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Division / Office	DVP /OVRR
Priority Review	No
Reviewer Name(s)	Andrea James, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lewis Schrager, MD
Applicant	ID Biomedical Corporation of Quebec dba GlaxoSmithKline Biologicals
Established Name	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted
(Proposed) Trade Name	<No Proprietary Name>
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	3.75 µg HA H5N1 antigen with AS03 adjuvant
Dosage Form(s) and Route(s) of Administration	Emulsion for intramuscular injection
Dosing Regimen	0.5 ml, administered as a 2 dose series approximately 21 days apart
Indication(s) and Intended Population(s)	For the prevention of influenza disease in persons 18 years and older at increased risk for exposure to H5N1 subtypes contained in the vaccine.

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GLOSSARY

AE	adverse event
AESI	adverse events of special interest
AI	avian influenza
ALT	alanine aminotransferase
AST	aspartate aminotransferase
Arepanrix H1N1	GSK's Quebec manufactured pandemic H1N1 influenza vaccine
ASPR	Assistant Secretary for Preparedness and Response
ATP-I	according to protocol-immunogenicity cohort
BLA	biologics license application
BARDA	Biomedical Advanced Research and Development Authority
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
DBA	doing business as
DHHS	Department of Health and Human Services
D-Pan	GSK's Dresden-manufactured pandemic influenza vaccine
eCRF	electronic case report forms
EMA	European Medicines Agency
FDA	Food and Drug Administration
Flulaval	GSK's Quebec manufactured seasonal trivalent influenza vaccine
Fluzone	GSK's Dresden manufactured seasonal trivalent influenza vaccine
GMT	geometric mean titer
GSK	Glaxo Smith Kline Biologicals
HA	hemagglutinin
HI	hemagglutination-inhibition
HLA	human leukocyte antigen
HPV	human papilloma virus
IR	information request
MAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Authorities
NOCD	new onset chronic disease
OBE	Office of Biostatistics and Epidemiology
Pandemrix H1N1	GSK's Dresden manufactured pandemic influenza vaccine
PMCs	post marketing commitments
Q-Pan H5N1	Influenza A (H5N1) virus monovalent vaccine, adjuvanted
SCR	seroconversion rate
VE	vaccine effectiveness
VRBPAC	Vaccine and Related Biologic Product Advisory Committee
BPCA	Best Pharmaceuticals for Children Act
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
OBE	Office of Biostatistics and Epidemiology

PeRC	Pediatric Review Committee (CDER)
PI	package insert
pIMD	potentially immune mediated disease
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
SAE	serious adverse event
SAP	statistical analysis plan
TVC	total vaccinated cohort
US	United States
VRBPAC	Vaccine and Related Biologic Products Advisory Committee

1. EXECUTIVE SUMMARY

Highly pathogenic H5N1 avian influenza virus has caused limited, but deadly human disease with a mortality rate of up to 60%. To date, the vast majority of human cases have occurred in people with exposure to poultry, and no human or avian cases have been identified in the U.S. If this virus were to acquire the ability to transmit easily from person-to-person while maintaining its pathogenicity, it would likely result in a severe influenza pandemic with potentially devastating global impact.

As part of the national strategy for pandemic influenza preparedness, the United States (US) Department of Health and Human Services (DHHS), Assistant Secretary for Preparedness and Response (ASPR), Office of Biomedical Advanced Research and Development Authority (BARDA) contracted GSK to develop and submit for licensure a candidate H5N1 influenza virus vaccine with antigen-sparing potential for inclusion in the U.S. Strategic National Stockpile.

On February 22, 2012, a BLA was submitted by ID Biomedical dba GlaxoSmithKline (GSK or the Applicant) to the Food and Drug Administration (FDA) for an adjuvanted H5N1 influenza virus monovalent vaccine. The vaccine does not have a trade name; its proper name is Influenza A (H5N1) virus monovalent vaccine, adjuvanted (hereafter referred to as Q-Pan H5N1 or the candidate vaccine in this review). The candidate vaccine contains 3.75 µg HA as compared to 15 µg HA/antigen in current seasonal influenza vaccines and 90 µg HA in the only other currently U.S.-licensed H5N1 pandemic influenza vaccine. Antigen dose sparing is made possible by including GSK's proprietary oil-in-water adjuvant, AS03.

The H5N1 influenza antigen is an inactivated, detergent-split virion, produced in eggs using the U.S.-licensed FluLaval manufacturing process (manufactured in Québec, Canada). The antigen is combined, prior to administration, in a 1:1 volume ratio with AS03 (manufactured in GSK's Rixensart, Belgium facility). AS03 contains squalene, D,L-α-tocopherol (vitamin E) and polysorbate 80 and is thought to induce both innate and adaptive immune responses by enhancing delivery of antigen to antigen-presenting cells, although its complete mechanism of action is unknown. The combination of the antigen (3.75 µg HA) and AS03 adjuvant yields a multi-dose (10 doses) presentation of

the vaccine. The multi-dose presentation contains 5µg per 0.5 mL dose of thimerosal as a preservative.

Immunogenicity and safety data from two pivotal trials, Q-Pan H5N1-001 and Q-Pan-H5N1-002, were submitted in support of licensure and product labeling. The database from these two studies includes 5,241 adult subjects, 3,574 of whom received the final formulation of Q-Pan H5N1 intended for licensure (containing 3.75 µg of H5N1 HA).

Q-Pan H5N1-001 was a phase I/II study, that enrolled 152 adult subjects 18-64 years of age who received a two dose series of Q-Pan H5N1 given 21 days apart. Several formulations of H5N1 vaccines were compared to Q-Pan H5N1 in the study: unadjuvanted H5N1 vaccine, Q-Pan H5N1 adjuvanted with half-strength AS03 adjuvant ($AS03_B$) and GSK's Dresden, Germany manufactured (D-Pan) H5N1-AS03 adjuvanted vaccine. Of note, an earlier D-Pan study was the basis for the selection of the antigen sparing 3.75 µg dose.

Q-Pan H5N1-001 demonstrated:

- activity of AS03 adjuvant as evidenced by the ability to reduce the antigen dose to 3.75 µg HA.
- the need for two doses of Q-Pan H5N1 to induce an HI antibody response that met the CBER pandemic influenza Guidance's suggested HAI immunogenicity criteria[1]
- the added immunogenicity benefit of AS03 adjuvanted H5N1 vaccine as compared to unadjuvanted H5N1 vaccine based on seroconversion rates (the proportion of subjects with a four-fold rise in baseline HI titers) and geometric mean titer (GMT) ratios
- immunogenic equivalence between Q-Pan H5N1 and D-Pan H5N1.

Results of this study formed the basis for GSK's selection of Q-Pan H5N1 3.75 µg HA adjuvanted with full dose AS03 adjuvant ($AS03_A$) as the final formulation for clinical development.

Q-Pan H5N1-002 was the pivotal Phase III study in which 3,422 adults ≥ 18 years of age received the final formulation of Q-Pan H5N1. On February 26, 2013, GSK notified CBER that it inadvertently submitted an incomplete study data package for Q-Pan-002 with the original BLA submission on February 22, 2012. This incomplete data package included 37 interim (D182) case report tabulations (CRTs, also known as datasets) instead of the final, "clean" (D364) 42 CRTs, and was missing 71 electronic case report forms (eCRFs) for pivotal study Q-Pan-002. GSK reports using the final, "clean" data for each study period (D42, D182 and D364) to generate the respective individual clinical study reports. However, since "cleaning" of the data continued beyond the time when both the D42 and D182 study reports were generated, some adverse event data in each of those study reports may differ from the data captured in the final D364 datasets. One major discrepancy noted by this reviewer between the interim unsolicited AE data set (WUNSOL) and the clinical study reports is the presence of two potentially immune-mediated adverse events of special interest (AESIs), a case of lupus and a case of

cutaneous vasculitis, that appear in the interim, D182 WUNSOL data set, but not in any of the three clinical study reports for Q-Pan-002, nor in the final D364 WUNSOL data set, (submitted to the BLA in November 2012 in response to an unrelated CBER information request, but not identified by GSK at the time as the final version of the D182 WUNSOL data set). Review of the final datasets is needed to ensure that no other major discrepancies exist between the interim and final data that might impact the safety conclusions.

Of note, GSK's assessment of the interim and final datasets found no impact on the primary immunogenicity endpoint data because no primary immunogenicity data were generated after D182 (the timing of the interim datasets). GSK also confirmed that Q-Pan-001 datasets were final datasets.

GSK was issued a complete response (CR) letter on March 22, 2013 requesting the D364 datasets (with comparative analyses between the D182 and D364 datasets), the missing eCRFs and the source data for the two AESI subjects.

All references in this review to Q-Pan-002 safety data results and conclusions are based on the interim datasets and may change pending review of the final datasets.
Results from Q-Pan-002 demonstrated that Q-Pan H5N1 elicited an immune response fulfilling CBER's acceptance criteria for Accelerated Approval[1] of pandemic vaccines after administration of two doses. It also provided clinical evidence of manufacturing consistency based on the similar immunological responses observed in study groups receiving Q-Pan H5N1 from 3 lots manufactured consecutively.

Following discussion with CBER, GSK submitted data to the BLA from a non-GSK sponsored, Canadian, case-control, test-negative, retrospective effectiveness study of GSK's H1N1 pandemic vaccine, Arepanrix. Data from this study were to be considered as a potential basis for confirming the clinical benefit of Q-Pan H5N1. However, due to many study limitations the data were deemed as supportive but not confirmatory of the effectiveness of Q-Pan H5N1.

The safety database from the two pivotal studies included 3,574 subjects receiving Q-Pan H5N1 3.75 µg + $AS03_A$. Based on interim safety data from the large, pivotal Phase III Q-Pan-002 study and final safety data from the small, Phase I/II Q-Pan-001 study, the most common safety outcome was injection site pain occurring in the majority of subjects (>80%) with nearly half of all subjects experiencing transient, at least moderately severe pain (44%) that interfered with the ability to attend work or school. Up to 6% of subjects experienced transient, severe pain that prevented subjects from attending work or school. Systemic reactions (excluding fever) were also commonly reported (in 12 - 49% of subjects). These rates are higher than observed in the unadjuvanted H5N1 vaccinees (all pain 23%; grade 3 pain 1%; systemic reactions 5-32%). Therefore, the majority of these reactions likely are attributable to the AS03 adjuvant.

GSK submitted to the BLA integrated safety analyses that pooled safety data from 24 controlled and uncontrolled studies of ASO3-adjuvanted influenza vaccines. These Q-Pan

and D-Pan H5N1 and H1N1 studies included 22,521 adult subjects. A tiered approach was taken: expanding from the most relevant and clean data (from controlled, adjuvanted H5N1 trials) to H5N1 plus H1N1 data from uncontrolled trials. GSK performed multiple pre-planned and *post hoc* analyses. A total of 16,160 persons received H5N1 or H1N1 + AS03 vaccine and 6,361 persons received an active (unadjuvanted H5N1, Fluarix, or Flulaval) or saline placebo control.

The pooled D-Pan/Q-Pan H5N1 safety data in nearly 10,000 recipients of D-Pan or Q-Pan H5N1 revealed a higher rate of all solicited adverse events, most notably pain, as compared to the controls. These results were consistent with what was observed in the pivotal clinical trials.

An imbalance in the proportion of subjects reporting certain unsolicited adverse events (AEs); serious adverse events (SAEs); and selected neuroinflammatory, musculoskeletal, gastrointestinal metabolic, skin and autoimmune disorders referred to as adverse events of special interest (AESI)/potential immune mediated diseases (pIMDs) was noted in the pivotal clinical trials as well as in the integrated safety summaries. These imbalances in reported adverse events in clinical trials reflect a strong inflammatory response following vaccination with Q-Pan H5N1, as evidenced by the commonly occurring local and systemic reactions. Also of concern to this reviewer is the potential for stimulation of innate and adaptive immune responses in ways that are not fully understood, which could precipitate or exacerbate an autoimmune condition.

Narcolepsy, autoimmune hepatitis (AIH), and solid organ transplant rejection are pIMD events spontaneously reported in association with GSK's AS03 adjuvanted H1N1 (2009) pandemic influenza vaccines, Pandemrix (narcolepsy and AIH) or Arepanrix (solid organ transplant rejection). Although definitive vaccine relatedness has not been confirmed for any of these events, the possibility that AS03 adjuvanted vaccines may have played a role in the development or exacerbation of these conditions cannot be discounted. Continued close monitoring of these and other potentially immune mediated events is warranted, which GSK is committed to doing as part of their AS03 adjuvanted pandemic influenza vaccines' pharmacovigilance plan.

No efficacy data exist for Q-Pan H5N1 and no clinical data are available demonstrating effectiveness of the vaccine in preventing disease caused by H5N1 influenza virus. Pediatric Research Equity Act (PREA) required pediatric studies are currently deferred pending further investigations of an identified safety signal, narcolepsy, with Pandemrix, GSK's AS03 adjuvanted H1N1 (2009) influenza vaccine. If additional pediatric studies are allowed to proceed to support a pediatric use, the studies will be reviewed and approval for use of the vaccine in children will be pursued under a supplemental BLA.

Given the high degree of morbidity and mortality associated with H5N1 disease, the plans to have the government stockpile and control the use of Q-Pan H5N1, no plans for GSK to market the vaccine for general use in the inter-pandemic period and the restricted usage to adults at increased risk of exposure to H5N1 or during a pandemic, all combined for an overall favorable risk/benefit profile for Q-Pan H5N1.

Any use outside of that previously mentioned will require a much larger pre-licensure safety database to further evaluate the aforementioned safety concerns.

Q-Pan H5N1 would be approved under the Accelerated Approval Regulations. GSK has submitted a proposal to confirm Q-Pan H5N1's effectiveness with a study in children evaluating the efficacy of their non-adjuvanted, quadrivalent, seasonal influenza vaccine (quadrivalent Flulaval) manufactured using the same process as Q-Pan H5N1. However, this reviewer believes that the effectiveness of Q-Pan H5N1 can only be confirmed by a study with the actual product in a scenario where H5N1 virus is in circulation (pandemic or outbreak) or in a large, high risk population, such as poultry workers in a country where H5N1 is endemic in the poultry. Data concerning the efficacy of vaccines targeting other influenza subtypes would only be supportive not confirmatory. Until the time of an H5N1 outbreak or pandemic, during which the clinical effectiveness of Q-Pan H5N1 can be evaluated, this reviewer's recommendation would be to maintain Q-Pan H5N1 under Accelerated Approval.

2. CLINICAL AND REGULATORY BACKGROUND

The candidate vaccine, Influenza A (H5N1) virus monovalent vaccine, adjuvanted (hereafter referred to as Q-Pan H5N1) is an inactivated, detergent split virion monovalent H5N1 antigen (manufactured using the same process as GSK's seasonal influenza vaccine Flulaval™) combined, prior to administration, in a 1:1 volume ratio with an oil-in-water emulsion adjuvant, AS03. The combination of the antigen (3.75 µg HA) and AS03 adjuvant yields a multi-dose (10 doses) presentation of the vaccine. AS03 contains squalene, D,L-α-tocopherol (vitamin E) and polysorbate 80 and is thought to enhance both innate and adaptive immune responses by enhancing delivery of antigen to antigen presenting cells. The multi-dose presentation contains 5µg per 0.5 mL dose of thimerosal as a preservative.

If approved, Q-Pan H5N1 would be indicated for the prevention of influenza disease caused by H5N1 subtypes contained in the vaccine.

2.1 Disease or Health-Related Condition(s) Studied

Influenza is an acute respiratory illness caused by infection with influenza viruses and occurs in distinct outbreaks of variable extent and severity every year. Influenza viruses are RNA viruses belonging to the *Orthomyxoviridae* family and include the genera influenza A, B and C viruses. Influenza A and B viruses cause the vast majority of human disease. Influenza A viruses are further classified into subtypes based on the two envelope glycoproteins hemaglutinin (HA) and neuraminidase (NA). In total, 16 HA antigenic subtypes (H1-H16) and 9 NA subtypes (N1-N9) exist. Influenza B viruses have only one HA and NA subtype. Since 1977, influenza A H1N1 and H3N2 viruses and influenza B viruses have co-circulated globally causing seasonal human disease.

