to 57.1% in the non-adjuvanted groups, versus 66.0% to 89.6% in the adjuvanted groups.

Although a trend for decrease in SCR is observed at Day 180 versus Day 42 (with overlapping 95% CIs), the Day 180 response remains similar across adjuvanted groups and is still higher than in non-adjuvanted groups.

No antigen dose effect was observed in the adjuvanted groups.

A good persistence of neutralizing antibody response against the vaccine strain was therefore observed up to Day 180 with all adjuvanted formulations.

2.7.3.5.4 Persistence of heterologous neutralizing antibody response (cross-reactive immunity)

Persistence of heterologous neutralizing antibody response following Q-Pan vaccine in study Q-Pan-001

Neutralizing antibody responses up to Day 182 in terms of the percentage of subjects with serum neutralization titre (SNT ≥1:28, ≥1:40 and ≥1:80) and GMTs against heterologous strain A/Vietnam/1194/2004 are presented for study Q-Pan-001 in Table 56 and Table 57.

Neutralizing antibody responses to the drift-variant A/Vietnam/1194/2004 were of smaller magnitude in terms of both vaccine response rates and GMTs. At Day 182, groups vaccinated with adjuvanted Q-Pan or D-Pan vaccine showed a modest decline in the proportion of subjects with A/Vietnam/1194/2004 neutralizing antibody titers ≥ 1:80, i.e. from 94.0-100% at Day 42 to 77.1-85.1% at Day 182.

GMTs of neutralizing antibodies against A/Vietnam/1194/2004 in AS03 adjuvanted vaccine groups declined to levels of 151.0-169.6 by Day 182, but were still well above pre-vaccination level.

At Day 182, vaccine response rates against A/Vietnam/1194/2004 had declined in all treatment groups, and ranged between 13.3% and 44.9%.

Reverse cumulative curves (RCCs) for titers of neutralizing antibodies against strain A/Vietnam/1194/2004 at the Day 182 time point are presented in Figure 15.

Persistence of neutralizing antibody responses against drift-variant virus strains H5N1 A/Anhui/1/05 and A/turkey/Turkey/1/05 in terms of GMTs and the percentage of subjects with serum neutralization titres (SNT) ≥1:28, ≥1:40 and ≥1:80 in study Q-Pan-001 are presented for the ATP immunogenicity cohort in Table 58 and Table 59.

Neutralizing antibody titers against A/Anhui declined fairly rapidly after Day 42 toward baseline values, and by Day 182 only 23.6% of vaccinees had detectable titers (≥1:28).

In contrast to A/Anhui, neutralizing antibody titers against A/turkey remained substantially elevated at Day 182, when 97.9% of vaccinees were seropositive and 60.7% were still considered vaccine responders, i.e. continued to have titers ≥ 4-fold increased over baseline.

Persistence of heterologous neutralizing antibody response following D-Pan vaccine in study H5N1-007

Neutralizing antibody titres were measured against H5N1 heterologous strain (A/Indonesia/05/2005) in all D-Pan vaccine groups from supportive study H5N1-007.

As shown in Table 60, 82.0% to 91.7% of subjects were seropositive for neutralizing antibodies with the adjuvanted formulations at Day 180, versus 6.0% to 49.0% with the non-adjuvanted formulations.

SCR and GMTs were statistically higher in the adjuvanted groups as compared to the non-adjuvanted groups at Day 180. At this time point, SCR ranged from 39.6% to 44.7% in the adjuvanted groups, versus 0.0% to 14.3% in the non-adjuvanted groups.

Neutralizing antibody responses against two other clade 2 strains A/Anhui/01/2005 and A/turkey/Turkey/1/2005 up to Day 180 are presented in Table 61.

With the adjuvanted formulation, the cross reactive immune response to both H5N1 variants persisted up to Day 180, as shown by a SCR of 60.0% and 70.0% against both strains respectively, and seropositivity rates of 100.0% and 95.0% respectively. In terms of neutralizing antibody production, almost no effect of vaccination was observed in the non-adjuvanted group.

Table 53 Neutralizing antibody responses (GMT, titre ≥1:28) against strain H5N1 A/Indonesia/05/2005 of the Q-Pan H5N1 (A/Indonesia) influenza vaccine up to Day 182 in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site‡	HA (µg per dose)	AS03	N	GMT			≥1:28			Vaccine response		
							Value	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**Pre**	H5N1 Indonesia	Quebec	3.8	AS03	47	**22.3**	17.4	28.5	**27.7**	15.6	42.6	**-**	**-**	**-**
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	**31.8**	23.0	43.8	**40.4**	26.4	55.7	**-**	**-**	**-**
		H5N1 Indonesia	Quebec	3.8	-	49	**25.7**	19.9	33.1	**36.7**	23.4	51.7	**-**	**-**	**-**
		H5N1 Indonesia	Dresden	3.8	AS03	48	**23.7**	18.3	30.8	**31.3**	18.7	46.3	-	-	-
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**25.7**	19.6	33.7	**34.0**	21.2	48.8	-	-	-
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	**199.0**	148.9	266.1	**100**	92.5	100	**76.6**	62.0	87.7
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	**240.1**	191.4	301.3	**96.0**	86.3	99.5	**68.1**	52.9	80.9
		H5N1 Indonesia	Quebec	3.8	-	49	**78.6**	57.7	107.1	**81.6**	68.0	91.2	**42.9**	28.8	57.8
		H5N1 Indonesia	Dresden	3.8	AS03	49	**260.5**	208.1	326.0	**100**	92.7	100	**79.2**	65.0	89.5
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	**248.7**	202.0	306.3	**100**	92.7	100	**71.4**	56.7	83.4
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	**1566.8**	1227.3	2000.2	**100**	92.5	100	**97.9**	88.7	99.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	48	**1242.1**	902.2	1710.0	**100**	92.6	100	**91.3**	79.2	97.6
		H5N1 Indonesia	Quebec	3.8	-	49	**183.8**	138.4	244.2	**93.9**	83.1	98.7	**73.5**	58.9	85.1
		H5N1 Indonesia	Dresden	3.8	AS03	49	**1497.2**	1192.0	1880.5	**100**	92.7	100	**95.8**	85.7	99.5
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**1352.8**	1075.5	1701.6	**100**	92.9	100	**96.0**	86.3	99.5
	Post II (D182)	H5N1 Indonesia	Quebec	3.8	AS03	47	**414.0**	346.2	495.1	**100**	92.5	100	**91.5**	79.6	97.6
		H5N1 Indonesia	Quebec	3.8	AS03/2	49	**417.1**	335.0	519.3	**100**	92.7	100	**78.3**	63.6	89.1
		H5N1 Indonesia	Quebec	3.8	-	49	**108.9**	81.9	144.7	**91.8**	80.4	97.7	**53.1**	38.3	67.5
		H5N1 Indonesia	Dresden	3.8	AS03	49	**456.2**	387.4	537.3	**100**	92.7	100	**87.5**	74.8	95.3
		H5N1 Indonesia	Dresden	3.8	AS03/2	48	**450.1**	384.7	526.5	**100**	92.6	100	**87.5**	74.8	95.3