Influenza pandemics occur when a new subtype of an influenza A virus emerges to which the population has not been exposed and to which it has little or no immunity. Three pandemic influenza outbreaks occurred during the 20th century (1918, 1957 and 1968) and one has occurred so far during the 21st century (2009). Pandemic influenza viruses evolve following genetic reassortment of animal and human influenza viruses, which allow the virus to adapt to and spread among humans.[2] The 1918-19 H1N1 pandemic virus, the most lethal of the 20th century, resulted in about 50 million deaths worldwide.[3]

The H5N1 virus subtype is a highly pathogenic avian influenza (AI) virus that results in high death rates (up to 100% mortality within 48 hours) in some poultry species and is on the WHO list of influenza viruses for development of candidate vaccines as part of pandemic preparedness. The first H5N1 virus known to have infected humans occurred in Hong Kong in 1997, causing 18 cases, including six deaths. Since mid-2003, this virus has caused the largest and most severe influenza outbreaks in poultry on record, and has caused disease in approximately 600 humans in 15 countries with a mortality rate of greater than 60%.[4]

As with many other communicable diseases, vaccines are considered the first line of defense against influenza viruses, including AI strains with pandemic potential. International efforts continue to address the production and licensure of influenza vaccines for prevention of influenza caused by pandemic strains. Towards this goal, BARDA contracted with GSK to develop and submit for US licensure an antigen sparing H5N1 influenza virus vaccine that will be owned and distributed by the US government.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, there is one vaccine approved for prevention of pandemic strain H5N1. In 2007, Sanofi's A/H5N1/Vietnam/2004 vaccine was granted traditional approval based on immunogenicity and safety data from a small Phase 1, randomized, placebo-controlled, dose-exploring study in which 91 subjects received the to-be-marketed 90 µg dose.

Reviewer comment: Please refer to the Clinical Review for STN 125244/0 and the Vaccine and Related Biologic Product Advisory Committee (VRBPAC) meeting transcript (February 27, 2007) for Sanofi's H5N1 vaccine, which both note that

- ***The approval of this vaccine was based on limited immunogenicity and safety data (n=91 subjects) from a single Phase 1 study that was not powered to make any immunogenicity, efficacy or safety conclusions.***
- ***The antibody responses resulting from two 90 µg doses of the Sanofi H5N1 vaccine were below CBER's suggested antibody responses as put forth in the 2007 Guidance for Industry on Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines[1].***
- ***The effectiveness of this product was not known nor inferred from its seasonal counterpart, Fluzone.***

- ***This product was approved as a "stop gap measure" in light of a perceived threat of a potential, impending pandemic, and in the absence of a product that produced a higher antibody response.***
- ***Potential approval pathways (i.e. accelerated vs. traditional) were not discussed nor were inferences of effectiveness made.***

Four US licensed antiviral agents (amantadine, ramantadine, oseltamavir and zanamavir) are available for prophylaxis and treatment of influenza disease. However, since 2005, emerging resistance to one or more of these licensed antivirals has complicated recommendation for their use.

2.3 Safety and Efficacy of Pharmacologically Related Products

The antigen dose, 3.75µg, was identified in study D-Pan-H5N1-007, where a range of GSK's Dresden-manufactured (Fluarix process) A/H5N1 influenza vaccine antigen (D-Pan) doses (3.75µg, 7.5µg, 15µg and 30µg) with and without $AS03_A$ (full dose) adjuvant were studied. The results of this study showed that HI antibody responses were low in an antigen dose-dependent fashion without AS03, but higher in an antigen dose-independent fashion for the dose levels evaluated when AS03 was present. The results of this study led GSK to select the lowest antigen dose studied, 3.75µg, to move forward with in clinical development. The applicability of the D-Pan antigen dose to Q-Pan was confirmed in clinical trial Q-Pan-001 (see Section 6.1).

GSK manufactured two AS03 adjuvanted pandemic vaccines, Pandemrix H1N1 and Arepanrix H1N1, which were non-US licensed and widely distributed outside of the US in 2009 during the mass vaccination campaigns conducted during the H1N1 influenza virus pandemic. Q-Pan H5N1 and Arepanrix H1N1 are both AS03 adjuvanted pandemic vaccines manufactured according to the FluLaval process. FluLaval is GSK's unadjuvanted, seasonal, trivalent influenza vaccine that is currently US licensed under Accelerated Approval for use in adults. Pandemrix H1N1 is an AS03 adjuvanted vaccine manufactured by GSK in Dresden, Germany, using the Fluarix manufacturing process. Fluarix is another of GSK's unadjuvanted, seasonal, trivalent influenza vaccine that is currently US licensed for you use in persons ≥ 3 years of age. Approximately ---(b)(4)---- doses of Pandemrix H1N1 were distributed during the 2009 pandemic and an estimated 31 million people received the vaccine. Approximately ----(b)(4)---- doses of Arepanrix H1N1 were distributed during the 2009 pandemic and an estimated 59 million people received the vaccine.

GSK conducted a variety of analyses on the spontaneously reported postmarketing safety reports received for Pandemrix H1N1 and Arepanrix H1N1 assessing for safety signals. Due to theoretical concerns of potential autoimmunity associated with Q-Pan H5N1 use the following reported events are relevant and of interest and concern.

- **Narcolepsy**: The BLA describes a total of 168 cases of narcolepsy reported after Pandemrix H1N1 (n=163) and Arepanrix H1N1 (n=5) through Jan 31, 2011, from 12 countries. Of the cases associated with Pandemrix, Sweden had the most reports (n=60), followed by Finland (n=54), France (n=20), Norway (n=11),

Germany (n=6), Canada (n=4), Switzerland (n=4), UK (n=3), Ireland (n=3), Netherlands (n=1), Portugal (n=1), and Brazil (n=1). Cases associated with Arepanrix H1N1 were received from Canada (n=4) and Brazil (n=1). The country- and age-specific observed/expected ratio analysis indicated an excess of cases was observed in Finland (in 0-9, 10-19, and 30-39 years old), Sweden (in 0-9, 10-19, and 40-49 years old), Norway (in 30-39 years old), and in all countries combined. At the time of the BLA submission two publications from Finland also reported an increased incidence (> 10-fold in each study) of narcolepsy following Pandemrix H1N1 vaccination in children.[5,6] A report by the European Centre for Disease Prevention and Control summarized the results from two epidemiological studies conducted by the Vaccine Adverse Event Surveillance and Communication Consortium.[7] This document reported an association between Pandemrix H1N1 and narcolepsy in children and adolescents in Finland and Sweden. A significant increase in risk of narcolepsy was also identified in a crude analysis for French adults who received Pandemrix H1N1; however, additional analyses were still ongoing at the time of the report publication.

Reviewer comment: Additional post-marketing reports of narcolepsy continued to be reported to GSK throughout this review cycle. As of November 5, 2012, GSK reported via electronic mail that over 800 spontaneous reports of narcolepsy associated with Pandemrix use had been reported to them.

Reviewer Comment: Narcolepsy is a rare and chronic sleep disorder characterized by excessive daytime sleepiness and manifestations of disrupted rapid eye movement sleep, such as cataplexy, sleep paralysis, and hypnagogic/hypnopompic hallucinations. Narcolepsy has a bimodal peak age of diagnosis: 14 years and 35 years. The mechanisms underlying narcolepsy are not fully understood. Experimental data indicate that the disease is caused by a significant loss of hypocretin-secreting neurons in the hypothalamus, likely due to an autoimmune process triggered by environmental factors in susceptible individuals carrying one or more alleles of human leukocyte antigen (HLA) DQB1*0602. HLAs are linked to many autoimmune diseases, and narcolepsy has the strongest known HLA association; HLA DQB1*0602 is found in approximately 90% of patients with narcolepsy. Simply being a carrier of this gene increases the risk of narcolepsy approximately 200 fold.[8,9] Recently, there has been a discovery of an autoantibody in individuals with narcolepsy with cataplexy. Elevated Tribbles homologue 2 (Trib2)–specific antibody levels in some narcoleptic patients rise during the first couple of years after onset of symptoms, then decline but remain elevated over controls without narcolepsy.[10] High titers correlate with higher severity of cataplexy, and serum from a narcoleptic patient has shown specific immunoreactivity with the hypocretin-secreting neurons in mouse hypothalamus.[10] However, these anti-Trib2 antibodies do not fully satisfy the autoimmune theory of narcolepsy because they are rarely found in narcoleptics without cataplexy and are only found in up to 50% of recently diagnosed narcoleptics with cataplexy. Additional studies are needed to fully understand the pathophysiology of narcolepsy.

Based on the increased rate of reporting of narcolepsy cases, additional epidemiologic studies are underway in countries where Arepanrix and Pandemrix were distributed.

Additional preclinical studies to evaluate the association between Pandemrix and narcolepsy are also planned. Narcolepsy has been added to the Pandemrix product labeling in the warning section, and use has been restricted in persons less than 20 years of age, in countries where Pandemrix has marketing approval. Currently, GSK has no plans to add a similar warning to the product label for Q-Pan H5N1. The extent to which the narcolepsy signal is related to H1N1 antigen vs. AS03 adjuvant vs. a combination of the two is unknown and under investigation. At this time no evidence exists to definitively link the Quebec manufacturing process or the H5N1 antigen or the AS03 adjuvant to the narcolepsy signal. Narcolepsy will be mentioned in the Q-Pan H5N1 package insert as part of the post-marketing experience with related products.

Additional research is needed to better estimate the potential risk of narcolepsy associated with AS03 adjuvanted pandemic vaccine in both the adult and pediatric populations. This reviewer strongly believes that GSK should carry out non-clinical investigations of their Quebec and Dresden H5N1 antigen and AS03, including investigations of the antigens alone, the AS03 adjuvant alone and each antigen in combination with AS03, to provide a comprehensive analysis of the potential association of narcolepsy with each major vaccine component.

- **Autoimmune hepatitis (AIH):** Five reports of AIH following vaccination with Pandemrix H1N1 were spontaneously submitted to GSK. GSK reports that according to the International Autoimmune Hepatitis Group diagnostic criteria (Table 1) one case met the criteria for definite AIH, one case met the criteria for probable AIH and the remaining cases did not meet diagnositic criteria for AIH. No AIH cases were spontaneously reported subsequent to Arepanrix H1N1 vaccination.

Table 1: Simplified Diagnostic Criteria for Autoimmune Hepatitis[1]

Variable	Cutoff	Points
ANA or SMA	≥ 1:40	1
ANA or SMA	≥ 1:80	2*
or LKM	≥ 1:40	2*
or SLA	Positive	2*
IgG	>Upper normal limit >1.10 times upper normal limit	1 2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH Typical AIH	1 2
Absence of viral hepatitis	Yes	2
Total		≥ 6: probable AIH ≥ 7: definite AIH

[1] Source: Hennes, et al 2008[11]

*Addition of points achieved for all autoantibodies (maximum, 2 points)

The definite case of AIH occurred in a 14 year-old female whose symptoms began 4 months post vaccination with Pandemrix and 1 month post vaccination with Cervarix (GSK's AS04 adjuvanted HPV vaccine). The probable case of AIH occurred in a 10 year-old female whose symptoms began 1 month post vaccination with Pandemrix with a histologic liver biopsy diagnosis made 8 months post vaccination.

Reviewer comment: Pandemrix appears to be temporally associated with these cases of AIH. The case of definite AIH was also temporally associated with Cervarix, GSK's AS04 adjuvanted human papilloma virus (HPV) vaccine.

Additionally, two cases of AIH were reported in clinical trials: one from a pediatric study of 300 children who received D-Pan H5N1 (100 children received an unadjuvanted comparator control) and one from Q-Pan-002 (see Section 6.2.12.5 for a description of the Q-Pan-002 case).

The D-Pan H5N1 case of AIH is in a three year old girl with moderately abnormal (Grade 2) liver enzymes at baseline, who received one dose of full-dose D-Pan H5N1 with half-dose adjuvant. Within one week of vaccination the subject experienced a severe increase of her already elevated liver enzymes to a Grade 3 and then Grade 4. Her post-vaccination work-up was significant for an ANA of 1:160, negative viral hepatitis serologies and a liver biopsy consistent with autoimmune hepatitis. She responded to treatment with steroids and azathioprine. At last follow-up in December of 2009 she was clinically stable and remained asymptomatic, but was unable to taper off medication without a rapid and severe increase in her liver enzymes.

Reviewer comment: AIH is seen in all ethnic groups and can occur at any age, though it is often diagnosed in patients in their 40s and 50s. It is more common in women (female to male ratio of 3.6 to 1), and studies from Europe report an incidence of 0.9 to 2 per 100,000 population per year with a prevalence of 11 to 25 per 100,000 population. Clinical manifestation varies from asymptomatic with incidental finding of liver enzyme abnormalities to fulminate acute liver failure.

In a clinical trial of 300 children receiving active vaccine and a clinical trial of approximately 3,400 adults receiving active vaccine even one case of AIH whether incident or prevalent would be extremely unusual. However, considering the entire adult D-Pan/Q-Pan H5N1 clinical trial database (approximately 16,000 receiving AS03 adjuvanted vaccine) up to two prevalent cases might be expected. Nevertheless, even if both clinical trial cases were prevalent cases they both appear to have been exacerbated post-vaccination given the clinical presentation, laboratory abnormalities, temporal association and lack of alternative plausible cause.

Solid organ transplant rejection: GSK received twelve spontaneous reports of transplant rejection following Pandemrix H1N1 vaccination: 5 kidney, 3 liver, 2 lung, 1 heart and 1 intestine rejection (in a subject who also underwent liver transplant). Patients ranged in age from 4 years to 67 years with a median of 27 years and were predominantly female (58%). The rejection event occurred at a median of 13 days post vaccination

(range 5 to 70 days). One patient died and 73% of subjects had unresolved rejection at the time of database closure. The time from transplant to rejection was known for 11 of the 12 patients. For these 11 patients the mean and median times from transplant were 9 and 10 years respectively.

Reviewer comment: GSK provided additional information for 7 of the 12 patients which pointed to other factors which may have contributed to the rejection episode including: possible compliance issues with immunosuppressive therapies in 2 patients (although in this reviewer's opinion, based on the Council for the International Organization of Medical Services (CIOMS) assessment this was speculative and seemed more part of a differential diagnosis than an evidence based assessment); physician prescribed decrease in immunosuppressive therapy in 1 patient; a possible infectious process in 3 patients and a prior history of rejection episodes in 2 patients. However, it is still striking to this reviewer that in most cases, patients were many years out from their transplant seemingly doing well until days to weeks post vaccination.Pandemerix appears to be temporally associated with these late, acute transplant rejections.

Reviewer comment: See Section 6.2.12.4 for details of a case of corneal transplant rejection.

Based on these reports and a paper from Schaffer, et al[12] suggesting that Arepanrix H1N1 may increase risk of higher grade rejection in cardiac transplant recipients, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) asked GSK to perform an assessment of available data related to organ transplant rejection. GSK's disproportionality analysis did not suggest that transplant rejection following Pandemrix H1N1 vaccine was reported at a higher-than-expected rate relative to background reporting.

Reviewer comment: It is not clear to this reviewer if GSK's analysis specifically considered the background reporting rate of patients with long-term (≥ 10 years) graft survival, and therefore if their conclusions of not higher-than-expected reporting is generalizable to this patient population.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

GSK received a marketing authorization for Q-Pan H5N1 by the European Medicines Agency (EMA) on April 3, 2011 under the trade name Pumarix. No post-marketing human experience exists with this product. See Section 2.3 above for human experience with related AS03 adjuvanted products.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

- Initial IND submitted on June 29, 2007 including a request for Fast Track Designation

- CBER granted Fast Track Designation for the Q-Pan-H5N1 development program on August 16, 2007.
- Pre-BLA meeting held on September 16, 2008 during which GSK requested a priority review.
- CBER denied the request for priority review on July 23, 2010 during a Type C meeting
- February 2011 meeting held to obtain CBER's guidance regarding potential pathways to confirm the clinical benefit to support traditional approval of Q-Pan H5N1.
- October 2011 meeting held to seek CBER's concurrence regarding submitting complete data from one Canadian observational effectiveness study of Q-Pan H1N1 to support Q-Pan H5N1 effectiveness.
- February 22, 2012 Q-Pan H5N1 BLA submitted.
- July 19, 2012 GSK submitted an amended pediatric plan for Q-Pan H5N1
- October 26, 2012 Q-Pan H5N1 pediatric plan presented to PeRC
- November 14, 2012 VRBPAC meeting
- November , 2012 Major amendment clock extension
- March 22, 2013 Complete Response (see Section 3.1 for details)

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

On February 26, 2013, GSK notified CBER that it inadvertently submitted an incomplete study data package with the original BLA submission on February 22, 2012. This incomplete data package included 37 interim (D182) case report tabulations (CRTs, also known as data sets) instead of the final, "clean" (D364) 42 CRTs, and was missing 71 electronic case report forms (eCRFs) for pivotal study Q-Pan-002. GSK reports using the final, "clean" data for each study period (D42, D182 and D364) to generate the respective individual clinical study reports.

Reviewer comment: CRTs included with BLA submissions are routinely used by FDA reviewers to analyze and verify summary data and line listings submitted by the Applicant. This reviewer drew clinical conclusions about the safety data in the Phase III pivotal clinical trial, Q-Pan-002, based on the interim, "unclean" data provided, which may be different than conclusions drawn from the final, "clean" data.

As mentioned above, GSK states that it used the final, "clean" data for each study period (D42, D182 and D364) to generate the respective individual clinical study reports. However, since "cleaning" of the data continued past the time both the D42 and D182 study reports were generated, some adverse event data in each of those study reports may differ from the data captured in the final D364 data sets.

As mentioned above, the final data sets contain 42 datasets including: 5 new datasets; 6 datasets identified by GSK as having no differences between the interim and final datasets; 23 datasets identified by GSK as having minor differences between the

interim and final datasets; and 6 data sets identified by GSK as having differences (not classified as minor) between the interim and final datasets. Of note, based on GSK's assessment of the differences between the interim and the final datasets only the safety data, but not the primary immunogenicity endpoint data, may be affected.

One major discrepancy noted by this reviewer between the interim unsolicited AE data set (WUNSOL) and the clinical study reports is the presence of two potentially immune-mediated adverse events of special interest (AESIs), a case of lupus and a case of cutaneous vasculitis, that appear in the interim, D182 WUNSOL dataset and the respective CRFs, but not in any of the three clinical study reports for Q-Pan-002, nor in the final D364 WUNSOL dataset, which was submitted to the BLA in November 2012 in response to an unrelated CBER IR and not identified by GSK at the time as the final version of the D182 WUNSOL dataset. A review of the final datasets is needed to ensure that no other major discrepancies exist between the interim and final data that might impact the safety conclusions.

GSK was issued a complete response (CR) letter on March 22, 2013 requesting the D364 datasets (with comparative analyses between the D182 and D364 datasets), the missing eCRFs and the source data for the two AESI subjects. Please refer to the CR letter for details.

No final conclusions regarding safety of the product can be made until the requested final data from the Phase III pivotal trial are submitted and reviewed.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Bioresearch Monitoring (BIMO) Branch issued inspection assignments on April 16, 2012 for four clinical investigators/study sites in the pivotal study Q-Pan-002. Study sites 049675, 049686, 049697 and 049705 were chosen because they all enrolled a relatively large number of subjects (> 100). No FDA 483s were issued as a result of these inspections, nor were any issues identified that might adversely impact the data submitted in the application.

Clinical reviewer comment: Please refer to Mr. Anthony Hawkins's October 3, 2012 review for complete details of the inspection findings.

3.3 Financial Disclosures

GSK provided financial interest information for the clinical investigators participating in studies covered by the Final Rule on Financial Disclosure by Clinical Investigators (published on February 2, 1998 (63 FR 5233) and revised on December 31, 1998 (63 FR 72171). These studies included 110028, 110464, 110624, 111626, 111729, and 106750. GSK found through investigator questionnaires that all Principal Investigators (PIs) and most sub-investigators for these studies had no financial interests/arrangements to disclose. GSK was unable to locate a total of 14 sub-investigators in studies 110028, 110464, 110624, and 111729, and therefore was unable to provide any financial

information as provided by them. However, internal GSK data did not suggest that any of the 14 sub-investigators had disclosable financial interests.

Reviewer comment: It appears that GSK made reasonable efforts to obtain financial information on all principal and sub-investigators, and that the missing information would not likely impact the overall integrity of the data.

Financial interest information was not collected from the investigators for the study, protocol number 116528, "A Test-negative Case-Control Study to Evaluate the Effectiveness of GSK Biologicals' Adjuvanted Monovalent Inactivated H1N1 Influenza Vaccine (Arepanrix) in Young Children (6 months to < 10 years of age), for which the study report is included in this application. This study was conducted by Paul van Buynder, MD et al. of the New Brunswick, Canada, Department of Health, independently of GSK involvement. GSK reports that the study was sponsored by the Communicable Disease Control Directorate, Office of the Chief Medical Officer of Health, New Brunswick Department of Health. GSK reports that the researchers were not directly involved in the treatment or evaluation of the research subjects, and as such are not "clinical investigators" as defined by 21 CFR 54.2(d). Therefore, GSK believes that this study is "out-of-scope for provision of financial disclosure information."

Reviewer comment: This reviewer agrees with GSK's assessment of Dr. van Buynder and there being no need for disclosure of his financial information.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please refer to Drs. Hana Golding and Surrender Khurana's CMC reviews.

4.2 Assay Validation

Please refer to Dr. Tielin Qin's BioAssay review.

4.3 Nonclinical Pharmacology/Toxicology

Nonclinical studies were pertinent for the finding of injection site reactions that resulted in limited mobility of the animals' hind limbs.

Clinical reviewer comment: The animal findings are similar to the human findings in that local reactions occurred with greater frequency and severity in association with Q-Pan-H5N1. Please refer to Sections 6 and 8 Clinical studies and Safety Evaluations where local reactions are discussed in detail.

Reproductive toxicology studies were conducted in female rats with 80 times the human dose of Q-Pan H5N1 administered based on a mcg/kg measurement. The results of this

study showed no clinically relevant untoward effects on mating, female fertility, pregnancy, parturition, lactation, or embryo-fetal or pre-weaning development.

Reviewer comment: These results appear to support a Pregnancy Category B. Please refer to the Dr. Nabil Al-Humadi's Toxicology review for a complete discussion of the relevant preclinical studies.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

GSK states that the mechanism of action of type A (H5N1) influenza virus vaccines is not well understood. Influenza vaccines induce antibodies against the viral HA in the vaccine thereby blocking viral attachment to human respiratory epithelial cells. Specific levels of HI antibody titer post-vaccination with inactivated influenza virus vaccines, including H5N1 influenza virus vaccines, have not been correlated with protection from influenza illness, but HI antibody titers have been used as a measure of vaccine activity. In some human challenge studies of seasonal influenza viruses, antibody titers of $\geq$ 1:40 have been associated with protection from influenza illness due to the homologous virus in up to 50% of subjects.[13]

The mechanism of action of AS03 is also not well understood. Please refer to Dr. Hana Golding's review for a comprehensive assessment of the AS03 adjuvant. Briefly, AS03 has been shown *in vitro* to induce pro-inflammatory cytokine production (IL-6, TNF alpha and IL1B). AS03 is thought to stimulate the adaptive and innate immune responses by enhancing the delivery of antigen to antigen presenting cells. *In vivo* NF-kB signaling, a master regulator of multiple immune genes, has been detected, but it is unclear whether it is induced directly or indirectly through cytokine secretion by AS03. Several studies have shown that the addition of α -tocopherol to AS03 results in a higher immune response. However, the MOA of α-tocopherol and how it exerts this added adjuvant effect is unknown.

4.5 Statistical

Please refer to Dr. Tsai-Lien Lin's Biostatistic review.

4.6 Pharmacovigilance

Please refer to Dr. Yandong Qiang's review for a comprehensive evaluation of the Q-Pan H5N1 pharmacovigilance plan. Briefly, GSK plans a multi-tiered approach that includes both passive and active surveillance before and during a declared pandemic. The active surveillance plan includes:

- sharing all safety information received by GSK with regulatory authorities around the world including FDA
- cooperating with US government agencies in the evaluation of safety data,
- conducting a post-licensure active surveillance cohort study during a pandemic (n=9,000) and

- establishing a US pregnancy registry if feasible.

Reviewer comment: Please refer to Dr. Qiang's review for details on post marketing commitments regarding narcolepsy

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

GSK submitted the results of two pivotal studies, Q-Pan-001 and Q-Pan-002, in support of this BLA. Each study is reviewed in this document in detail for immunogenicity and safety outcomes.

Reviewer comment: Of note, the safety outcomes for Q-Pan-002 are based on interim safety data, and may change upon review of the final, safety data that will be submitted in the Applicant's CR.

Additionally, GSK submitted the results of a case-control, test-negative effectiveness study conducted by Dr. Van Buynder, et al (hereafter, also referred to as the Canadian effectiveness study), which assessed GSK's H1N1 pandemic vaccine (Arepanrix) manufactured using the same process as Q-Pan H5N1 and adjuvanted with the same adjuvant, AS03, but containing a different antigen subtype. The Canadian effectiveness study was submitted in support of demonstrating the effectiveness of Q-Pan H5N1 thereby allowing approval of Q-Pan H5N1 via the Traditional Approval licensure pathway. That study is also reviewed in detail in this document. The remaining data submitted by GSK in support of this BLA are reviewed as a pooled assessment of safety.

Reviewer comment: Although the Canadian effectiveness study was submitted to potentially permit approval of Q-Pan H5N1 via the Traditional Approval licensure pathway, this reviewer did not concur with this strategy. Please see the reviewer comments in Section 5.4.1 and 6.3.11.1 for a full explanation.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following sections were assigned to and reviewed in detail by this clinical reviewer.

Table 2: BLA components reviewed by the clinical reviewer

Module	Section/Study
5.3.5.1	Clinical study reports for Q-Pan-001, -002, -005, -009, -010, D-Pan-007
5.3.5.3.28	Integrated Summary of Safety (ISS)-1 (H5N1) and ISS-2 (H5N1+H1N1)
5.3.5.4.3	116528 Flu Q-Pan H1N1-AS03-049 DB (Van Buynder study)
5.3.5.4.4	Protocol
5.3.5.4.6	IEC IRB Consent Form List
5.3.5.4.7	List Description Investigator Site

5.3.5.4.8	Signatures Investigators
5.3.5.4.14	Publications Based on study
5.3.5.4.15	Publications Referenced in Report
5.3.5.4.25	Individual Subject Data Listing

In addition, this reviewer reviewed Financial Disclosure information (Module 1.3.4), the Fast Track Designation Request (1.7.1), the Request for Deferral of Pediatric Studies (Module 1.92.), Labeling (Module 1.14) the Reports of Post marketing Experience (Module 5.3.6), Literature References (5.4), and the data submitted in response to clinical information requests (IRs) in amendments to the original BLA (125419/0.5 received 7/19/12; 125419/0.14 received 11/6/12; 125419/0.16 received 11/15/12; 125419/0.19 received 11/30/12) and all amendments pertaining to labeling negotiations (125419/0.25 and 125419/0.30) .

Reviewer comment: All the amendments listed above adequately addressed (either in the initial amendment or in a subsequent IR and amendment) the respective clinical question or issue. At the time this review was finalized PI negotiations were still ongoing and amendments 125419/0.31, 125419/0.32 and 125419/0.33 were in part responses to the CR and not yet reviewed.

5.3 Table of Studies/Clinical Trials

Table 3: Overview of clinical studies considered pivotal to Q-Pan H5N1+ $AS03_A$ Licensure

Study	Study Type	Study Design	Subjects	Treatment Groups	Total # of Subjects Entered (Completed)
Q-Pan-H5N1-001	Pivotal immunogenicity and safety evaluating: Adjuvant effect of two adjuvant doses $AS03_A$ (full strength) and $AS03_B$ (half strength). The equivalence of Q-Pan to the GSK Dresden-manufactured H5N1 vaccine, D-Pan	Randomized, observer-blind, parallel group, active control Study duration 6 months	Adults 18 – 64 years old	2 IM doses, 21-day interval Core groups: A. Q-Pan H5N1: 3.8µg HA alone B. Q-Pan H5N1: 3.8µg HA; $AS03_A$ C. Q-Pan H5N1: 3.8µg HA;$AS03_B$ D. D-Pan H5N1: 3.8µg HA; $AS03_A$ E. D-Pan H5N1: 3.8µg HA;$AS03_B$ Contingency groups: F. Q-Pan H5N1 1.9µg HA; $AS03_A$ G. Q-Pan H5N1 1.9µg HA;$AS03_B$	Total 680 (673) 78 (76) 152 (150) 151 (151) 151 (151) 148 (145) 100 (99) 50 (50) 50 (49)
Q-Pan-H5N1-002	Pivotal immunogenicity, safety and lot-to-lot consistency	Randomized, placebo-controlled, observer-blind, parallel group Study duration originally 6 months, amended to 12 months.	Adults $\geq$ 18 years old	2 IM doses, 21-day interval Q-Pan H5N1: 3.8µg HA; $AS03_A$ Saline placebo	Total 4561 (4457) 3422 (3343) 1139 (1114)

Study	Study Type	Study Design	Subjects	Treatment Groups	Total # of Subjects Entered (Completed)
VanBuynder et al., 2010	Pivotal effectiveness study	Retrospective cohort, community-based, case-control, test-negative	Children 6 months to 9 years old with medically attended ILI for whom pandemic H1N1 influenza testing was sought in New Brunswick, Canada	1 or 2 IM doses of Q-Pan H1N1 pandemic 1.9µg HA, $AS03_B$	28 cases 63 controls

Reviewer comment: The remaining study reports submitted in support of the BLA were viewed as non-pivotal, supportive studies and are only briefly discussed in this document.

5.4 Consultations
5.4.1 Advisory Committee Meeting

The Vaccine and Related Biologic Products' Advisory Committee (VRBPAC) convened on November 14, 2012 to discuss Q-Pan-H5N1. The immunogenicity and safety data submitted in support of the BLA were presented by the Applicant and CBER, as well as the H1N1 effectiveness data from the Canadian effectiveness study (see section 6.3 for a detailed review of this study). The Committee was asked to vote on whether the immunogenicity and safety data supported licensure of Q-Pan H5N1. The Committee voted unanimously (14 yes, 0 no) that both the immunogenicity and safety data supported licensure of Q-Pan H5N1 for the specified indication under the Accelerated Approval regulations. The Committee was asked to discuss, but not vote on, the preferred pathway to confirm clinical benefit of Q-Pan H5N1: either using efficacy data generated with a US-licensed seasonal influenza virus vaccine made according to the same manufacturing process (i.e. Flulaval-006, a study of a quadrivalent, unadjuvanted seasonal influenza vaccine in children) or by conducting an effectiveness study (or studies) during an H5N1 influenza virus pandemic. The Committee was reminded at the outset that it had supported the former option during the February 2012 VRBPAC. It should be noted that at the February VRBPAC a post-marketing effectiveness study to-be-conducted during an influenza pandemic was considered unfeasible and not specifically discussed as an option. However, in the November 2012 VRBPAC CBER requested a discussion of a post-marketing effectiveness study during the pandemic as an option to confirm the effectiveness of Q-Pan H5N1. In the November meeting the Committee members discussed the "uncertainty" of influenza viruses in general and the novelty surrounding the pathophysiology of H5N1 specifically. One Committee member pointed out that a number of variables distinguished quadrivalent Flulaval and Q-Pan H5N1: quadrivalent vs. monovalent formulations; unadjuvanted vs. adjuvanted formulations; seasonal vs. pandemic indications; and a vaccine assessed in a pediatric study (FluLaval) being used to support a vaccine with a proposed adult indication (Q-PAN H5N1).

In a further exploration of the regulatory options available, the Committee asked whether Q-PAN H5N1 could remain under Accelerated Approval, whether strain changes could occur under Accelerated Approval, whether there would be a negative impact if the product was left under Accelerated Approval (i.e., not granted traditional approval for an indeterminant time while awaiting the onset of an H5N1 pandemic for confirmation of efficacy). The Committee was informed that strain changes could occur under Accelerated Approval and that FDA interpretation of the Accelerated Approval regulations when dealing with a disease that was not exigent (i.e., making an efficacy study of the intervention against the disease in question difficult or unfeasible) permitted the vaccine to remain under Accelerated Approval indefinitely. This reviewer cited one such precedent: the use of levofloxacin for inhalation anthrax.

GSK inquired about the possibility of extending the licensure to the pediatric population while the vaccine was under Accelerated Approval for the adult population. CBER acknowledged that this subject has yet to be internally discussed. Additional discussion took place regarding the feasibility of an intra-pandemic study. Multiple committee members expressed that Q-Pan should remain under Accelerated Approval until effectiveness could be confirmed during an H5N1 influenza pandemic, and many members stressed the importance of confirming effectiveness during a pandemic, regardless of the approach to licensure.