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

N = number of subjects with available results; % = percentage of subjects with titre within the specified range; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Vaccine response defined as antibody titer at Day 21, 42, or 182 ≥ 4-fold the pre-vaccination antibody titer

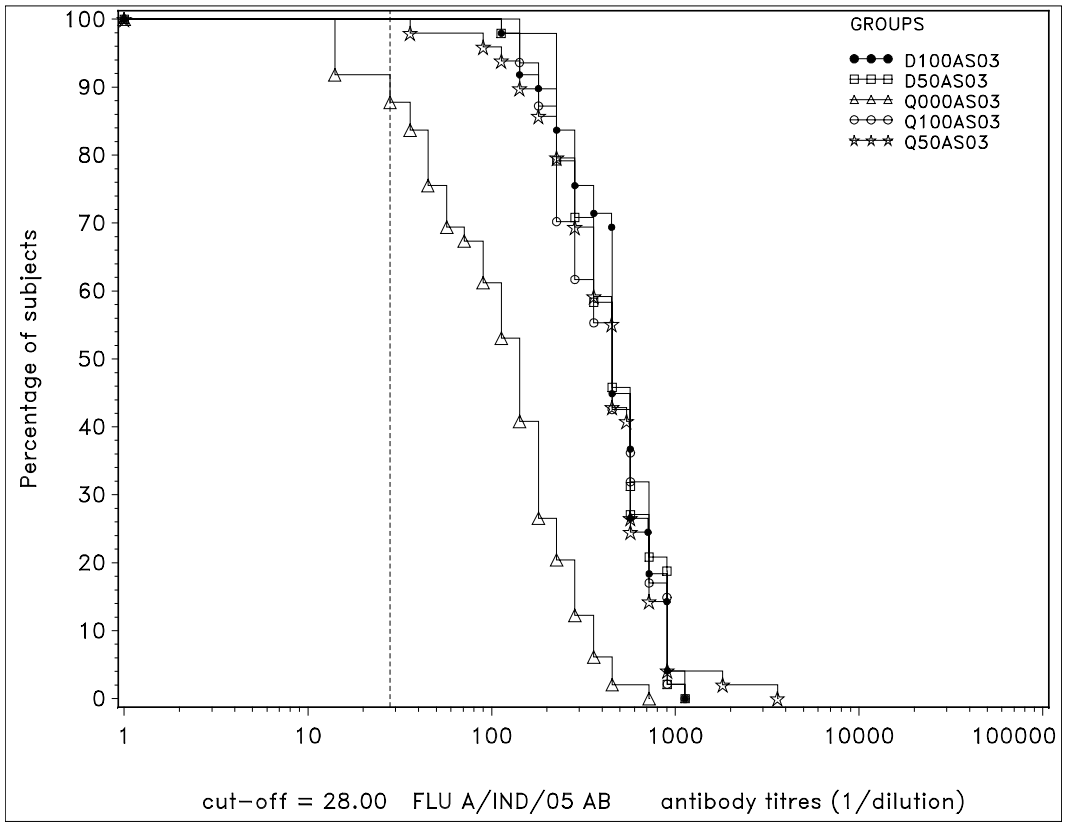
Table 54 Neutralizing antibody responses (titre ≥1:40 and ≥1:80) against strain H5N1 A/Indonesia/05/2005 of the H5N1 (A/Indonesia) influenza vaccine up to Day 182 in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site‡	HA (µg per dose)	AS03	N	≥1:40			≥1:80		
							%	95% CI		%	95% CI	
								LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**Pre**	H5N1 Indonesia	Quebec	3.8	AS03	47	**21.3**	10.7	35.7	**12.8**	4.8	25.7
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	**36.2**	22.7	51.5	**23.4**	12.3	38.0
		H5N1 Indonesia	Quebec	3.8	-	49	**28.6**	16.6	43.3	**16.3**	7.3	29.7
		H5N1 Indonesia	Dresden	3.8	AS03	48	**22.9**	12.0	37.3	**14.6**	6.1	27.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**26.0**	14.6	40.3	**20.0**	10.0	33.7
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	**93.6**	82.5	98.7	**80.9**	66.7	90.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	**96.0**	86.3	99.5	**96.0**	86.3	99.5
		H5N1 Indonesia	Quebec	3.8	-	49	**75.5**	61.1	86.7	**53.1**	38.3	67.5
		H5N1 Indonesia	Dresden	3.8	AS03	49	**98.0**	89.1	99.9	**93.9**	83.1	98.7
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	**98.0**	89.1	99.9	**95.9**	86.0	99.5
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	**100**	92.5	100	**100**	92.5	100
		H5N1 Indonesia	Quebec	3.8	AS03/2	48	**100**	92.6	100	**100**	92.6	100
		H5N1 Indonesia	Quebec	3.8	-	49	**91.8**	80.4	97.7	**81.6**	68.0	91.2
		H5N1 Indonesia	Dresden	3.8	AS03	49	**100**	92.7	100	**100**	92.7	100
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**100**	92.9	100	**100**	92.9	100
	Post II (D182)	H5N1 Indonesia	Quebec	3.8	AS03	47	**100**	92.5	100	**100**	92.5	100
		H5N1 Indonesia	Quebec	3.8	AS03/2	49	**98.0**	89.1	99.9	**98.0**	89.1	99.9
		H5N1 Indonesia	Quebec	3.8	-	49	**83.7**	70.3	92.7	**67.3**	52.5	80.1
		H5N1 Indonesia	Dresden	3.8	AS03	49	**100**	92.7	100	**100**	92.7	100
		H5N1 Indonesia	Dresden	3.8	AS03/2	48	**100**	92.6	100	**100**	92.6	100

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden

N = number of subjects with available results; % = percentage of subjects with titre within the specified range; 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Figure 14 Reverse cumulative curves of neutralising antibody titres against A/Indonesia/05/2005 strain at Day 182 in study Q-Pan-001 (ATP cohort for immunogenicity)