Reviewer comment: Pandemic H5N1virus has proven itself to be different in many ways from seasonal influenza viruses, including preferences for binding to different sialic acids predominately found in different anatomic sites, markedly increased morbidity and mortality for H5N1 (approximately 60%), and a need for higher vaccine antigen content (90 mcg vs. 15mcg) or inclusion of an adjuvant in pandemic H5N1 vaccines to reach an HI antibody titer that is believed to afford some level of protection based on seasonal influenza efficacy data. Given these differences this reviewer cannot with any degree of certainty extrapolate estimations of vaccine efficacy from a seasonal, unadjuvanted product to Q-Pan H5N1. Traditional approval implies a level of certainty in the product's ability to prevent or ameliorate the disease for which it is intended. Therefore, by definition "traditional approval" must involve demonstration via a well-designed, well-controlled study, that the product can provide protection against the disease in question. Neither the feasibility to conduct a study nor the lack of the opportunity to conduct a study (in this case due to limited circulation of the virus) should impact the rigor with which FDA evaluates and determines the safety and effectiveness of a product and communicates those findings to the public. The Accelerated Approval regulations allow the FDA to approve products for life threatening diseases for which no other products exist (21 CFR 601 Subpart E). Approval under this regulation is based on the product's effect on a surrogate marker, in this case HI antibody titer, that is "reasonably likely", to predict clinical benefit, and a requirement that the applicant study the biological product further, to verify and describe its clinical benefit. Without evidence that Q-Pan H5N1 prevents or ameliorates disease caused by H5N1 virus, the only efficacy-relatedcriteria for licensure is an assessment, based on HI responses, that there is a reasonable likelihood that the vaccine will prevent or ameliorate disease due to H5N1.

5.5 Literature Reviewed

1. Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines, 2007 http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091985.pdf
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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1
Q-Pan H5N1-001 (NCT 005108740)

6.1.1 Objectives

Q-Pan-001 was designed to evaluate the immunogenicity, safety and reactogenicity of Q-Pan H5N1 with two different adjuvant strengths [$AS03_A$ (full strength) and $AS03_B$ (half strength) as compared to Q-Pan H5N1 with no adjuvant to determine effect of adjuvant on both immunogenicity and safety. The study was also intended to provide a comparison of the antigen manufactured in GSK's Quebec facility (Q-Pan) to the antigen manufactured in GSK's Dresden facility (D-Pan).

6.1.2 Design Overview

Q-Pan-H5N1-001 is a Phase 1/2, randomized, observer-blind, multi-centered, active-controlled trial to evaluate the immunogenicity and safety of two doses of Q-Pan H5N1 with $AS03_A$ or $AS03_B$ adjuvant administered on Days 0 and 21 intramuscularly (IM) to healthy adults 18 to 64 years old. The study was conducted in 7 sites in the US and 3 sites in Canada.

Randomization was 1:2:2:2:2 to 1 of 5 treatment arms with a targeted enrollment of 675 subjects.

- Group A: Q-Pan H5N1 3.75 µg HA, IM on Day 0 and 21 (N≈75) or
- Group B: Q-Pan H5N1 3.75 µg HA + $AS03_A$, IM on Day 0 and 21 (N≈150) or
- Group C: Q-Pan H5N1 3.75 µg HA + $AS03_B$, IM on Day 0 and 21 (N≈150) or
- Group D: D-Pan H5N1 3.75 µg HA + $AS03_A$, IM on Day 0 and 21 (N≈150) or
- Group E: D-Pan H5N1 3.75 µg HA + $AS03_B$, IM on Day 0 and 21 (N≈150)

Randomization was stratified by site and age (18 – 40 years and 41 – 64 years). Contingency treatment arms with a higher and lower antigen dose were planned based on the immunogenicity outcomes in Group B and C.

Reviewer comment: The immunogenicity results triggered further testing of a lower antigen dose. Those data are not presented in this review; however, the data confirmed that a lower antigen dose of 1.9 µg + AS03$_A$ or AS03$_B$ resulted in immune responses similar to those observed with 3.75 µg of HA antigen.

6.1.3 Population
Subjects eligible for the study were males or females 18 to 64 years of age inclusive at the time of vaccination and in good general health as established by pre-enrollment medical history and physical examination.

Subjects with the following were excluded:

- An oral temperature ≥ 37.8º C, or acute symptoms greater than "mild" severity on the day of first vaccination.
- Any confirmed or suspected immunosuppressive or immunodeficient condition including history of human immunodeficiency virus (HIV) infection.
- Receiving systemic glucocorticoids within 1 month of study enrollment or any other cytotoxic immunosuppressive drug within 6 months of study enrollment.
- Any significant disorder of coagulation or treatment with Coumadin® or heparin.
- Receipt of immunoglobulins and/or any blood products within 3 months of study enrollment
- Administration of any vaccines within 30 days before study enrollment.
- Previous administration of any H5N1 vaccine.
- Known use of any analgesic or antipyretic medication within 12 hours prior to first treatment.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Q-Pan H5N1 is developed and manufactured at GSK Biologicals' facilities in Quebec, Canada. The vaccine was produced using the A/Indonesia/5/05 (H5N1) strain. The vaccine is formulated from split virus. The vaccine was formulated to provide a target of 15 µg/mL of HA content. The antigen contains thimerosal at a concentration of 20 µg/mL, a level 20% of that present in typical multi-dose seasonal influenza vaccine presentations.

The AS03 adjuvant is an oil-in-water emulsion containing DL-α-tocopherol in squalene in an aqueous phase with the non-ionic detergent polysorbate 80. The adjuvant does not contain preservative.

The antigen and adjuvant are mixed in a 1:1 ratio and given at a final volume of 0.5 mL. The actual antigen content is 3.75 µg. Mixed for use, the active test article contains 10 µg/mL of thimerosal per 0.5 mL dose (approximately 10% of the thimerosal contained in a dose of typical seasonal influenza vaccine from a multi-dose presentation). The vaccine administered to Group A contained no adjuvant. The vaccine administered to Groups B and C was mixed with adjuvant.

D-Pan (monovalent influenza pandemic candidate vaccine manufactured by GSK Biologicals at facilities in Dresden, Germany) was also produced using the A/Indonesia/5/05 (H5N1) strain and contained split virus. The vaccine administered to Groups D and E was mixed with AS03 adjuvant.

6.1.5 Directions for Use

As described in section 6.1.4.

6.1.6 Sites and Centers

This study was conducted by 10 investigators in 2 countries, including 7 in the US and 3 in Canada.

Table 4: Principal Investigators by center numbers and sites, study Q-Pan H5N1-001

Investigators	Center number	Investigational site	Location
Segall, Nathan, MD	040952	Clinical Research Atlanta	Stockbridge, GA
Sheldon, Eric, MD	040953	Miami Research Associates	Miami, FL
Folkerth, Steven, MD	040955	Clinical Research Center of Nevada	Las Vegas, NV
Johnson, Casey, MD	040603	Johnson County Clinical Trials	Lenexa, KS
Middleton, Randle, MD	040605	Accelovance	Hunstville, AL
Riff, Dennis, MD	040969	Advanced Clinical Research Institute	Anaheim, CA
Risi, George, MD	040611	Infectious Disease Specialists, PC	Missoula, MT
Ferguson, Linda, MD	040984	Colchester Research Group	Truro, NS
Frenette, Louise, MD	040985	Q&T Research	Sherbrooke, QC
Langley, Joanne, MD	040986	IWK Health Centre	Halifax, NS

Source: BLA 125419, Day 42 CSR 110028 (FLU Q-PAN-001 PRI), Table 1

Reviewer comment: Each site enrolled exactly 10% of the study population (n=68 subjects) with each treatment arm having nearly the same number of subjects enrolled at each site.

6.1.7 Surveillance/Monitoring

Written informed consent and demographics data were obtained from all subjects at the Screening visit. Inclusion and exclusion criteria were checked. A review of eligibility criteria, elimination criteria, and contraindications was conducted during all study visits.

A complete physical examination, including a medical history, was performed at the Screening visit. Physical examination included a targeted assessment of the bilateral axillary and supraclavicular lymph nodes on Days 7, 21, and 28.

Vital signs were included as part of all study visits except Day 84. Urine pregnancy tests were performed on all female subjects on the days of vaccination. Medications and vaccinations within 21 days prior to Day 0 were recorded. Concomitant medications were recorded on Days 0, 7, 21, 28, 42, 84 and 182.

Blood samples were taken from all subjects for immunogenicity analyses on Days 0, 21, 42, and 182, and for safety assessments (CBC, BUN, creatinine, ALT and AST levels) on Days 0, 7 and 42.

Diary cards were provided to collect local and solicited reactogenicity events and unsolicited AEs on Days 0 – 6 post each vaccination. Unsolicited AEs were collected through Day 84. All SAEs, medically attended events (MAEs) and new onset chronic diseases (NOCDs) were collected through Day 182.

6.1.8 Endpoints and Criteria for Study Success

The primary immunogenicity endpoint was:

- Vaccine-homologous virus antibody response in subjects receiving 2 doses of study vaccine, as demonstrated by the HI antibody titer at Day 42.

The primary safety endpoints were:

- The occurrence of specifically-solicited local and general signs and symptoms during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after each vaccination, and overall per subject considering both post-immunization periods.
- The occurrence of all unsolicited adverse events during a 21-day follow-up period for each vaccination, as well as overall (Day 0 through Day 84).
- The occurrence of serious adverse events and medically-attended events Day 0 through Day 182.

Secondary endpoints included measured immune response after a single dose of vaccine and persistence of response through 6 months.

Exploratory endpoints included vaccine-homologous antibody response as measured by microneutralization (MN) and immune response to drift variants as measured by HI and MN assays.

Reviewer comment: Secondary and exploratory endpoints are described for completeness. However, with the exception of HI antibody response at 21 days post dose 1 and persistence through Month 6 post dose 1, none of these endpoints will be shown or discussed further in this review.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Reviewer comment: Please refer to Dr. Tsai-Lien Lin's review for a comprehensive discussion of the Statistical considerations and Statistical Analysis Plan (SAP).

The initial data analysis consisted of clean immunogenicity and safety data through Day 42. The second and final analyses consisted of the six month (Day 182) immunogenicity and extended safety follow-up.

The primary immunogenicity analyses were performed on the According-to-Protocol Immunogenicity (ATP-I) cohort (see Section 6.1.10.1 for a definition of the ATP-I) the GMT ratio of antibody against the H5N1 antigen and the difference in SCR, for Q-Pan H5N1 antigen with adjuvant as compared to unadjuvanted H5N1. Activity of the adjuvant formulation would be established if the lower bound of the 95% confidence interval (CI) on the GMT ratio (Q-Pan H5N1/unadjuvanted H5N1) exceeded 2.0 and the lower bound of the 95% CI of the difference in seroconversion rates (SCR), defined as Q-Pan H5N1 - unadjuvanted H5N1, exceeded 15%. Proportion of subjects achieving HI titers $\geq$ 1:40 was also calculated, descriptive statistics tabulated, and treatment groups compared with 95% CIs.

Primary safety analyses were performed on the total vaccinated cohort (TVC – see section 6.1.10.1 for a definition of TVC). Counts and proportions of subjects in each vaccine group with solicited reactogenicity data were tabulated by severity grade of each local and general reactogenicity event and, separately, by the total number of days in the reactogenicity interval (Days 0 to 6) with a non-zero severity grade for each category of solicited reaction. Descriptive summaries by vaccine group included the proportion (with 95% CI) of subjects with each solicited event, the mean, median, 75th, 90th and 95th percentiles of total days with any non-zero severity grade.

Counts and proportion of subjects with unsolicited AEs reported up to 21 days after each vaccination, and overall (Days 0 through 84), were tabulated. Tabulations were produced for all AEs, in addition to those that were vaccine-related, Grade 3 (severe), and both Grade 3 and vaccine-related. AEs were to be coded and summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term (PT). Data were presented by vaccine group within age stratum and across both age strata.

6.1.10 Study Population and Disposition

A total of 680 subjects were enrolled and randomized into the study. The first volunteer was enrolled in the study on July 28, 2007 and the last volunteer completed the study through Day 42 on September 21, 2007; the data lock point for the Day 42 analysis was June 4, 2008.

Table 5: Subject Enrollment and Disposition, study Q-Pan H5N1-001

Cohort	Total n (%)	Q-Pan n	Q-AS03$_A$ n	Q-AS03$_B$ n	D-AS03$_A$ n	D-AS03$_B$ n
Total enrolled cohort	680 (100%)	-	-	-	-	-
Total vaccinated cohort	680 (100%)	78	152	151	151	148
ATP safety cohort	672 (98.8%)	78	149	149	149	147
ATP immunogenicity cohort	648 (95.3%)	75	144	146	140	143

n = number of subjects
Source: BLA 125419, Day 42 CSR 110028 (FLU Q-PAN-001 PRI), Table 12

6.1.10.1 Populations Enrolled/Analyzed

The mean age of study subjects was 38.6 years, with a minimum age of 18 years and a maximum age of 64 years. A total of 371 (54.6%) subjects were between the ages of 18 and 40, and the remaining 309 (45.4%) subjects were between the ages of 41 and 65. A total of 393 (57.8%) subjects were female and 287 (42.2%) subjects were male. The majority (86.8%) of subjects were Caucasian. Of the remaining subjects, 5.6% were African American, 4% were unspecified race, 1.3% were Southeast Asian, and all other races were less than 1%. Mean height was 170 cm and mean weight was 80.7 kg.

The following subject populations were evaluated and used for presentation and analysis of the data. Subject analysis sets were identified and finalized prior to breaking the blind.

- Total Vaccinated Cohort (TVC) was to include all subjects who received at least one dose of vaccine for whom any post-vaccination data were available. The TVC analysis for immunogenicity and safety was to be performed based on the treatment **actually received.** The primary analysis of safety was to be performed on the TVC.
- According-To-Protocol Cohort for Analysis of Safety (ATP-S) was to include all subjects:
    - Who received at least one dose of study vaccine/control according to randomization
    - With sufficient data to perform an analysis of safety (defined as having returned at least one diary card and/or having at least one documented post-treatment visit with a query to detect unsolicited AEs)
    - Who had not received a prohibited vaccine or medication
    - And for whom the randomization code had not been broken unless due to an SAE.

  A separate analysis of the ATP-S cohort was not to be performed unless more than 5% of subjects in the TVC were excluded from the ATP-S cohort in any vaccine group.
- According-To-Protocol Cohort for Analysis of Immunogenicity (ATP-I) was to include all evaluable subjects (i.e. meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the study) for whom a complete set of data concerning immunogenicity endpoint measures required for the primary endpoints was available (i.e. Day

0 and Day 42 HI titer results). Subjects had to have received the correct vaccine. The primary analysis for immunogenicity was based on the ATP-I cohort.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Subjects enrolled were from the general population and did not have specific medical or behavioral characteristics that require further discussion here.

6.1.10.1.3 Subject Disposition

All 680 subjects enrolled and randomized received at least one dose of vaccine and made up the TVC. The majority of subjects (97.8%) received 2 doses of vaccine, and 99% and 97.4% completed the study through Day 42 and Day 182, respectively.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity analysis was performed on the ATP-I cohort, which included 648 subjects. The primary outcomes for immunogenicity were met at Day 42 demonstrating the activity of AS03 with the LB of the 95% CI around the SCRs equaling 69.4; above the pre-specified difference of > 15, and the LB of the 95% CI around the adjusted GMT ratio equaling 29.9; above the pre-specified LB of > 2 (Table 6).

Table 6: Comparison of seroconversion rates and GMTs at Day 42, study Q-Pan-001

Treatment Group	N	n	%	Difference in SCR % (Q-Pan H5N1 – unadjvuanted H5N1) (95% CI)	Adjusted GMT	Adjusted GMT Ratio (Q-Pan H5N1 – unadjvuanted H5N1) (95% CI)
H5N1 unadjuvanted, 3.75 µg	75	13	17.3	79.89 (69.36, 87.27)	10.4	43.40 (29.93, 62.94)
Q-Pan H5N1 ($AS03_A$)	144	140	97.2	79.89 (69.36, 87.27)	450.8	43.40 (29.93, 62.94

N= number of subjects with pre- and pos-vaccination results available
n/% = number/percentage of subjects with a vaccine response
Source: BLA 125419, Module 5.3.5.1.3, CSR 110028 (FLU Q-PAN-001 PRI) Day 42 Tables 18 and 19

Table 7 presents secondary HI immunogenicity results for Q-Pan H5N1 ($AS03_A$) and unadjuvanted H5N1 showing SCRs, percent of subjects with HI titers ≥ 1:40 and GMTs at Days 21, 42 and 182.