Q000AS03 = Q000AS03: 3.8 µg Quebec manufactured H5N1 antigen A/Indonesia/05/2005 without AS03
Q100AS03 = Q100AS03: 3.8 µg Quebec manufactured H5N1 antigen A/Indonesia/05/2005 with full dose AS03
Q50AS03 = Q50AS03: 3.8 µg Quebec manufactured H5N1 antigen A/Indonesia/05/2005 with half dose AS03
D100AS03 = D100AS03: 3.8 µg Dresden manufactured H5N1 antigen A/Indonesia/05/2005 with full dose AS03
D50AS03 = D50AS03: 3.8 µg Dresden manufactured H5N1 antigen A/Indonesia/05/2005 with half dose AS03

Table 55 Neutralizing antibody responses of the D-Pan pandemic influenza A vaccine (H5N1) against vaccine strain H5N1 A/Vietnam/1194/2004 up to Day 180 in adults from study H5N1-007 (ATP immunogenicity cohort)

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	≥1:28			SCR			GMT		
						%	95% CI		%	95% CI		Value	95% CI	
							LL	UL		LL	UL		LL	UL
H5N1-007 18-60 yrs	Pre	H5N1 split	30	-	49	24.5	13.3	38.9	-	-	-	18.9	16.0	22.3
		H5N1 split	15	-	49	34.7	21.7	49.6	-	-	-	22.6	18.2	28.2
		H5N1 split	7.5	-	49	30.6	18.3	45.4	-	-	-	20.9	17.2	25.2
		H5N1 split	3.8	-	50	28.0	16.2	42.5	-	-	-	20.2	16.8	24.3
		H5N1 split	30	AS03	48	18.8	8.9	32.6	-	-	-	17.3	15.1	20.0
		H5N1 split	15	AS03	49	32.7	19.9	47.5	-	-	-	22.0	17.9	27.0
		H5N1 split	7.5	AS03	50	34.0	21.2	48.8	-	-	-	23.3	18.4	29.4
		H5N1 split	3.8	AS03	50	32.0	19.5	46.7	-	-	-	21.7	17.8	26.4
	Post I (D21)	H5N1 split	30	-	49	89.8	77.8	96.6	57.1	42.2	71.2	80.1	61.0	105.3
		H5N1 split	15	-	48	79.2	65.0	89.5	47.9	33.3	62.8	66.9	47.9	93.4
		H5N1 split	7.5	-	49	67.3	52.5	80.1	22.4	11.8	36.6	40.3	31.2	52.1
		H5N1 split	3.8	-	50	62.0	47.2	75.3	14.0	5.8	26.7	35.5	27.8	45.4
		H5N1 split	30	AS03	47	95.7	85.5	99.5	83.0	69.2	92.4	146.6	113.3	189.8
		H5N1 split	15	AS03	49	100.0	92.7	100.0	83.7	70.3	92.7	181.3	144.6	227.3
		H5N1 split	7.5	AS03	49	95.9	86.0	99.5	63.3	48.3	76.6	134.6	101.3	178.7
		H5N1 split	3.8	AS03	50	96.0	86.3	99.5	66.0	51.2	78.8	117.9	93.7	148.3
	Post II (D42)	H5N1 split	30	-	48	95.8	85.7	99.5	64.6	49.5	77.8	113.6	85.5	150.9
		H5N1 split	15	-	49	87.8	75.2	95.4	53.1	38.3	67.5	80.1	60.1	107.0
		H5N1 split	7.5	-	49	77.6	63.4	88.2	36.7	23.4	51.7	53.4	41.6	68.6
		H5N1 split	3.8	-	50	72.0	57.5	83.8	22.0	11.5	36.0	40.7	32.4	51.0
		H5N1 split	30	AS03	47	100.0	92.5	100.0	97.9	88.7	99.9	258.2	205.5	324.5
		H5N1 split	15	AS03	49	100.0	92.7	100.0	85.7	72.8	94.1	400.1	319.3	501.4
		H5N1 split	7.5	AS03	50	98.0	89.4	99.9	86.0	73.3	94.2	343.0	260.5	451.5
		H5N1 split	3.8	AS03	49	98.0	89.1	99.9	85.7	72.8	94.1	314.7	243.1	407.3
	Post II (D180)	H5N1 split	30	-	49	91.8	80.4	97.7	57.1	42.2	71.2	81.7	61.9	107.9
		H5N1 split	15	-	49	65.3	50.4	78.3	16.3	7.3	29.7	38.3	29.2	50.3
		H5N1 split	7.5	-	48	58.3	43.2	72.4	20.8	10.5	35.0	32.8	25.6	42.1
		H5N1 split	3.8	-	50	42.0	28.2	56.8	8.0	2.2	19.2	23.5	19.0	29.0
		H5N1 split	30	AS03	48	100	92.6	100	89.6	77.3	96.5	130.8	109.7	155.9

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	≥1:28			SCR			GMT		
						%	95% CI		%	95% CI		Value	95% CI	
							LL	UL		LL	UL		LL	UL
		H5N1 split	15	AS03	49	100	92.7	100	71.4	56.7	83.4	130.0	106.0	159.5
		H5N1 split	7.5	AS03	50	100	92.9	100	66.0	51.2	78.8	116.3	97.7	138.4
		H5N1 split	3.8	AS03	50	98.0	89.4	99.9	72.0	57.5	83.8	101.8	84.8	122.3