Table 7: Post-vaccination HI antibody immune responses to Q-Pan H5N1 (A/Indonesia/5/2005) formulated with and without AS03 at Days 21, 42 and Day 182, study Q-Pan-001 (ATP-I)

Treatment Group	N	n	% SCR (95% CI)	% of Subjects with HI titer ≥ 1:40 (95% CI)	GMT (95% CI)
Day 21					
H5N1 unadjuvanted	75	13	6.7 (2.2, 14.9)	6.7 (2.2, 14.9)	6.1 (5.2, 7.1)
Q-Pan H5N1 (AS03A)	144	140	41.7 (33.5, 50.2)	41.7 (33.5, 50.2)	22.5 (17.8, 28.6)
Day 42					
H5N1 unadjuvanted	75	13	17.3 (9.6, 27.8)	17.3 (9.6, 27.8)	10.5 (8.2, 13.5)
Q-Pan (AS03A)	144	140	97.2 (93, 99.2)	97.2 (93, 99.2)	464.7 (383.4, 563.4)
Day 182					
H5N1 unadjuvanted	74	2	2.7 (0.3, 9.4)	2.7 (0.3, 9.4)	5.6 (5.1, 6.2)
Q-Pan H5N1 (AS03A)	141	77	54.6 (46, 63)	54.6 (46, 63)	27.8 (22.8, 33.8)

N = number of subjects with available data
n = number of responders
Source: BLA 125419, Module 5.3.5.1.3, CSR 110028 (FLU Q-PAN-001 PRI) Day 42 Tables 22, 23 and 24 and (FLU Q-PAN-001 PRI) Day 182 Annex Tables 9, 10 and 11

Reviewer comment: The Day 21 results demonstrate the need for a second dose of vaccine. The Day 182 results demonstrate that although seroconversion rates were > 50% (LB > 40), GMTs were greatly reduced compared to the Day 42 results (464.7 to 27.8)

GMTs (not shown) also demonstrated that Q-Pan and D-Pan elicited equivalent HI antibody responses providing additional support for the chosen 3.75µg antigen dose.

6.1.11.2 Analyses of Secondary Endpoints

See Section 6.1.11.1 for important secondary endpoints.

6.1.11.3 Subpopulation Analyses

No prespecified subpopulation analyses were performed.

6.1.11.4 Dropouts and/or Discontinuations

Dropouts and discontinuations were handled in an acceptable manner and per protocol. Please refer to Sections 6.1.10.1.3 Subject Disposition and 6.1.12.7 Dropouts and/or Discontinuations for a detailed discussion of this topic.

6.1.11.5 Exploratory and Post Hoc Analyses

GSK performed a *post hoc* analysis to assess the adjuvant effect of $AS03_B$ in subjects 18 to 40 years of age and in subjects 41 to 64 years of age. The analysis showed that the proportion of subjects who achieved HI titers of ≥ 1:40 with $AS03_A$ and $AS03_B$ were not statistically significantly different for any age group. However, GMTs for the 41 – 64 year old group were lower [209.7 (160.4, 274.2)] than the GMTs for the 18 – 40 year old group [364.1 (299.2, 443.1]. Based on the results of this *ad hoc* analysis GSK decided to proceed with development of an adult formulation of the vaccine that contains $AS03_A$.

Reviewer comment: This analysis was post hoc and not statistically powered to draw any conclusions. Because the Applicant intends to develop only one vaccine presentation for adults, however, this analysis provided a reasonable degree of evidence to support choosing the higher dose adjuvant.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety analyses were performed on the TVC. All 680 subjects were included in the TVC.

Local and systemic reactogenicity events were solicited by diary card during the 7 day period (Days 0-6) following each dose of study vaccine. Local symptoms included pain, redness and swelling. Systemic symptoms included fatigue, headache, joint pain (arthralgia) or muscle aches (myalgias) at locations other than the injection site, shivering, sweating, and oral temperature.

Pain and all general systemic AEs, except temperature (Table 8), were graded on a 4-point scale, with Grade 0 being no AE up to a Grade 3 which prevented normal activity. Redness and swelling were recorded in millimeters with Grade 3 reactions measuring > 100 mm.

Table 8: Temperature grading scale

Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
< 38 ° C	≥ 38 – 38.4 ° C	≥38.5 – 38.9 ° C	≥ 39 - 40 ° C	> 40 ° C (report also as an SAE)

Source: BLA 125419, Module 5.3.5.1.3, CSR 10028 (FLU Q-PAN-001 PRI), Table 8.

6.1.12.2 Overview of Adverse Events

SOLICITED ADVERSE EVENTS

Reviewer comment: Solicited reactogenicity rates did not differ significantly from Dose 1 to Dose 2. Safety results, therefore, are presented overall by subject, which includes either Dose 1 or Dose 2 related events.

As seen in Table 9, pain was the most commonly reported solicited local symptom in all treatment groups, but it was reported at a higher rate in the Q-Pan H5N1 + $AS03_A$ group (88%) as compared to the unadjuvanted Q-Pan H5N1 vaccine group (23%). Severe pain at the injection site was also reported more frequently in the Q-Pan H5N1 + $AS03_A$ group (6%) as compared to the unadjuvanted Q-Pan H5N1 group (1%).

The median time to pain resolution was three days for subjects who received $AS03_A$ adjuvanted vaccine and two days for subjects who received $AS03_B$ and unadjuvanted vaccine. No subject sought medical attention for any solicited local event.

Table 9: Incidence of solicited local reactions overall by subject, Days 0-6, study Q-Pan H5N1-001 (TVC)

Local Symptom, n (%)	Group A Q-Pan unadjuvanted N=78	Group B Q-$AS03_A$ N=152	Group C Q-$AS03_B$ N=151
All Pain	18 (23.1)	133 (87.5)	130 (86.1)
Gr 3 Pain	1 (1.3)	9 (5.9)	2 (1.3)
All Redness,	0	7 (4.6)	2 (1.3)
Gr 3 Redness	0	0	0
All Swelling,	0	12 (7.9)	10 (6.6)
Gr 3 Swelling	0	0	0

N = number of subjects with at least one documented dose
n = number of subjects reporting AE at least once
Gr 3 - Grade 3, severe
Source: BLA 125419, Module 5.3.5.1.3, CSR 110028 (FLU Q-PAN-001 Table 30

The incidence of solicited general reactions is presented in Table 10. Overall, the adjuvanted groups reported general symptoms at a higher rate than the unadjuvanted group. Severe, Grade 3, symptoms were reported at higher rates in the Q-Pan H5N1 ($AS03_A$) group (4 – 7%) as compared to the unadjuvanted H5N1 group (1 – 3%) for myalgias, headache, fatigue and arthralgias. Similarly, the incidence of severe shivering, sweating, and temperature was low overall (< 4% of subjects in any treatment group), but it is noteworthy that no severe shivering, sweating or temperature events occurred in the $AS03_B$ or H5N1 unadjuvanted groups. No subject sought medical attention for any

solicited general adverse event. Overall, the median time to resolution of general symptoms was similar for all treatment groups.

Table 10: Incidence of solicited general reactions overall by subject, study Q-Pan H5N1-001 (TVC)

General Symptom, n (%)	Group A Q-Pan unadjuvanted N=78	Group B Q-AS03$_A$ N=152	Group C Q-AS03$_B$ N=151
All Fatigue	16 (20.5)	64 (42.1)	50 (33.1)
Gr 3 Fatigue	2 (2.6)	6 (3.9)	3 (2.0)
All Headache	25 (32.1)	71 (46.7)	61 (40.4)
Gr 3 Headache	1 (1.3)	10 (6.6)	2 (1.3)
All Arthralgias	12 (15.4)	49 (32.2)	36 (23.8)
Gr 3 Arthralgias	1 (1.3)	7 (4.6)	2 (1.3)
All Myalgias	15 (19.2)	74 (48.7)	64 (42.4)
Gr 3 Myalgias	1 (1.3)	9 (5.9)	4 (2.6)
All Shivering	4 (5.1)	18 (11.8)	21 (13.9)
Gr 3 Shivering	0	5 (3.3)	0
All Sweating	6 (7.7)	23 (15.1)	12 (7.9)
Gr 3 Sweating	0	3 (2.0)	0
All Temperature $\geq$ 38 ° C	0	4 (2.6)	4 (2.6)
Temperature $\geq$ 39 ° C	0	0	0

N = number of subjects with at least one documented dose
n = number of subjects reporting AE at least once
Gr 3 - Grade 3, severe
Source: BLA 125419, Module 5.3.5.1.3, CSR 110028 (FLU Q-PAN-001 Table 31

Reviewer comment: Decreasing the adjuvant dose by half resulted in a significant (2-7 fold) decrease in severe, Grade 3 general events for all solicited reactions except fever and sweating.

A higher proportion of subjects (32%) receiving Q-Pan H5N1 (AS03$_A$) took a concomitant antipyretic during the 7-days post vaccination period as compared to the unadjuvanted H5N1 group (21%).

Reviewer comment: The higher concomitant antipyretic use is consistent with the higher reported rates of reactogenicity events.

UNSOLICITED ADVERSE EVENTS

Unsolicited AEs were collected through Day 84. At least one unsolicited adverse event (AE) was reported by 45% of unadjuvanted H5N1 subjects and 51% in Q-Pan H5N1 (AS03$_A$) subjects. No adverse event preferred term was reported by more than 10% of subjects in a treatment group.

The most commonly reported events were headache, nausea, pharygolaryngeal pain, nasopharyngitis, upper respiratory infection, and back pain. Lymph node pain and/or lymphadenopathy AEs occurred exclusively in recipients of the adjuvanted vaccines and were reported by up to 4% of subjects in a treatment group. In the Q-Pan H5N1 ($AS03_A$) group, the most commonly reported events were nausea (7.2%); pharygolaryngeal pain (3.3%); diarrhea, anemia, dizziness, nasopharyngitis and sinusitis (all at 2.6%); and lymphadenopathy, upper respiratory tract infection, back pain, and muscle spasms (all at 2%). When comparing the unadjuvanted H5N1 group to the Q-Pan H5N1 ($AS03_A$) group, nasopharyngitis, back pain, upper respiratory tract infection and pharyngolaryngeal pain all occurred at a higher rate in the unadjuvanted H5N1 group than in the Q-Pan H5N1 ($AS03_A$) group. All other adverse events (diarrhea, anemia, lymphadenopathy, dizziness, muscle spasms, sinusitis) occurred exclusively in the Q-Pan H5N1 ($AS03_A$) group or in the case of nausea at a higher rate than in the unadjuvanted H5N1 group (6.6% vs. 3.8%). Of note, rates of unsolicited AEs in the Q-Pan $AS03_B$ group were similar to the $AS03_A$ group with the exception of anemia, which was reported at the highest rate (2.6%) in the Q-Pan $AS03_A$ group.

Grade 3 unsolicited AEs were reported by 5% of subjects overall. The only Grade 3 unsolicited AE reported by more than one subject in a treatment group was nasopharyngitis, which was reported by two subjects in Group C (Q-Pan H5N1 $AS03_B$). The other most commonly reported Grade 3 unsolicited AEs included sinusitis and back pain (three subjects each group), upper abdominal pain, headache, migraine, upper respiratory tract infection, and pharyngolaryngeal pain (two subjects each group). All other Grade 3 unsolicited AEs were reported by a maximum of one subject.

Overall, 21% of subjects required a medically attended visit for their unsolicited AE with rates evenly distributed amongst the treatment groups (unadjuvanted H5N1 (19%) and Q-Pan-H5N1 (21%)). The only preferred term reported for more than one Q-Pan H5N1 ($AS03_A$) subject was urinary tract infection, which was reported in three (2%) subjects. Only one of the medically attended events in the Q-Pan H5N1 $AS03_A$ group was deemed vaccine-related (severe heat exhaustion occurring two days post vaccination) by the investigator; the others were deemed unrelated. Additionally, one subject in the Q-Pan H5N1 $AS03_A$ group, who experienced a breast mass was classified as a "new onset chronic disease" by the investigator.

Reviewer comment: Few unsolicited events required a medical visit. The reported medically-attended events appear unlikely to be related to vaccine including the event of heat exhaustion that was deemed related to vaccine by the investigator.

Reviewer comment: Because the sample sizes for each study group are relatively small, even the more commonly occurring unsolicited AEs only occurred in a small number of subjects. Therefore, it is difficult to draw firm conclusions regarding any rare (<1/1000) AEs from these unsolicited AE data.

LYMPHADENOPATHY

Reviewer comment: In study D-Pan H5N1-008, a disproportionate, albeit small, amount of lymphadenopathy was observed in 1.7% of adult subjects (> 18 years of age) who received the test vaccine (15 µg H5N1 HA + $AS03_A$) versus 0.8% of adult subjects

who received the control vaccine (Fluarix). Based on these results evaluation of lymphadenopathy was prospectively defined in the Q-Pan H5N1 pivotal trials.

Axillary and supraclavicular lymph nodes were examined for enlargement, tenderness, heat, overlying erythema or fluctuance at Screening and Days 0, 7, 21, and 28; with a contingent Day 42 re-examination of any sites with grade 2 or greater findings at Day 28.

Overall, the incidence of objective lymphadenopathy was low and the presence or dose of adjuvant did not appear to have an effect on the incidence. In the Q-Pan H5N1 ($AS03_A$) group, a total of 3 subjects (2%) had Grade 1, axillary lymphadenopathy – 1 each on Day 0, Day 7 and Day 28. One subject (1.3%) in the unadjuvanted Q-Pan group experienced Grade 1 axillary lymphadenopathy on Day 7 and Day 21.

Reviewer comment: Lymphadenopathy does not appear to be a frequent or clinically important finding in association with Q-Pan H5N1 administration in adults.

6.1.12.3 Deaths

No subjects died during the six month study period.

6.1.12.4 Nonfatal Serious Adverse Events

Two SAEs, deemed vaccine unrelated by investigators, occurred in one Q-Pan H5N1 subject through Day 42. An additional vaccine unrelated SAE occurred in this treatment group for a total of 3 SAEs in 2 Q-Pan H5N1 subjects through Day 182. All 15 SAEs reported in 6 subjects through Day 182 are presented in Table 11.

Table 11: SAEs by subject and treatment group through Day 182, study Q-Pan-001

Treatment Group	Subject Number	SAE	Dose	Day of Onset	Outcome
Q-$AS03_A$	1744	Cholelithiasis	1	13	Resolved
	1744	Pancreatitis	1	13	Not resolved
	1425	Chest pain	1	94	Resolved
Q-$AS03_B$	1119	Basal cell carcinoma	2	32	Resolved
D-$AS03_A$	567	Ovarian cyst	2	9	Resolved
	567	Uterine leiomyoma	2	9	Resolved
	2024	Pulmonary embolism	2	146	Resolved
D-$AS03_B$	1422	Cervical carcinoma	2	27	Resolved
	1422	Ascites	2	75	Not resolved
	1422	Gastroenteritis, clostridial	2	75	Not resolved
	1422	Hematoma	2	75	Not resolved
	1422	Hydronephrosis	2	75	Not resolved
	1422	Pelvic abscess	2	75	Not resolved

Treatment Group	Subject Number	SAE	Dose	Day of Onset	Outcome
	1422	Pleural effusion	2	75	Not resolved
	1422	Rectal perforation	2	75	Not resolved

Source: BLA 125419, Module 5.3.5.1.3, Day 182 CSR 110028 (FLU Q-PAN-001 PRI) Annex SAE summary tables

None of the SAEs were deemed vaccine related by the investigator.

Reviewer comment: This reviewer concurs that none of the reported SAEs were likely related to receipt of vaccine.

PREGNANCIES

Three subjects became pregnant through Day 182, all in the D-Pan H5N1 arms. No subjects experienced pregnancy in the first 42 days of the study and no subjects who received Q-Pan H5N1 became pregnant.

Reviewer comment: All three D-Pan H5N1 subjects, who became pregnant on study delivered healthy infants.

6.1.12.5 Adverse Events of Special Interest (AESI)

In Q-Pan-001, potential immune mediated diseases (pIMDs) were sought by querying the database for a broad range of preferred terms that included symptoms as well as diagnoses. Overall, < 3% of subjects reported AEs with pIMD preferred terms. These AE reports included common or non-specific ailments such as back pain (n=8), allergies (n=1), asthma (n=2), elevated serum creatinine (n=1), localized allergic reaction (n=1), fire ant sting reaction (n=1), and sensation of generalized hyperesthesia (n=1).

Reviewer comment: None of these events suggested a new or exacerbated autoimmune event.

6.1.12.6 Clinical Test Results

Clinical laboratory evaluation means remained within normal range throughout the study. Laboratory values outside of the normal range were reported as sporadic and occurring in less than 10% of subjects in a treatment group except for hemoglobin and hematocrit which declined slightly in all treatment groups over the course of the study. Most low hematocrit or hemoglobin values were of small magnitude (≤ 1% hematocrit or < 3g/L hemoglobin below the lower limit of normal). Three subjects had hematocrit values > 3% below the lower limit of normal at baseline. All were women who had documented iron deficiency anemia. All had stable or improved hematocrit and hemoglobin values during the study. No other lab values showed clinically significant changes.

Reviewer comment: The small changes in hemoglobin and hematocrit can likely be ascribed to the number of study blood draws. No evidence was presented that indicates vaccine relatedness.

Vitals signs were checked on Day 0, 21 and 42. No clinically relevant trends were observed in association with vaccination.

6.1.12.7 Dropouts and/or Discontinuations

A total of 7 subjects withdrew from the study through Day 42 (6 withdrawn consents, 1 migration from the study area). An additional 11 subjects withdrew from the study through Day 182 (9 lost to follow-up and 3 migration from study area). No subjects withdrew from the study due to an AE. The ATP-I cohort consisted of 648 (95%) subjects.