SCR: seroconversion rate defined as the percentage of vaccinees with a minimum 4-fold increase in titre at post-vaccination
N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 56 Neutralizing antibody responses (GMT and titre ≥1:28) against strain H5N1 A/Vietnam/1194/2004 of the H5N1 (A/Indonesia) influenza vaccine up to Day 182 in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site‡	HA (µg per dose)	AS03	N	GMT			≥1:28			Vaccine response		
							Value	95% CI		%	95% CI		%	95% CI	
								LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**Pre**	H5N1 Indonesia	Quebec	3.8	AS03	47	**57.0**	41.3	78.6	**70.2**	55.1	82.7	**-**	**-**	**-**
		H5N1 Indonesia	Quebec	3.8	AS03/2	46	**82.3**	59.0	114.7	**80.4**	66.1	90.6	**-**	**-**	**-**
		H5N1 Indonesia	Quebec	3.8	-	49	**55.7**	38.7	80.2	**67.3**	52.5	80.1	**-**	**-**	**-**
		H5N1 Indonesia	Dresden	3.8	AS03	49	**51.3**	34.6	76.2	**55.1**	40.2	69.3	-	-	-
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**59.6**	44.2	80.5	**72.0**	57.5	83.8	-	-	-
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	**250.9**	203.6	309.2	**100**	92.5	100	**44.7**	30.2	59.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	**260.9**	205.1	331.9	**96.0**	86.3	99.5	**30.4**	17.7	45.8
		H5N1 Indonesia	Quebec	3.8	-	49	**145.2**	108.0	195.3	**91.8**	80.4	97.7	**34.7**	21.7	49.6
		H5N1 Indonesia	Dresden	3.8	AS03	49	**201.9**	151.9	268.4	**98.0**	89.1	99.9	**49.0**	34.4	63.7
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	**215.0**	174.3	265.3	**100**	92.7	100	**40.8**	27.0	55.8
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	**264.8**	216.7	323.6	**100**	92.5	100	**53.2**	38.1	67.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	**327.1**	269.8	396.6	**100**	92.5	100	**45.5**	30.4	61.2
		H5N1 Indonesia	Quebec	3.8	-	49	**143.9**	111.2	186.2	**98.0**	89.1	99.9	**30.6**	18.3	45.4
		H5N1 Indonesia	Dresden	3.8	AS03	49	**319.2**	261.6	389.4	**100**	92.7	100	**67.3**	52.5	80.1
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**254.0**	213.0	302.9	**100**	92.9	100	**42.0**	28.2	56.8
	Post II (D182)	H5N1 Indonesia	Quebec	3.8	AS03	47	**159.5**	128.1	198.5	**97.9**	88.7	99.9	**38.3**	24.5	53.6
		H5N1 Indonesia	Quebec	3.8	AS03/2	49	**169.6**	130.9	219.8	**100**	92.7	100	**13.3**	5.1	26.8
		H5N1 Indonesia	Quebec	3.8	-	49	**102.9**	79.5	133.1	**95.9**	86.0	99.5	**20.4**	10.2	34.3
		H5N1 Indonesia	Dresden	3.8	AS03	49	**169.0**	131.5	217.0	**100**	92.7	100	**44.9**	30.7	59.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	48	**151.0**	121.4	187.9	**100**	92.6	100	**27.1**	15.3	41.8

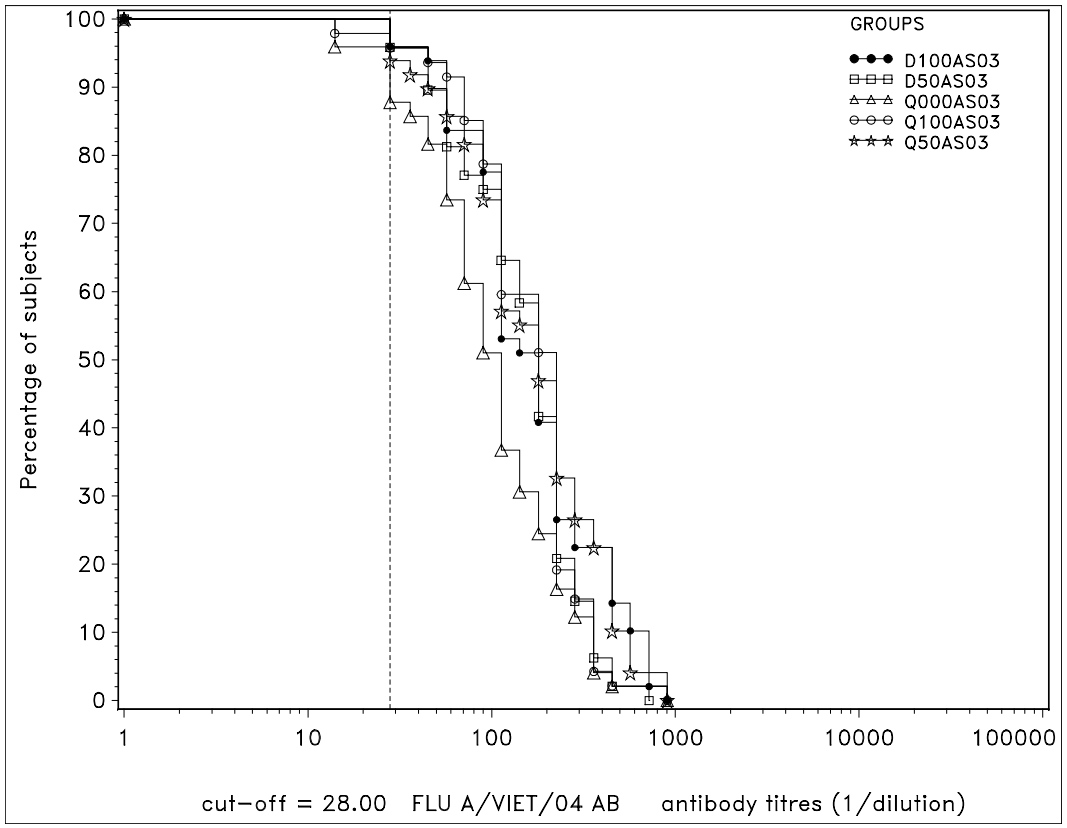
N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 57 Neutralizing antibody responses (titre ≥1:40 and ≥1:80) against strain H5N1 A/Vietnam/1194/2004 of the H5N1 (A/Indonesia) influenza vaccine up to Day 182 in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Timepoint	Strain	Manuf. site‡	HA (µg per dose)	AS03	N	≥1:40			≥1:80		
							%	95% CI		%	95% CI	
								LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**Pre**	H5N1 Indonesia	Quebec	3.8	AS03	47	**61.7**	46.4	75.5	**51.1**	36.1	65.9
		H5N1 Indonesia	Quebec	3.8	AS03/2	46	**71.7**	56.5	84.0	**58.7**	43.2	73.0
		H5N1 Indonesia	Quebec	3.8	-	49	**57.1**	42.2	71.2	**32.7**	19.9	47.5
		H5N1 Indonesia	Dresden	3.8	AS03	49	**55.1**	40.2	69.3	**42.9**	28.8	57.8
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**66.0**	51.2	78.8	**48.0**	33.7	62.6
	Post I (D21)	H5N1 Indonesia	Quebec	3.8	AS03	47	**97.9**	88.7	99.9	**95.7**	85.5	99.5
		H5N1 Indonesia	Quebec	3.8	AS03/2	50	**96.0**	86.3	99.5	**96.0**	86.3	99.5
		H5N1 Indonesia	Quebec	3.8	-	49	**91.8**	80.4	97.7	**77.6**	63.4	88.2
		H5N1 Indonesia	Dresden	3.8	AS03	49	**93.9**	83.1	98.7	**85.7**	72.8	94.1
		H5N1 Indonesia	Dresden	3.8	AS03/2	49	**98.0**	89.1	99.9	**89.8**	77.8	96.6
	Post II (D42)	H5N1 Indonesia	Quebec	3.8	AS03	47	**100**	92.5	100	**95.7**	85.5	99.5
		H5N1 Indonesia	Quebec	3.8	AS03/2	47	**100**	92.5	100	**97.9**	88.7	99.9
		H5N1 Indonesia	Quebec	3.8	-	49	**89.8**	77.8	96.6	**77.6**	63.4	88.2
		H5N1 Indonesia	Dresden	3.8	AS03	49	**100**	92.7	100	**100**	92.7	100
		H5N1 Indonesia	Dresden	3.8	AS03/2	50	**100**	92.9	100	**94.0**	83.5	98.7
	Post II (D182)	H5N1 Indonesia	Quebec	3.8	AS03	47	**95.7**	85.5	99.5	**85.1**	71.7	93.8
		H5N1 Indonesia	Quebec	3.8	AS03/2	49	**91.8**	80.4	97.7	**81.6**	68.0	91.2
		H5N1 Indonesia	Quebec	3.8	-	49	**85.7**	72.8	94.1	**61.2**	46.2	74.8
		H5N1 Indonesia	Dresden	3.8	AS03	49	**95.9**	86.0	99.5	**83.7**	70.3	92.7
		H5N1 Indonesia	Dresden	3.8	AS03/2	48	**95.8**	85.7	99.5	**77.1**	62.7	88.0

N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Figure 15 Reverse cumulative curves of neutralising antibody titres against A/Vietnam/1194/2004 strain at Day 182 in study Q-Pan-001 (ATP cohort for immunogenicity)



Q000AS03 = Q000AS03: 3.8 µg Quebec manufactured H5N1 antigen A/Indonesia/05/2005 without AS03
Q100AS03 = Q100AS03: 3.8 µg Quebec manufactured H5N1 antigen A/Indonesia/05/2005 with full dose AS03
Q50AS03 = Q50AS03: 3.8 µg Quebec manufactured H5N1 antigen A/Indonesia/05/2005 with half dose AS03
D100AS03 = D100AS03: 3.8 µg Dresden manufactured H5N1 antigen A/Indonesia/05/2005 with full dose AS03
D50AS03 = D50AS03: 3.8 µg Dresden manufactured H5N1 antigen A/Indonesia/05/2005 with half dose AS03

Table 58 Neutralizing antibody responses (GMT, titre ≥1:28 and vaccine response) against strains H5N1 A/Anhui/05 and A/Turkey/05 of the H5N1 (A/Indonesia) influenza vaccine up to Day 182 in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Antibody	Vaccine strain and adjuvant	Timepoint	N	GMT			≥1:28			Vaccine Response		
					Value	95% CI		%	95% CI		%	95% CI	
						LL	UL		LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**A/Anhuil/05**	H5N1 3.8µg (Quebec) Indonesia + full AS03	**Pre**	143	**14.0**	14.0	14.0	**0.0**	0.0	2.5	**-**	**-**	**-**
			Post II (D42)	142	**91.3**	78.4	106.4	**95.1**	90.1	98.0	**78.9**	71.2	85.3
			Post II (D182)	140	**16.7**	15.8	17.7	**23.6**	16.8	31.5	**2.1**	0.4	6.1
	A/Turkey/05	H5N1 3.8µg (Quebec) Indonesia + full AS03	**Pre**	143	**25.6**	21.9	29.9	**35.7**	27.8	44.1	**-**	-	-
			Post II (D42)	143	**594.4**	523.6	674.7	**100**	97.5	100	**88.8**	82.5	93.5
			Post II (D182)	140	**121.6**	106.3	139.2	**97.9**	93.9	99.6	**60.7**	52.1	68.9

N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
Vaccine response defined as antibody titer ≥ 4-fold the pre-vaccination titer (samples seronegative at pre-vaccination were assigned a reciprocal titer of 14)

Table 59 Neutralizing antibody responses (titre ≥1:40 ≥1:80) against strains H5N1 A/Anhui/05 and A/Turkey/05 of the H5N1 (A/Indonesia) influenza vaccine up to Day 182 in study Q-Pan-001 (ATP immunogenicity cohort, subset)

Study (Age of vaccination)	Antibody	Vaccine strain and adjuvant	Timepoint	N	≥1:40			≥1:80		
					%	95% CI		%	95% CI	
						LL	UL		LL	UL
Q-Pan-001 18-64 yrs	**A/Anhuil/05**	H5N1 3.8µg (Quebec) Indonesia + full AS03	**Pre**	143	**0.0**	0.0	2.5	**0.0**	0.0	2.5
			Post II (D42)	142	**80.3**	72.8	86.5	**60.6**	52.0	68.7
			Post II (D182)	140	**2.1**	0.4	6.1	**0.0**	0.0	2.6
	A/Turkey/05	H5N1 3.8µg (Quebec) Indonesia + full AS03	**Pre**	143	**25.2**	18.3	33.1	**15.4**	9.9	22.4
			Post II (D42)	143	**98.6**	95.0	99.8	**98.6**	95.0	99.8
			Post II (D182)	140	**93.6**	88.1	97.0	**70.7**	62.4	78.1

N = number of subjects with available results
% = percentage of subjects with titre within the specified range, 95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 60 Neutralizing antibody responses of the D-Pan pandemic influenza A vaccine (H5N1) against H5N1 A/Indonesia/05/2005 up to Day 180 in adults from study H5N1-007 (ATP immunogenicity cohort)