Reviewer comment: Overall the number of withdrawals was small in all treatment groups.

Reviewer Conclusion: Overall, the immunogenicity data from Q-Pan-001 supported the selected antigen-sparing dose of 3.75 µg; the selected full-dose of the AS03 adjuvant ($AS03_A$); and the need for two doses of vaccine to produce an adequate HI antibody response. The safety data showed that $AS03_A$ adjuvanted H5N1 vaccine was associated with significantly more subjects experiencing pain (and more severe pain) at the injection site as compared to $AS03_B$ adjuvanted and unadjuvanted vaccinees. Other solicited local and general AEs were also more common with $AS03_A$ adjuvanted vaccine than with the comparator vaccines. No other safety signals were identified in this study.

6.2 Trial #2
Q-Pan H5N1-002 (NCT00616928)

6.2.1 Objectives

The primary objectives were:

- to demonstrate that Q-Pan-H5N1 + $AS03_A$ elicits an immune response measured by post-immunization vaccine-homologous virus HI titers that meets or exceeds the 95% CI lower bounds set forth in CBER's Guidance for Industry[1] for seroconversion rate and proportions of subjects with reciprocal titers $\geq$ 40 based on post-immunization reciprocal HI titers. This was to be tested separately for the 2 age strata: 18 to 64 years of age and > 64 years of age
- to demonstrate the immunogenic equivalence of 3 consecutive lots of Q-Pan H5N1 vaccine antigen combined with 3 consecutive lots of AS03
- to describe the safety of Q-Pan H5N1 + $AS03_A$ in terms of solicited local and systemic reactogenicity events, unsolicited adverse events (AEs), and serious adverse events (SAEs) in comparison to placebo in adult subjects $\geq$ 18 years of age

6.2.2 Design Overview

Q-Pan-002 was a Phase 3, observer-blind, saline-placebo controlled, multicenter study designed to evaluate the safety and immunogenicity of a two-dose series of Q-Pan-H5N1 3.75µg + $AS03_A$ administered IM in adults ≥ 18 years of age. This study also evaluated three lots of antigen and three lots of adjuvant for consistency. The study was conducted at 30 sites in the US and 10 sites in Canada.

Subjects were randomly assigned at a 3:1 ratio to treatment with active product from 1 of 3 lots of study vaccine or saline placebo. Randomization was stratified by age.
Target sample size was approximately 4440 healthy adult subjects aged 18 years or older in 8 dose groups. Of the 4440 subjects, 3330 were to receive active study vaccine and 1110 were to receive placebo. A total of approximately 1,680 subjects 18-64 years old and 420 subjects >64 year old were to be randomly chosen by a blinded study statistician prior to immunogenicity testing to provide immunogenicity data. A small number of placebo recipients (80, 18-64 year olds and 40, > 64 year olds) were to be randomly chosen for immunogenicity testing.

All subjects were to receive 2 doses of study vaccine (at a dose of 3.75µg of HA plus $AS03_A$) or saline placebo on Days 0 and 21.

Table 12: Study group by age strata and study vaccine lot, study Q-Pan-002

Study Arms	Age in Years[1]	Antigen lot	Adjuvant lot	Saline placebo	Subject (N)	Lot Consistency[2]	SCR/SPR 18-64 yrs[2,3]	SCR/SPR >64 yrs[2,3]
A	18-49	A	1		555	420	420	
B	18-49	B	2		555	420	420	
C	18-49	C	3		555	420	420	
D	18-49			PBS	555		60	
E	50-64	A	1		185		140	
		B	2		185		140	
		C	3		185		140	
F	50-64			PBS	185		20	
G	> 64	A	1		370			140
		B	2		370			140
		C	3		370			140
H	> 64			PBS	370			40

[1]Subjects in Groups A-D were to be stratified by age 18-30 years and 31-49 years. Subjects in Groups G & H were to be stratified by age 64-75 years and >75 years.
[2]Study groups tested for immunogenicity;
[3] Antigen lot groups combined for the immunogenicity analyses of each age cohort
SCR - number of subjects with a 4-fold or greater HI titer rise
SPR - number of subjects with a ≥ 1:40 HI titer
Source: BLA 125419, Module 5.3.5.1.3, CSR 110464 (FLU Q-PAN-002 PRI) Table 2

Reviewer comment: The study was adequately designed to meet its stated objectives.

6.2.3 Population

Subjects eligible for the study were males or females 18 years of age or older at the time of vaccination. Subjects 18 to 49 years of age were expected to be in good general health as established by pre-enrollment medical history and physical examination. Subjects older than 49 years of age needed to be in stable health, as defined by absence of a serious health event or change to ongoing medication necessitated by therapeutic failure or drug toxicity within a month prior to enrollment. Noteworthy exclusion criteria were the same as for Q-Pan-H5N1-001.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Please refer to section 6.1.4 for a description of the Q-Pan H5N1 vaccine and AS03 adjuvant.

6.2.5 Directions for Use

As described in section 6.1.4.

6.2.6 Sites and Centers

This study was conducted by 40 investigators in 2 countries, including 30 sites in the US and 10 sites in Canada.

Table 13: Principle Investigators by site, study Q-Pan-002

Investigators	Center number*	Investigational site
Baron, Mira, MD	049676	Rapid Medical Research
Bennett, Nathan, MD	049678	PPCP Research
Berwald, Bruce, MD	049679	Radiant Research, Inc.
Brune, Daniel, MD	049680	Accelovance
Caldwell, Michael, MD	049681	Dutchess Country DOH
Coats, Teresa, MD	049682	Benchmark Research
Collins, Harry, MD	049675	Anderson & Collins, Clinical
Davis, Matthews, MD	049683	Rochester Clinical Research
Folkerth, Steven, MD	049684	Clinical Research Center
Geohas, Jeff, MD	049686	Radiant Research, Inc.
Gilderman, Larry, MD	049687	University Clinical Research
Harper, Wayne, MD	049688	Wake Research Associates
Helman, Laura, MD	049689	Accelovance
Herrington, Darrell, MD	049690	Benchmark Research
Jacqmein, Jeffry, MD	049691	JCCR
Jeanfreau, Robert, MD	049716	Benchmark Research
Johnson, Casey, MD	049692	Johnson County Clin-Trial
Middleton, Randle, MD	049715	Accelovance
Phillips, Fatima, MD	049694	Accelovance
Poling, Terry, MD	049695	Heartland Research Assoc.
Riff, Dennis, MD	049697	ACRI
Riffer, Ernie, MD	049698	Central Phoenix Medical C
Risi, George, MD	049699	Infectious Disease Specialists, PC
Segall, Nathan, MD	049700	Clinical Research Atlanta
Seger, William, MD	049701	Benchmark Research
Sharp, Stephan, MD	049702	Clinical Research Associates
Sheldon, Eric, MD	049703	Miami Research Associates
Shapard, Marc, MD	049704	Accelovance, Inc.
Yakish, Jack, MD	049705	Westminster Family Medicine
Fogarty, Charles, MD	50119	Spartanburg Medical Research
Blouin, Francois, MD	049331	Pro-Recherche
Dionne, Marc, MD	049332	Unite de Recherche en Sante Publique
Dzongowski, Peter, MD	049334	London East Medical Centre
Ferguson, Linda M., MD	49335	Colchester Research Group
Frenette, Louise, MD	049336	Q & T Research Inc.
Janzen, Jeannette L., MD	049338	Kells Medical Research Group
Langley, Joanne, MD	049339	Clinical Trials Research Centre
O'Mahony, Michael F. J., MD	049340	London Road Diagnostic Clinic and Medical Centre
Reich, Dennis, MD	049341	Medicor Research Inc.
Willoughby, Paul, MD	049343	Office of Paul Willoughby

Source: BLA 125419, Module 5.3.5.1.3, Day 42 CSR Q-Pan-002 Table 1

6.2.7 Surveillance/Monitoring

A complete physical examination (including vital signs) and medical history were performed at the Screening visit. This examination included a targeted assessment of

bilateral axillary and supraclavicular lymph nodes, which was repeated on Days 21, 42, and if deemed necessary on Days 182 and 364.

Subjects reported to the study site for safety and immunogenicity assessments on Days 0, 21, 42, and 182. In addition, a safety evaluation by telephone was conducted on Day 84. Amendment 1 to the protocol added a contact for an additional safety evaluation at Day 364 which could be conducted via telephone or as an in-clinic visit at the convenience of the subject and investigator. The investigator was given the option to require a clinic visit for Day 364 if deemed necessary for adequate safety follow-up in a particular subject. Subjects were also given the option to enroll in an extension study either at Day 182 or 364.

6.2.8 Endpoints and Criteria for Study Success

The primary safety endpoints were:

- The occurrence of specifically-solicited local and general signs and symptoms during a 7-day follow-up period (i.e., day of vaccination and 6 subsequent days) after each vaccination, and overall per subject considering both post-immunization periods.
- The occurrence of all unsolicited adverse events during a 21-day follow-up period for each vaccination, as well as overall (Day 0 through Day 84).
- The occurrence of serious adverse events and medically-attended events Day 0 through Day 364.

The primary immunogenicity endpoint was based on:

- Vaccine-homologous virus antibody response in subjects receiving 2 doses of study vaccine, as demonstrated by the HI antibody titer at 21 days after the second dose of H5N1 vaccine for younger adults age 18 to 64 years and older adults age > 64 years.

Secondary endpoints included measured immune response after two doses according to the CHMP analysis strata for age; persistence of immune response through 6 months; and vaccine-homologous antibody response as measured by microneutralization (MN) and immune response to drift variants as measured by HI and MN assays.

Reviewer comment: Secondary and exploratory endpoints are described for completeness. However, with the exception of persistence of HI antibody through Month 6 post dose 1, none of these endpoints will be shown or discussed further in this review.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Reviewer comment: Please refer to Dr. Tsai-Lien Lin's review for a comprehensive discussion of the statistical considerations and SAP.

Table 14 shows the power calculations used for each of the primary immunogenicity endpoints. Safety data analyses were to be descriptive and include tabulations and

summaries of solicited and unsolicited AEs for all subjects by treatment group and age strata.

Table 14: Calculation of Power/Criteria of Q-Pan with Respect to SCR and SPR for anti-HI and GMT Equivalence, study Q-Pan-002

Endpoint	Reference value	Clinical limit	Number of evaluable subjects in Group	Evaluation criteria	Power based on reference value
Anti-HI: SCR for subjects age 18-64 years	SCR≥90%[1]	LL of 95% CI of SCR ≥40%[3]	1596 (Total of Study Arms A,B,C, E)	The lower limit of the 95% CI will be greater than 40% if at least 680 subjects out of 1596 reach SC	>0.9999
Anti-HI: SCR for subjects age >64 years	SCR=0.70[2]	LL of 95% CI of SCR ≥30%[3]	399 (Study Arm G)	The lower limit of the 95% CI will be greater than 30% if at least 139 subjects out of 399 reach SC	>0.9999
Anti-HI: SCR for subjects age 18-64 years	SCR≥90%[1]	LL of 95% CI of SCR ≥70%[3]	1596 (Total of Study Arms A,B,C, E)	The lower limit of the 95% CI will be greater than 70% if at least 1160 subjects out of 1596 reach an HI titer ≥ 1:40	>0.9999
Anti-HI: SCR for subjects age >64 years	SCR=0.70[2]	LL of 95% CI of SCR ≥60%[3]	399 (Study Arm G)	The lower limit of the 95% CI will be greater than 60% if at least 259 subjects out of 399 reach an HI titer ≥ 1:40	-0.988
Anti-HI: GMT equivalence for subjects	[0.67,1.5]	LL and UL of 95% CI for the GMT ratio: 0.67 and 1.5[4]	399 in each group (Study Arms A,B,C) (log SD=0.65)	2-sided equivalence tests for Study Arms A vs. B, B vs. C and A vs. C (three comparisons)	-0.971

LL=Lower Limit; SC=Seroconversion; UL=Upper Limit; SCR=Seroconversion rate
1. Source of reference values: Lower 95% confidence bound for SCR/SPR in prior Q-Pan, D-Pan studies
2. Source of reference values: Lower 95% confidence bound for SCR/SPR in young adults minus arbitrary 20%
3. Pass 2005, 2-sided test, alpha=0.05, one proportion.
4. Pass 2005, 2-sided equivalence test, alpha=0.05.

Source: BLA 125419, module 5.3.5.1.3, Day 42 CSR 110464 (FLU Q-PAN-002), Table 16

6.2.10 Study Population and Disposition

Subject enrollment and disposition are summarized in Table 15. A total of 4,561 subjects were enrolled and randomized into the study. The first volunteer was enrolled on January 28, 2008 and the last volunteer completed the study through Day 42 on April 22, 2008.

Table 15: Subject enrollment and disposition, Q-PAN-002

Cohort	18-64 years Total n(%)	>64 years Total n(%)	18-64 years Q-Pan n(%)	18-64 years Placebo n(%)	>64 years Q-Pan n(%)	>64 years Placebo n(%)
Total enrolled cohort	3072 (100%)	1489 (100%)	2304 (100%)	768 (100%)	1118 (100%)	371 (100%)
TVC	3072 (100%)	1489 (100%)	2304 (100%)	768 (100%)	1118 (100%)	371 (100%)
ATP-S	2952 (96.1%)	1447 (97.2%)	2220 (96.4%)	732 (95.3%)	1087 (97.2%)	360 (97.6%)
ATP-I	1647 (53.6%)	436 (29.3%)	1571 (68.2%)	76 (9.9%)	396 (35.4%)	40 (10.8%)

Source: BLA 125419/0, Module 5.3.5.1.3, CSR 110464 (FLU Q-PAN-002 PRI) Day 42 Tables 18

Reviewer comment: GSK missed their pre-specified target for enrollment in the younger age strata for the ATP-I cohort by a small margin (targeted 1,680 in the 18-64 year old age strata) and exceeded the targeted enrollment in the > 64 year old age strata for the ATP-I. Refer to Sections 6.1.2 and 6.1.10.1 for additional details on this study cohort.

Each study site enrolled between 2 – 2.9% of subjects 18-64 years of age (average 2.5%). The older age strata enrollment was more variable among sites ranging from 0.3% – 4%.

Reviewer comment: The variability was mainly contributed by one site (site 49332), which enrolled a very small number of older subjects (0.3%). Similarly this site enrolled the fewest number of younger subjects as well (2%). Even taking this site into account the mean percentage of older subjects enrolled by site was 2.6% and the median was 2.4%, which shows that, for the most part, enrollment was similar across the different sites.

6.2.10.1 Populations Enrolled/Analyzed

Please refer to section 6.1.10.1 for the complete definition of each analysis population. Briefly, the same analysis populations were used as in Q-Pan-H5N1-001: the TVC was used for the primary analysis of safety and the ATP-I was used for the primary analysis of immunogenicity.

6.2.10.1.1 Demographics

The mean age of study subjects for the 18 to 64 years age group was 39 years (range 18 to 64 years) and the mean age of subjects in the > 64 years age group was 72 years (range 65 to 91 years). In the 18 to 64 years age stratum for both the Q-Pan and placebo groups, 74% of subjects were between 18 to 49 years of age and 26% of subjects were between 50 to 64 years of age.

A total of 2,569 (56%) subjects were female and 1,992 (44%) subjects were male, with no notable difference in gender distribution between age strata and treatment groups. The majority of subjects (86% of the 18 to 64 years age group and 94% of the > 64 years age group) were Caucasian.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Not applicable.

6.2.10.1.3 Subject Disposition

All enrolled subjects received at least 1 dose of study treatment. Of the 4,561 enrolled subjects, 135 subjects (3%) received only 1 dose of study treatment. The remaining 4,426 (97%) subjects received 2 doses of study treatment.

A total of 4,457 subjects (98%) completed the study through Day 42 and 95.2% completed the study through Day 182. Withdrawals occurred at similar rates across treatment groups.

Through the primary endpoint of Day 42, a total of 2 subjects in the 18 - 64 age stratum [1 Q-Pan (fatal MI) and 1 placebo (pneumococcal pneumonia)] and 2 subjects, who received Q-Pan (1 with septic arthritis, pulmonary embolism, spinal abscess and compression and 1 with "fatal carcinoma"), in the > 64 age stratum, withdrew due to SAEs. A total of 6 subjects in the 18 - 64 age stratum and 3 subjects in the > 64 age stratum withdrew because of non-serious adverse events.

Reviewer comment: Overall the number of withdrawals was small and well balanced across both treatment groups and age strata.