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	≥1:28			SCR			GMT		
						%	95% CI		%	95% CI		Value	95% CI	
							LL	UL		LL	UL		LL	UL
H5N1-007 18-60 yrs	Pre	H5N1 split	30	-	49	4.1	0.5	14.0	-	-	-	14.5	13.8	15.2
		H5N1 split	15	-	45	0.0	0.0	7.9	-	-	-	14.0	14.0	14.0
		H5N1 split	7.5	-	44	2.3	0.1	12.0	-	-	-	14.2	13.8	14.7
		H5N1 split	3.8	-	43	0.0	0.0	8.2	-	-	-	14.0	14.0	14.0
		H5N1 split	30	AS03	47	0.0	0.0	7.5	-	-	-	14.0	14.0	14.0
		H5N1 split	15	AS03	44	2.3	0.1	12.0	-	-	-	14.2	13.8	14.7
		H5N1 split	7.5	AS03	47	21.3	10.7	35.7	-	-	-	17.3	15.2	19.5
		H5N1 split	3.8	AS03	48	8.3	2.3	20.0	-	-	-	15.8	13.9	17.9
	Post I (D21)	H5N1 split	30	-	48	41.7	27.6	56.8	18.8	8.9	32.6	24.9	20.0	30.8
		H5N1 split	15	-	43	14.0	5.3	27.9	4.7	0.6	15.8	16.9	14.2	20.2
		H5N1 split	7.5	-	43	11.6	3.9	25.1	0.0	0.0	8.2	15.4	14.2	16.8
		H5N1 split	3.8	-	43	2.3	0.1	12.3	2.3	0.1	12.3	14.5	13.5	15.4
		H5N1 split	30	AS03	46	82.6	68.6	92.2	54.3	39.0	69.1	54.6	42.5	70.1
		H5N1 split	15	AS03	44	79.5	64.7	90.2	27.3	15.0	42.8	38.1	30.0	48.5
		H5N1 split	7.5	AS03	47	72.3	57.4	84.4	36.2	22.7	51.5	43.7	33.7	56.6
		H5N1 split	3.8	AS03	48	66.7	51.6	79.6	31.3	18.7	46.3	36.6	28.8	46.5
	Post II (D42)	H5N1 split	30	-	48	31.3	18.7	46.3	8.3	2.3	20.0	20.6	17.2	24.6
		H5N1 split	15	-	44	15.9	6.6	30.1	2.3	0.1	12.0	16.5	14.6	18.7
		H5N1 split	7.5	-	44	6.8	1.4	18.7	0.0	0.0	8.0	15.0	13.8	16.3
		H5N1 split	3.8	-	43	2.3	0.1	12.3	2.3	0.1	12.3	14.5	13.5	15.7
		H5N1 split	30	AS03	46	91.3	79.2	97.6	63.0	47.5	76.8	66.8	53.4	83.5
		H5N1 split	15	AS03	44	93.2	81.3	98.6	68.2	52.4	81.4	72.9	58.5	90.9
		H5N1 split	7.5	AS03	46	97.8	88.5	99.9	67.4	52.0	80.5	95.7	75.3	121.7
		H5N1 split	3.8	AS03	48	87.5	74.8	95.3	77.1	62.7	88.0	80.3	62.0	103.9

Study (Age of vaccination)	Timepoint	Strain	HA (µg per dose)	AS03	N	≥1:28			SCR			GMT		
						%	95% CI		%	95% CI		Value	95% CI	
							LL	UL		LL	UL		LL	UL
	Post II (D180)	H5N1 split	30	-	49	49.0	34.4	63.7	14.3	5.9	27.2	25.4	20.7	31.2
		H5N1 split	15	-	49	32.7	19.9	47.5	6.7	1.4	18.3	19.9	16.8	23.5
		H5N1 split	7.5	-	49	24.5	13.3	38.9	4.5	0.6	15.5	18.5	15.7	21.9
		H5N1 split	3.8	-	50	6.0	1.3	16.5	0.0	0.0	8.2	14.7	13.9	15.5
		H5N1 split	30	AS03	48	91.7	80.0	97.7	44.7	30.2	59.9	48.7	40.1	59.2
		H5N1 split	15	AS03	49	87.8	75.2	95.4	43.2	28.3	59.0	52.9	41.7	67.2
		H5N1 split	7.5	AS03	50	82.0	68.6	91.4	40.4	26.4	55.7	45.8	37.5	55.9
		H5N1 split	3.8	AS03	50	82.0	68.6	91.4	39.6	25.8	54.7	46.1	36.9	57.6

SCR: seroconversion rate defined as the percentage of vaccinees with a minimum 4-fold increase in titre at post-vaccination
N = number of subjects with available results
% = percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 61 Neutralizing antibody responses of the monovalent D-Pan pandemic influenza A vaccine (H5N1) against H5N1 A/Anhui and A/Turkey strains up to Day 180 in adults from study H5N1-007 (ATP immunogenicity cohort)

Strain		Timepoint	HA (µg per dose)	AS03	N	≥1:28			SCR			GMT		
						Value	95% CI		%	95% CI		Value	95% CI	
							LL	UL		LL	UL		LL	UL
A/ANHUI/05	H5N1 split	Pre	3.8	AS03	20	20.0	5.7	43.7	-	-	-	17.9	13.7	23.3
	H5N1 split		3.8	-	20	5.0	0.1	24.9	-	-	-	14.5	13.5	15.6
	H5N1 split	Post I (D21)	3.8	AS03	20	75.0	50.9	91.3	35.0	15.4	59.2	37.7	26.8	53.1
	H5N1 split		3.8	-	20	20.0	5.7	43.7	0.0	0.0	16.8	16.3	14.1	18.9
	H5N1 split	Post II (D42)	3.8	AS03	20	100	83.2	100	75.0	50.9	91.3	97.3	72.5	130.6
	H5N1 split		3.8	-	20	15.0	3.2	37.9	0.0	0.0	16.8	16.1	13.6	19.1
	H5N1 split	Post II (D180	3.8	AS03	20	100	83.2	100	60.0	36.1	809	61.4	45.5	82.8
	H5N1 split		3.8	-	20	5.0	0.1	24.9	0.0	0.0	16.8	15.0	13.0	17.4
A/ TURK/05	H5N1 split	Pre	3.8	AS03	20	0.0	0.0	16.8	-	-	-	14.0	14.0	14.0
	H5N1 split		3.8	-	17	5.9	0.1	28.7	-	-	-	14.8	13.2	16.6
	H5N1 split	Post I (D21)	3.8	AS03	20	75.0	50.9	91.3	45.0	23.1	68.5	42.3	27.7	64.5
	H5N1 split		3.8	-	17	17.6	3.8	43.4	0.0	0.0	19.5	17.2	13.3	22.3
	H5N1 split	Post II (D42)	3.8	AS03	20	100	83.2	100	85.0	62.1	96.8	113.2	80.7	158.9
	H5N1 split		3.8	-	17	11.8	1.5	36.4	0.0	0.0	19.5	16.7	12.4	22.5
	H5N1 split	Post II (D180	3.8	AS03	20	95.0	75.1	99.9	70.0	45.7	88.1	80.9	52.8	123.8
	H5N1 split		3.8	-	17	11.8	1.5	36.4	0.0	0.0	19.5	16.3	13.0	20.4

GMT = geometric mean antibody titre calculated on all subjects

Seroconversion defined as: antibody titre after vaccination ≥ 4 fold the pre-vaccination antibody titre

N = number of subjects with available results

n/% = number/percentage of subjects with titre within the specified range

95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

PRE = pre-vaccination dose 1 ; PI(D21) = Post vaccination at day 21

PII(D42) = Post vaccination at day 42 ; PII(D180) = Post-vaccination at day 180

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2.7.3.6 Appendix

Appendix Table 1 Pre-vaccination seropositivity rates for HI antibodies against vaccine strain H5N1 A/Indonesia/05/2005 in pivotal study Q-Pan-001 (ATP cohort for immunogenicity)

Study (Age of vaccination)	Strain	Manuf. site‡	HA (µg /dose)	AS03	>= 10 1/DIL				
					N	n	%	95% CI	
								LL	UL
Q-Pan-001 (18-64 yrs)	H5N1 Indonesia	Quebec	3.8	AS03	144	0	0.0	0.0	2.5
	H5N1 Indonesia	Quebec	3.8	AS03/2	146	0	0.0	0.0	2.5
	H5N1 Indonesia	Quebec	3.8	-	75	0	0.0	0.0	4.8
	H5N1 Indonesia	Dresden	3.8	AS03	140	1	0.7	0.0	3.9
	H5N1 Indonesia	Dresden	3.8	AS03/2	143	1	0.7	0.0	3.8

‡ Manufacturing site: Quebec = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Quebec; Dresden = H5N1 Indonesia antigen produced at GSK Biologicals' manufacturing site in Dresden
N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Appendix Table 2 Pre-vaccination seropositivity rates for HI antibodies against vaccine strain H5N1 A/Vietnam/1194/2004 in supportive D-Pan study H5N1-007 (ATP cohort for immunogenicity)

Study (Age of vaccination)	Strain	HA (µg per dose)	AS03	>= 10 1/DIL				
				N	n	%	95% CI	
							LL	UL
H5N1-007 (18-60 yrs)	**H5N1** split	30	-	49	1	**2.0**	0.1	10.9
	H5N1 split	15	-	49	2	**4.1**	0.5	14.0
	H5N1 split	7.5	-	49	0	**0.0**	0.0	7.3
	H5N1 split	3.8	-	50	0	**0.0**	0.0	7.1
	H5N1 split	30	AS03	48	1	**2.1**	0.1	11.1
	H5N1 split	15	AS03	49	1	**2.0**	0.1	10.9
	H5N1 split	7.5	AS03	50	2	**4.0**	0.5	13.7
	H5N1 split	3.8	AS03	50	2	**4.0**	0.5	13.7

N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Appendix Table 3 Pre-vaccination seropositivity rates for HI antibodies against heterologous H5N1 strain A/Indonesia/05/2005 in supportive D-Pan study H5N1-007 (ATP cohort for immunogenicity)

Study (Age of vaccination)	Strain	HA (µg per dose)	AS03	>= 10 1/DIL				
				N	n	95% CI		
						%	LL	UL
H5N1-007 (18-60 yrs)	**H5N1 split**	30	-	49	0	**0.0**	0.0	7.3
	H5N1 split	15	-	49	0	**0.0**	0.0	7.3
	H5N1 split	7.5	-	49	0	**0.0**	0.0	7.3
	H5N1 split	3.8	-	49	0	**0.0**	0.0	7.3
	H5N1 split	30	AS03	48	0	**0.0**	0.0	7.4
	H5N1 split	15	AS03	48	0	**0.0**	0.0	7.4
	H5N1 split	7.5	AS03	50	0	**0.0**	0.0	7.1
	H5N1 split	3.8	AS03	50	0	**0.0**	0.0	7.1

N = number of subjects with available results
n/% = number/percentage of subjects with titre within the specified range
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Appendix Table 4 Vaccine response rates for A/Indonesia/05/2005 neutralizing antibody at Days 21 and 42 in study Q-Pan-001, by prevaccination serostatus (ATP cohort for immunogenicity, subset)

Study (Age of vaccination)	Group	Pre-vaccination status	Day 21					Day 42				
			Vaccine Responders					Vaccine Responders				
			N	n	%	95 % CI		N	n	%	95 % CI	
						LL	UL				LL	UL
Q-Pan-001 18-64 yrs	H5N1 Indonesia Dresden 3.8 µg HA + AS03	S-	33	31	93.9	79.8	99.3	33	33	100	89.4	100
		S+	15	7	46.7	21.3	73.4	15	13	86.7	59.5	98.3
		Total	48	38	79.2	65.0	89.5	48	46	95.8	85.7	99.5
	H5N1 Indonesia Dresden 3.8 µg HA +AS03/2	S-	32	30	93.8	79.2	99.2	33	33	100	89.4	100
		S+	17	5	29.4	10.3	56.0	17	15	88.2	63.6	98.5
		Total	49	35	71.4	56.7	83.4	50	48	96.0	86.3	99.5
	H5N1 Indonesia Quebec 3.8 µg HA+ AS03	S-	34	29	85.3	68.9	95.0	34	34	100	89.7	100
		S+	13	7	53.8	25.1	80.8	13	12	92.3	64.0	99.8
		Total	47	36	76.6	62.0	87.7	47	46	97.9	88.7	99.9
	H5N1 Indonesia Quebec 3.8 µg HA+ AS03/2	S-	28	26	92.9	76.5	99.1	28	28	100	87.7	100
		S+	19	6	31.6	12.6	56.6	18	14	77.8	52.4	93.6
		Total	47	32	68.1	52.9	80.9	46	42	91.3	79.2	97.6
	H5N1 Indonesia Quebec 3.8 µg HA	S-	31	17	54.8	36.0	72.7	31	26	83.9	66.3	94.5
		S+	18	4	22.2	6.4	47.6	18	10	55.6	30.8	78.5
		Total	49	21	42.9	28.8	57.8	49	36	73.5	58.9	85.1

S- = seronegative subjects (antibody titer < 28 1/DIL for FLU A/IINDO/05 AB) prior to vaccination
S+ = seropositive subjects (antibody titer ≥ 28 1/DIL for FLU A/IINDO/05 AB) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Vaccine response defined as antibody titer at DAY 42 ≥ 4-fold the pre-vaccination antibody titer (samples which were seronegative at baseline were presumed to have a reciprocal titer of 14)
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

Appendix Table 5 Vaccine response rates for A/Vietnam/1194/2004 neutralizing antibody at Days 21 and 42 in study Q-Pan-001, by prevaccination serostatus (ATP cohort for immunogenicity, subset)