The SAEs and non-serious AEs leading to withdrawal are discussed in Section 6.2.12.3.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity analysis (proportion of subjects who seroconverted as defined per CBER guidance) was performed on the ATP-I cohort. A total of 1647

subjects in the 18 to 64 years of age stratum were included in the ATP-I cohort (1571 Q-Pan H5N1 subjects and 76 placebo subjects). A total of 436 subjects in the > 64 years of age stratum were included in the ATP-I cohort (396 Q-Pan H5N1 subjects and 40 placebo subjects). Overall, greater than 5% of the set of subjects randomly selected for immunologic testing were excluded from the ATP-I cohort due to various protocol deviations and therefore a confirmatory secondary immunogenicity analysis was also performed on all members of the TVC with immunogenicity data.

Reviewer comment: The TVC analysis results (not shown) were similar to the ATP-I analysis results.

The primary outcomes for immunogenicity were met; Q-Pan H5N1 3.75 µg + $AS03_A$ fulfilled the prespecified immune criteria at Day 42 for both age strata as set forth in CBER guidance[1]. Although the Day 182 immune parameters (a secondary endpoint) declined relative to the Day 42 parameters, the Q-Pan H5N1group maintained immune responses at levels well above those in the placebo group (Table 16).

Table 16: Post-vaccination HI antibody immune responses according to age at Day 42 and Day 182, study Q-Pan-002 (ATP-I)

Treatment Group	N	N	% of Subjects with 4-Fold Rise in HI Titer (95% CI)[1]	% of Subjects with HI titer ≥ 1:40 (95% CI)	GMT (95% CI)
Day 42					
Q-Pan 18-64 yrs	1571	1427	90.8 (89.3, 92.2)	90.8 (89.3, 92.2)	249 (231.8, 267.5)
Placebo 18-64 yrs	76	1	1.3 (0, 7.1)	1.3 (0, 7.1)	5.1 (4.9, 5.4)
Q-Pan >64 years	396	295	74 (69.4, 78.2)	74 (69.4, 78.2)	81.9 (69.7, 96.2)
Placebo >64 years	40	1	2.5 (0.1, 13.2)	2.5 (0.1, 13.2)	5.5 (4.5, 6.8)
Day 182					
Q-Pan 18-64 yrs	366	255	61.5 (56.3, 66.5)	61.5 (56.3, 66.5)	36.2 (31, 42.2)
Placebo 18-64 yrs	37	1	2.7 (0.1, 17.8)	2.7 (0.1, 17.8	5.5 (4.8, 6.5)
Q-Pan >64 years	91	59* 60**	64.8 (54.1, 74.6)	65.9 (55.3, 75.5)	44.8 (33.3, 60.4)
Placebo >64 years	19	0	0 (0, 17.6)	0 (0, 17.6)	5.4 (4.6, 6.3)

N – Number of subjects with both pre- and post- vaccination results available
n – number of responders
[1]Proportion of subjects with a 4-fold rise in HI titer ≥ 95% CI LB of 40% at Day 42 was the primary endpoint.
Source: BLA 125419, Module 5.3.5.1.3, CSR 110464 (FLU Q-PAN-002 PRI) Day 42 Tables 24, 25, and Supplement 29; and Day 182 Annex Tables 10, 11 and 12.

Reviewer comment: Q-Pan H5N1 met its primary and secondary immunogenicity outcomes in both age strata with 95% CI lower bounds of 89% and 74% in the 18-64 year olds and > 64 year olds respectively.

The GMTs, the proportion of subjects who seroconverted, and the proportion of subjects who had an HI titer of at least 1:40, were all much lower on Day 182 compared to Day 42. The older cohort had a less robust immune response initially when compared to the younger cohort, but then had a less drastic fall in titers than did the younger cohort. It is unclear what, if any, relevance the magnitude of the fall in titers has. If the 1:40 HI titer is relevant with regard to protection against pandemic influenza, then these Day 182 values are reassuring in that more than half of all subjects maintained titers at or above 1:40 for approximately 4.5 months (140 days) after their last vaccination.

Another primary objective in this study was to demonstrate the immunologic equivalence of three consecutive lots of H5N1 vaccine antigen manufactured in Quebec combined with three 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 to 1.5. The results are provided in the table below.

Table 17: Adjusted ratios of H5N1 GMTs for 3 consecutive lots of Q-Pan H5N1 at Day 42 in subjects 18-49 years of age (ATP cohort for immunogenicity), study Q-Pan-002

	Q-Pan H5N1 Lot A N = 394	Q-Pan H5N1 Lot B N=379	Q-Pan H5N1 Lot C N=394
Adjusted GMT	275.8	291.7	333.5

Adjusted GMT = geometric mean antibody titer adjusted for baseline titer
N = Number of subjects with both pre- and post-vaccination results available
Source: BLA 125419, CSR Q-Pan 002, Table 26, p. 96

The 95% CI for the GMT ratio between Q-Pan Lot A and Q-Pan Lot B was 0.78 to 1.15; the 95% CI for the GMT ratio between Q-Pan Lot A and Q-Lot C was 0.68 to 1.00; and the 95% CI for the GMT ratio for Q-Pan Lot B and Q-Pan Lot C was 0.72 to 1.06.

Reviewer comment: The 2-sided 95% confidence bounds for all GMT ratios were within the interval of 0.67 and 1.5 albeit just marginally for the comparison between Lot A and Lot C. When analyzed using the TVC the 95% CIs for the GMT ratios between lots were similar to the ATP-I analysis: Lot A-to-Lot B comparison (0.78 – 1.15), the Lot A-to-Lot C comparison (0.70 – 1.03), and the Lot B-to-Lot C comparison (0.73 – 1.08).

6.2.11.2 Analyses of Secondary Endpoints

See section 6.2.11 for a discussion of the secondary endpoint of persistence of immune response.

6.2.11.3 Subpopulation Analyses

At CBER's request GSK performed *post hoc* analyses by age, race and gender. In general the younger subjects (18-40 years of age), younger male subjects and younger non-white subjects had a higher HI antibody response when measuring SCR, proportion with HI titer ≥ 1:40 and GMTs when compared to the older subjects (> 40 years of age), younger female subjects and younger white subjects, respectively. Conversely, older females and older white subjects had higher HI antibody responses than older males and older non-whites, respectively.

Reviewer comment: It is difficult to draw any conclusions from these post-hoc analyses results given that the study population was predominantly young (75%), female (56%) and white (90%).

6.2.11.4 Dropouts and/or Discontinuations

Reviewer comment: Please refer to Section 6.2.10.1.3 Subject Disposition for a detailed discussion on subject withdrawals.

A total of 162 subjects were excluded from the ATP-S cohort, including 120 subjects in the 18 to 64 years age group and 42 subjects in the > 64 years age group. Of the 120 subjects in the 18-64 years age group excluded from the ATP-S cohort, 19 subjects were administered a concomitant vaccine forbidden in the protocol and 101 subjects did not have study vaccine administered according to the protocol. Of the 42 subjects in the > 64 years age group excluded from the ATP-S cohort, 6 subjects were administered a concomitant vaccine forbidden in the protocol and 37 subjects did not have study vaccine administered according to the protocol.

Reviewer comment: As described in Q-Pan-001, Section 6.1.10.1, the ATP-S cohort analysis in Q-Pan-002 was a secondary analysis that would only be performed if more than 5% of the TVC in any treatment group was excluded from the ATP-S cohort. A total of 3.9% of 18-64 year olds and 2.8% of > 64 year olds were excluded from the ATP-S cohort, and a total of 3.3% of Q-Pan recipients and 4.1% of placebo recipients were excluded from the ATP-S cohort. Therefore, GSK did not perform the ATP-S cohort analysis due to the relatively low protocol deviation and exclusion rate.

6.2.12 Safety Analyses

Reviewer comment: The safety results and conclusions described below are based on interim data and may change upon review of the final safet y datasets.

6.2.12.1 Methods

Safety/reactogenicity evaluations:

- Seven day follow-up (i.e., day of vaccination and 6 subsequent days) of subjects after each vaccination (Day 0 and Day 21) for solicited local and general signs

and symptoms recorded on diary cards given to the subject at each vaccination.
  - Solicited local adverse events included: redness, swelling or induration, and pain.
  - Solicited general adverse events included: fever, headache, fatigue, joint pain, muscle aches, shivering (chills), and increased sweating.
- From Day 0 up to Day 84 for all unsolicited signs and symptoms (i.e., adverse events).
- Recording of serious adverse events and medically-attended events in a prospective manner beginning with the first vaccine administration and ending at the Day 364 follow-up visit/telephone contact for all subjects.

Local reactions were presumed product related (i.e., no causality assessment needed), but investigators were to provide causality assessments for solicited general reactions as for other AEs. Causality was either assessed as "Yes", there is a reasonable possibility that the vaccine(s) contributed to the AE; or "No", the AE is not causally related to administration of the study vaccine(s). There are other, more likely causes and administration of the study vaccine(s) is not suspected to have contributed to the AE.

Local and systemic reactogenicity events were solicited during the 7 day period (Days 0-6) following each dose of study vaccine. Local symptoms included pain, redness and swelling. Systemic symptoms included fatigue, headache, joint pain (arthralgia) or muscle aches (myalgias) at locations other than the injection site, shivering, sweating, and oral temperature.

The same reactogenicity grading scale used in Q-Pan-H5N1-001 was used in Q-Pan-H5N1-002.

Lymphadenopathy was assessed and graded as follows:

Table 18 Severity Grading for Lymphadenopathy

Grade	Definition
Grade 0 (none)	No palpable nodes, or all nodes < 1 cm (pea-sized), mobile, and non-tender
Grade 1 (mild)	At least one node > 1 cm (pea-sized) but less than 2.5 cm (cherry-sized), but mobile and non-tender or tender only with firm pressure.
Grade 2 (moderate)	At least one node ≥ 2.5 cm (cherry-sized) or tender to light touch or spontaneously reported as painful, but not causing significant limitation of normal everyday activities
Grade 3 (severe)	At least one node that is tender to light touch or spontaneously reported as painful AND causing significant limitation of normal everyday activities. Any one of palpable fluctuance or heat, fixation to underlying tissues, or visible erythema. If ulceration or drainage is present, must also report as SAE.

Source: BLA 125419, Module 5.3.5.1.3, CSR 110464 (FLU Q-PAN-002), Table 13

6.2.12.2 Overview of Adverse Events

Reviewer comment: As in Q-Pan-H5N1-001 solicited reactogenicity rates did not differ significantly from Dose 1 to Dose 2. Safety results, therefore, are presented overall by subject, which includes either Dose 1 or Dose 2 related events.

All 4561 subjects, including 3072 subjects in the 18 to 64 years age group (Q-Pan H5N1 n = 2304; placebo n = 768) and 1489 subjects in the > 64 years age group (Q-Pan H5N1 n = 1118; placebo n = 371) are included in the safety cohort, the TVC.

Reviewer comment: A small percentage (2-4%) of TVC subjects in each group were excluded from the local and systemic reacotogenicity analyses due to missing data. The likelihood of these missing data contributing to reporting bias is decreased since the proportion of subjects with missing data was similar in each treatment group.

The overall results per subjects are presented in Table 19. Pain was the most commonly reported solicited local symptom in both the Q-Pan H5N1 group and the placebo group. However, any grade pain was reported at greater than a 4-fold higher rate in the Q-Pan H5N1 group (83%) than in the placebo group (20%). At least moderate (Grade 2) and severe pain (Grade 3) were also reported at significantly higher rates in the Q-Pan H5N1 group, nearly 10-fold and 5-fold higher than the rates reported in the placebo group. Overall, pain lasted a median of three days in the Q-Pan H5N1 group compared to one day in the placebo group.

Similarly any grade redness and swelling were reported at rates 10-fold and 8-fold higher in the Q-Pan group than in the placebo group. No subjects reported seeking medical attention for any of these solicited events.

Table 19: Incidence of solicited local reactions overall by subject, Dose 1 or Dose 2, Days 0 – 6, study Q-Pan-H5N1-002 (TVC)

Local Symptom, n (%)	Q-Pan H5N1 Overall N = 3376	Saline Placebo Overall N = 1122	Q-Pan H5N1 18-64 years N = 2267	Saline Placebo 18-64 years N = 754	Q-Pan H5N1 > 64 years N = 1109	Saline Placebo > 64 years N = 368
All Pain	2808 (83.2)	224 (20.0)	2024 (89.3)	171 (22.7)	784 (70.7)	53 (14.4)
Gr > 2 Pain	1244 (36.8)	43 (3.8)	1059 (46.7)	33 (4.4)	185 (16.7)	10 (2.7)
Gr 3 Pain	156 (4.6)	8 (0.7)	141 (6.2)	6 (0.8)	15 (1.4)	2 (0.5)
All Redness,	287 (8.5)	8 (0.7)	181 (8)	7 (0.9)	106 (9.6)	1 (0.3)
Gr 3 Redness	4 (0.1)	0	4 (0.2)	0	0	0
All Swelling,	351 (10.4)	8 (0.7)	241 (10.6)	7 (0.9)	110 (9.9)	1 (0.3)

Local Symptom, n (%)	Q-Pan H5N1 Overall N = 3376	Saline Placebo Overall N = 1122	Q-Pan H5N1 18-64 years N = 2267	Saline Placebo 18-64 years N = 754	Q-Pan H5N1 > 64 years N = 1109	Saline Placebo > 64 years N = 368
Gr 3 Swelling	4 (0.1)	0	3 (0.1)	0	1 (0.1)	0

N = number of subjects with at least one documented dose
n = number of subjects reporting reaction at least once
Gr ≥ 2 – at least moderate, Grade 2
Gr 3 - Grade 3, severe
Source: BLA 125419, Module 5.3.5.1.3, CSR 110464 (FLU Q-PAN-002 PRI) Table 42

Reviewer comment: Although younger subjects reported local reactions more frequently, the higher rate at which the Q-Pan subjects reported relative to the placebo subjects were similar regardless of age.

Reviewer comment: Local reactogenicity occurs more often, with greater severity and for a longer duration in association with Q-Pan H5N1. However, local events appear to resolve without sequelae or need for medical intervention.

Myalgias were the most commonly reported solicited general symptom overall, and were reported at a 2-fold higher rate for the Q-Pan H5N1 group (45%) than the placebo group (21%). The incidence of severe myalgias (Grade 3) was relatively low, with a rate of 3% in the Q-Pan H5N1 group and a rate of 2% in the placebo group. The remainder of the general reactogenicity events are presented in Table 20.

Table 20: Incidence of solicited general reactions overall by subject, study Q-Pan-H5N1-002 (TVC)

General Symptom, n (%)	Q-Pan Overall N = 3375	Saline Placebo Overall N = 1123	Q-Pan 18-64 years N = 2266	Saline Placebo 18-64 years N = 755	Q-Pan > 64 years N = 1109	Saline Placebo > 64 years N = 368
All Fatigue	1148 (34)	253 (22.5)	890 (39.3)	189 (25)	258 (23.3)	64 (17.4)
Gr 3 Fatigue	107 (3.2)	26 (2.3)	89 (3.9)	21 (2.8)	18 (1.6)	5 (1.4)
All Headache	1179 (34.9)	312 (27.8)	932 (41.1)	249 (33)	247 (22.3)	63 (17.1)
Gr 3 Headache	97 (2.9)	27 (2.4)	89 (3.9)	24 (3.2)	8 (0.7)	3 (0.8)
All Arthralgias	853 (25.3)	136 (12.1)	645 (28.5)	97 (12.8)	208 (18.8)	39 (10.6)
Gr 3 Arthralgias	63 (1.9)	10 (0.9)	55 (2.4)	8 (1.1)	8 (0.7)	2 (0.5)
All Myalgias	1526 (45.2)	231 (20.6)	1188 (52.4)	175 (23.2)	338 (30.5)	56 (15.2)
Gr 3 Myalgias	109 (3.2)	21 (1.9)	95 (4.2)	17 (2.3)	14 (1.3)	4 (1.1)
All Shivering	563 (16.7)	109 (9.7)	456 (20.1)	87 (11.5)	107 (9.6)	22 (6.0)
Gr 3 Shivering	66 (2.0)	12 (1.1)	58 (2.6)	9 (1.2)	8 (0.7)	3 (0.8)
All Sweating	362 (10.7)	82 (7.3)	314 (13.9)	67 (8.9)	48 (4.3)	15 (4.1)

General Symptom, n (%)	Q-Pan Overall N = 3375	Saline Placebo Overall N = 1123	Q-Pan 18-64 years N = 2266	Saline Placebo 18-64 years N = 755	Q-Pan > 64 years N = 1109	Saline Placebo > 64 years N = 368
Gr 3 Sweating	28 (0.8)	13 (1.2)	26 (1.1)	11 (1.5)	2 (0.2)	2 (0.5)
All Temperature ≥ 38 ºC	156 (4.6)	38 (3.4)	121 (5.3)	32 (4.2)	35 (3.2)	6 (1.6)
Temperature ≥ 39 ºC	31 (0.9)	10 (0.9)	28 (1.2)	10 (1.3)	3 (0.3)	0
Temperature > 40 ºC	4 (0.1)	4 (0.4)	4 (0.2)	4 (0.5)	0	0

N = number of subjects with at least one documented dose
n = number of subjects reporting reaction at least once
Gr 3 - Grade 3, severe
Source: BLA 125419, Module 5.3.5.1.3, CSR 110464 (FLU Q-PAN-002 PRI) Table 45

Reviewer comment: Myalgias and arthralgias occurred at twice the rate in Q-Pan recipients than in placebo recipients. Headache and fatigue were also more commonly reported, albeit not at twice the rate, in the Q-Pan group versus the placebo group. All of these symptoms appeared to be transient in nature and to resolve without medical intervention or sequelae.