Study (Age of vaccination)	Group	Pre-vaccination status	Day 21					Day 42				
			Vaccine Responders					Vaccine Responders				
			N	n	%	95 % CI		N	n	%	95 % CI	
						LL	UL				LL	UL
Q-Pan-001 18-64 yrs	H5N1 Indonesia Dresden 3.8 µg HA + AS03	S-	22	19	**86.4**	65.1	97.1	22	22	**100**	84.6	100
		S+	27	5	**18.5**	6.3	38.1	27	11	**40.7**	22.4	61.2
		Total	49	24	**49.0**	34.4	63.7	49	33	**67.3**	52.5	80.1
	H5N1 Indonesia Dresden 3.8 µg HA +AS03/2	S-	13	12	**92.3**	64.0	99.8	14	14	**100**	76.8	100
		S+	36	8	**22.2**	10.1	39.2	36	7	**19.4**	8.2	36.0
		Total	49	20	**40.8**	27.0	55.8	50	21	**42.0**	28.2	56.8
	H5N1 Indonesia Quebec 3.8 µg HA+ AS03	S-	14	13	**92.9**	66.1	99.8	14	14	**100**	76.8	100
		S+	33	8	**24.2**	11.1	42.3	33	11	**33.3**	18.0	51.8
		Total	47	21	**44.7**	30.2	59.9	47	25	**53.2**	38.1	67.9
	H5N1 Indonesia Quebec 3.8 µg HA+ AS03/2	S-	9	8	**88.9**	51.8	99.7	9	9	**100**	66.4	100
		S+	37	6	**16.2**	6.2	32.0	35	11	**31.4**	16.9	49.3
		Total	46	14	**30.4**	17.7	45.8	44	20	**45.5**	30.4	61.2
	H5N1 Indonesia Quebec 3.8 µg HA	S-	16	13	**81.3**	54.4	96.0	16	12	**75.0**	47.6	92.7
		S+	33	4	**12.1**	3.4	28.2	33	3	**9.1**	1.9	24.3
		Total	49	17	**34.7**	21.7	49.6	49	15	**30.6**	18.3	45.4

S- = seronegative subjects (antibody titer < 28 1/DIL for FLU A/IINDO/05 AB) prior to vaccination
S+ = seropositive subjects (antibody titer ≥ 28 1/DIL for FLU A/IINDO/05 AB) prior to vaccination
Total = subjects either seropositive or seronegative at pre-vaccination
Vaccine response defined as antibody titer at DAY 42 ≥ 4-fold the pre-vaccination antibody titer (samples which were seronegative at baseline were presumed to have a reciprocal titer of 14)
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval; LL = lower limit, UL = upper limit

Appendix Table 6 Comparison of seroconversion rates at Day 42 in 18- 40 year old subjects receiving Quebec antigen with adjuvant and Quebec antigen without adjuvant in study Q-Pan-001 (ATP cohort for immunogenicity)

								Difference in seroconversion rate		
								%	95% CI	
Antibody		N	n	%	N	n	%		LL	UL
		Q-Pan AS03 full dose			Q-Pan withoutAS03			(Q-Pan AS03 full dose minus Q-Pan withoutAS03)		
A/Indonesia		80	77	96.3	39	4	10.3	85.99	71.89	93.27
A/Vietnam/1194/2004		80	51	63.8	39	1	2.6	61.19	47.40	71.61
		Q-Pan AS03 half dose			Q-Pan withoutAS03			(Q-Pan AS03 half dose minus Q-Pan withoutAS03)		
A/Indonesia		81	75	92.6	39	4	10.3	82.34	67.70	90.50
A/Vietnam/1194/2004		81	49	60.5	39	1	2.6	57.93	44.15	68.59

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

Appendix Table 7 Comparison of seroconversion rates at Day 42 in 41-64 year old subjects subjects receiving Quebec antigen with adjuvant and Quebec antigen without adjuvant in study Q-Pan-001 (ATP cohort for immunogenicity)

								Difference in seroconversion rate		
								%	95% CI	
Antibody		N	n	%	N	n	%		LL	UL
		Q-Pan AS03 full dose			Q-Pan withoutAS03			(Q-Pan AS03 full dose minus Q-Pan withoutAS03)		
A/Indonesia		64	63	98.4	36	9	25.0	73.44	56.87	85.07
A/Vietnam/1194/2004		64	38	59.4	36	0	0.0	59.38	47.08	70.59
		Q-Pan AS03 half dose			Q-Pan withoutAS03			(Q-Pan AS03 half dose minus Q-Pan withoutAS03)		
A/Indonesia		65	56	86.2	36	9	25.0	61.15	42.54	74.99
A/Vietnam/1194/2004		65	37	56.9	36	0	0.0	56.92	44.77	68.29

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

Appendix Table 8 Comparison of adjusted ratios of GMTs at Day 42 in 18- 40 year old subjects receiving Quebec antigen with adjuvant and Quebec antigen without adjuvant in study Q-Pan-001 (ATP cohort for immunogenicity)

						Adjusted GMT ratio		
						Value	95% CI	
Antibody		N	value	N	value		LL	UL
		Q-Pan AS03 full dose		Q-Pan withoutAS03		(Q-Pan AS03 full dose versus Q-Pan withoutAS03)		
A/Indonesia		80	602.4	39	8.0	75.29	45.61	124.28
A/Vietnam/1194/2004		80	41.0	39	5.4	7.65	4.52	12.97
		Q-Pan AS03 half dose		Q-Pan withoutAS03		(Q-Pan AS03 half dose versus Q-Pan withoutAS03)		
A/Indonesia		81	488.8	39	8.0	61.09	37.04	100.73
A/Vietnam/1194/2004		81	37.0	39	5.4	6.90	4.07	11.68

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit

Appendix Table 9 Comparison of adjusted ratios of GMTs at Day 42 in 41-64 year old subjects subjects receiving Quebec antigen with adjuvant and Quebec antigen without adjuvant in study Q-Pan-001 (ATP cohort for immunogenicity)

						Adjusted GMT ratio		
						Value	95% CI	
Antibody		N	value	N	value		LL	UL
		Q-Pan AS03 full dose		Q-Pan withoutAS03		(Q-Pan AS03 full dose versus Q-Pan withoutAS03)		
A/Indonesia		64	334.5	36	14.1	23.77	13.80	40.94
A/Vietnam/1194/2004		64	39.3	36	6.2	6.30	3.80	10.44
		Q-Pan AS03 half dose		Q-Pan withoutAS03		(Q-Pan AS03 half dose versus Q-Pan withoutAS03)		
A/Indonesia		65	188.8	36	14.1	13.42	7.80	23.08
A/Vietnam/1194/2004		65	29.8	36	6.2	4.77	2.88	7.91

N = number of subjects with pre- and post-vaccination results available
n/% = number/percentage of subjects with a booster response
95% CI = Standardized asymptotic 95% confidence interval; LL = lower limit, UL = upper limit