Reviewer comment: The younger age cohort reported solicited systemic events much more frequently than the older age cohort both for the active and placebo treatment groups. In most instances the younger placebo group reported systemic symptoms more frequently than the older Q-Pan H5N1 group with the exception of myalgias and arthralgias, which were reported at the highest rates by the Q-Pan H5N1 group in each age stratum. These findings are consistent with older subjects having a relatively diminished immune/inflammatory response as compared to younger subjects, but may have other contributing factors e.g. younger subjects having a lower threshold for pain/discomfort.

Overall, oral temperature elevations of ≥ 38° C occurred in 4.6% of Q-Pan H5N1 recipients and 3.4% of placebo recipients. Temperatures ≥ 39° C were reported by < 1% in each treatment group.

Eight subjects (4 Q-Pan H5N1 subjects and 4 placebo subjects), all in the 18-64 year age strata, reported severe fever (temperature > 40° C). Five subjects (1 Q-Pan H5N1 subject and 4 placebo subjects) reported their severe fever after Dose 1. For these five subjects fever (any grade) came on between Days 2 and 4 with the maximum fever (> 40° C) occurring between Days 4 and 6 and fever (any grade) lasting for 2 to 4 days. Three (2placebo and 1 Q-Pan H5N1) of the five subjects, who reported severe fever after Dose 1 did not report any temperature data after Dose 2, and the one placebo subject withdrew after Dose 1 due to AEs (including solicited adverse events and unsolicited cough, sore throat, chest congestion). The remaining placebo subject had no fevers recorded post Dose 2.

Reviewer comment: The three subjects who did not withdraw and did not have any temperature data recorded after Dose 2 also had no AEs reported after Dose 2 nor any other significant solicited events recorded, which was reassuring.

Three subjects (all Q-Pan H5N1 subjects) reported their severe fever after Dose 2. Fever (any grade) onset appeared to be earlier (Days 0 to 2) with the maximum grade occurring between Days 0 and 3, and the duration of fever was shorter (lasting 1 to 2 days).

Seven of the eight subjects with severe fevers used acetaminophen or a non-steroidal anti-inflammatory drug. None of the eight sought medical attention for the severe fever.

Reviewer comment: Per the protocol all investigators were instructed to report temperatures of 40° C or higher as SAEs. However, none of the 8 subjects (4 Q-Pan H5N1 and 4 placebo) with temperatures reported at or above 40° C had SAE reports. Of note, there is no evidence that any of the subjects had other signs or symptoms that would fulfill the definition of serious.

Although it is concerning that none of the investigators adhered to the protocol in assessing severe fevers as SAEs, the lack of association with other severe or serious manifestations and the same number of febrile events occurring in the test and placebo groups is reassuring.

Overall, more Q-Pan H5N1 subjects (23%) took concomitant antipyretic medication during the 7-day solicited AE period as compared to placebo subjects (13%). Q-Pan H5N1 subjects also took more concomitant medications in general during that time period than placebo subjects (30% vs. 21% respectively).

Reviewer comment:

- ***The higher rate of concomitant medication use can be expected given the increased rate and severity of local and systemic adverse events associated with Q-Pan H5N1 use.***
- ***GSK used the TVC (N=3422 for Q-Pan H5N1 and N=1139 for placebo) to determine the proportion of subjects using concomitant medications during this reporting period. However, this is the same reporting period for which data were missing for reactogenicity events. Therefore, this reviewer also calculated the rates of concomitant medication use using the Ns used to generate reactogenicity rates. Using N=3,376 for Q-Pan H5N1 and N=1,123 for placebo the proportion of subjects using concomitant antipyretics is exactly the same as when the TVC numbers are used.***

At least one unsolicited AE was reported by 38% of subjects in the Q-Pan H5N1 group and 35% in the placebo group through Day 42, and 43% and 40%, respectively, through Day 84. No MedDRA preferred term was reported by more than 4.1% of subjects in either treatment group. The most frequently reported events (in $\geq$ 2% of subjects) in the Q-Pan H5N1 group (nasopharyngitis, pharyngolaryngeal pain, headache, nausea,

diarrhea, cough, upper respiratory infection, nasal congestion) occurred at a similar rate in the placebo group. Events reported in the Q-Pan H5N1 group at a rate of at least 1% and at least twice that of the placebo group include injection site pruritus (1.6% vs. 0.4%), injection site warmth (1.3% vs. 0.2%) and dizziness (1.4% vs. 0.7%).

Of note, insomnia occurred in Q-Pan subjects (n=17) at a rate nearly 5 times that of placebo subjects (n=1), albeit at a relatively low frequency in both study groups (0.4% vs 0.09%). A similar number of Q-Pan subjects experienced insomnia after each injection (n=9 after the initial injection and n=8 after the second injection). One subject experienced transient insomnia after both injections. For most subjects insomnia had a rapid onset (within 1-2 days of vaccination with onset as far as out as 83 days post vaccination) and lasted for a median of 2 – 2.5 days. In three subjects it was ongoing at the time of database lock with one of the three subjects experiencing worsening of baseline insomnia. Insomnia was considered vaccine related for 8 of the Q-Pan subjects, unrelated for the 1 placebo subject. The majority of Q-Pan reports (n=10) were moderate in intensity with 3 subjects reporting severe intensity (i.e. preventing attending work or school). In addition three subjects sought medical attention for their insomnia. The placebo subject reported mild insomnia with onset on Day 3 post 1st vaccination, lasting 3 days.

Reviewer comment: Although insomnia is reported at a much higher rate in the Q-Pan group than placebo, the transient nature of most of the cases and the high rate of reactogenicity in Q-Pan subjects makes it difficult to tease out insomnia as a stand-alone diagnosis versus insomnia as a sequelae of some other adverse event e.g. pain at the injection site. Of note, the three subjects with ongoing insomnia had AE onset beyond the 7-day reactogenicity period (9, 49 and 83 days post vaccination) and it was associated with depression in 2 of the 3 case and attributed to a concomitant medication in the other case.

The number of subjects with ongoing insomnia is small and the diagnosis of insomnia is common and is easily confounded by other diagnoses. Therefore, the increased rate in the Q-Pan group may be a chance finding or clinically insignificant. However, insomnia can also be an early symptom of narcolepsy. Please refer to Section 2.3 and 6.2.12.5 for further discussion on narcolepsy.

Grade 3 unsolicited AEs were reported by 5% of subjects in the Q-Pan H5N1 group and 6% of subjects in the placebo group. The most commonly reported Grade 3 unsolicited AEs were influenza-like illness, upper respiratory tract infection, nasopharyngitis, and headache. All Grade 3 MedDRA preferred terms were reported at similar rates across treatment groups and all at < 1%.

Each treatment group reported seeking medical attention for unsolicited adverse events at similar rates (9% of subjects in the Q-Pan H5N1 group and 10% of subjects in the placebo group).

Reviewer comment: Both treatment groups appear to be similar with regard to reporting of unsolicited AEs regardless of the severity of the event or the need to seek medical attention. The notable exceptions are vaccine related injection site pruritus and warmth and reportedly unrelated dizziness.

6.2.12.3 Deaths

A total of 11 subjects died during the study through the end of the Day 364 visit, 4 (0.1%) in the Q-Pan H5N1 group and 7 (0.6%) in the placebo group. None of the deaths were considered vaccine-related by the investigator.

From Day 0 through Day 42, one subject in the Q-Pan H5N1 treatment group died due to a myocardial infarction (MI).

- Subject 04253 was a 59 year old male with a past medical history of diabetes mellitus and hypercholesterolemia being treated with metformin and low-dose aspirin. The subject experienced an MI (b)(4) days after one dose of Q-Pan H5N1 and died. No autopsy was performed. This event was considered by the investigator as unrelated to vaccination.

During the study period from Day 42 through Day 182, 5 subjects died, including 3 subjects in the Q-Pan group and 2 subjects in the placebo group.

- Subject 1663, a 78-year-old female, had metastases to the liver and presumptive metastatic ovarian cancer 168 days following one dose of Q-Pan H5N1, 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, an ovarian origin. These events were considered by the investigator to be unrelated to vaccination.
- Subject 4308, a 69-year-old female, presented with a malignant neoplasm of unknown type 155 days following 2 doses of Q-Pan H5N1, and died. This event was considered by the investigator as unrelated to vaccination.
- Subject 6568, a 53-year-old male, presented with aggravated diabetes mellitus and exacerbation of liver disease 154 days following 2 doses of Q-Pan H5N1, 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. These events were considered by the investigator to be unrelated to vaccination.
- Subject 6120, a 73-year-old male with hypertension and chronic obstructive lung disease was diagnosed with a malignant brain neoplasm of unknown type on 09 April 2008, Day 42 following 2 doses of placebo. Palliative therapy was given on an outpatient basis and the subject died on -----(b)(4)-----. This event was considered by the investigator to be unrelated to vaccination.
- Subject 6567 (Case ID R0000520A), a 60-year-old male, developed cardiomegaly 25 days following 2 doses of placebo, and died. A coroner's report listed cardiomegaly as the proximate cause of death. The subject had a history of morbid obesity, and was also subsequently found to have a history of chronic

obstructive lung disease, and sleep apnea. This event was considered by the investigator to be unrelated to vaccination.

During the period from Day 183 through Day 364, 5 subjects in the placebo group died. Two of these events (death NOS and gunshot wound) were not captured in the clinical database because these subjects failed to show up for Day 182 and Day 364 safety follow-up and were therefore not enrolled in the long term safety follow-up period. However, the Sponsor was able to obtain CIOMS detailing these events and provided them as part of the BLA submission.

- Subject 3548, an 80-year-old male with a history of coronary heart disease and type II diabetes experienced a cardiac disorder (possible acute myocardial infarction) prior to a motor vehicle accident on Day 244 (8 months) following 2 doses of placebo, and died. This event was considered by the investigator to be unrelated to vaccination.
- Subject 5514, an 89-year-old female with a history of hypertension and thrombotic thrombocytopenia was reported to have died due to an unspecified cause on Day (b)(4) (9 months) following 2 doses of placebo. This event was considered by the investigator to be unrelated to vaccination due to the length of time between vaccination and the subject's death.
- Subject 2856, a 60-year-old male experienced a gunshot wound on Day ----------(b)(4)--------, (10 months) following 2 doses of placebo, and died. This event was considered by the investigator to be unrelated to vaccination.
- Subject 7304, a 69-year-old male with a history of hypertension, smoking, and alcohol use was diagnosed with a malignant neoplasm of the tongue (stage not specified) on Day 274, 26 November 2008, (9 months) following 2 doses of placebo. The subject died ---(b)(4)--- later in ----(b)(4)---- due to squamous cell carcinoma of the tongue. This event was considered by the investigator to be unrelated to vaccination.
- Subject 8078, an 85-year-old male with a history of hyperlipidemia, hypertension, arrhythmia, hypothyroidism, and depression was diagnosed with pneumonia on Day 162 following 2 doses of placebo. The subject died --(b)(4)-- later. This event was considered by the investigator to be unrelated to vaccination.

Reviewer comment: Based on the data presented above, Q-Pan H5N1 vaccination does not appear to be associated with the reported fatal outcomes. The placebo group reported a higher death rate than the Q-Pan group (0.6% vs 0.1%). However, given that the placebo subjects were elderly (mean age 73.7) and died as the result of accidents (n=2, gunshot and motor vehicle accident) or reported many comorbid illnesses that contributed to the causes of death, this reviewer believes the imbalance is likely due to chance.

6.2.12.4 Nonfatal Serious Adverse Events

Overall, 149 subjects (109 (3.2%) Q-Pan H5N1 subjects and 40 (3.5%) placebo subjects) reported at least one SAE through Day 364 visit.

The most commonly reported SAEs for Q-Pan H5N1 subjects through day 364 were chest pain (n=5), pneumonia (n=5), myocardial infarction (n=4), intestinal obstruction (n=4), atrial fibrillation (n=3), osteoarthritis (n=3), thyroid cancer (n=3), cerebrovascular accident (n=3), convulsion (n=3) and pulmonary embolism (n=3). The most commonly reported SAEs for placebo subjects were myocardial infarction (n=2), coronary artery disease (n=2), acute coronary syndrome (n=2), coronary artery stenosis (n=2), pneumonia (n=2) and osteoarthritis (n= 2). Of the most commonly reported SAEs in the Q-Pan H5N1 group, thyroid cancer, convulsion, intestinal obstruction and pulmonary embolism (PE) were reported exclusively by Q-Pan H5N1 subjects. Table 21 presents the SAEs seen exclusively in the Q-Pan H5N1 with additional subject information.

Table 21: SAEs reported only in Q-Pan H5N1 Subjects, study Q-Pan-002

SAE	Day(s) of Onset	Vaccine Dose	Gender/Age	Medical History	Outcome
Intestinal obstruction	19	2	M/68	HTN	Recovered
Intestinal obstruction	22	2	M/66	Colostomy	Recovering
Intestinal obstruction	110 132	2	F/53	Obese, multiple prior abdominal surgeries	Recovered w/ sequelae
Intestinal obstruction	124	2	F/71	Polyps, Diverticulosis	Recovered
PE	21	1	M/59	None	Not recovered
PE	113	2	M/76	HTN, MV regurgitation, PVD	Recovered
PE	142	2	F/78	HTN,hypothyroidism	Not recovered
Convulsion	35	2	F/25	none reported	Recovered
Convulsion	252	2	M/69	none reported	Recovered
Convulsion	346	2	M/34	Irritable bowel	Not recovered
Thyroid Cancer	21	2	F/68	Seizure disorder	Not recovered
Thyroid Cancer	29	2	M/72	CAD, insomnia, eczema	Recovered
Thyroid Cancer	223	2	F/32	↑Cholesterol, insomnia, joint pains	Not recovered

Source: BLA 125419/0.15, Module 5.3.5.1.25.3.1, D182 WUNSOL Analysis Dataset

Reviewer comment: Subjects with intestinal obstruction had co-morbid conditions that likely predisposed them to the SAE. In contrast, the subjects with PE, convulsion and thyroid cancer did not have evidence of predisposing, co-morbid illnesses. Given the pro-inflammatory, and not well understood immune stimulatory nature of the AS03 adjuvant, it is conceivable that it may have contributed to or precipitated these events.

However, it's also conceivable that, due to the uneven (3:1) randomization, these 3:0 imbalances in the number of events could be due to chance alone.

All SAEs were deemed unrelated to vaccine by the investigator.

Reviewer comment: This reviewer concurs that no obvious relationship between the SAEs and vaccine administration exists with the following exceptions:

- Subject 3521, a 65-year-old female with a history of hypertension, experienced cerebrovascular accidents on Day 1 and Day 9, following the second dose of active study vaccine. Computed tomography (CT) scan after the second of these events revealed no evidence of hemorrhage and magnetic resonance imaging (MRI) revealed multiple punctuate ischemic infarcts of the right basal ganglia and paraventricular white matter. These events were considered resolved with sequelae 4 days and 10 days after onset, respectively.

Reviewer comment: Given the proximity of vaccination to the events and the lack of relevant clinical history other than hypertension, not reported to be poorly controlled or even requiring medication, this reviewer believes that vaccine relatedness cannot be ruled out.

- Subject 4060, a 59-year-old male, was diagnosed with a pulmonary embolism on Day 21, following 1 dose of active study vaccine; the event was treated with anti-coagulants and was categorized as ongoing, with further data pending. However, no further data have become available.

Reviewer comment: No history is provided that would indicate this subject had risk factors for pulmonary embolism. Based on the limited data provided, this reviewer believes that vaccine relatedness cannot be ruled out.

- Subject 6835, a 52 year old female with a history of corneal transplants 18 years prior, experienced a transplant rejection episode involving the left cornea manifested by eye pain and decreased visual acuity on Day 103 following the second dose of Q-Pan H5N1. The event was treated with ophthalmic glucocorticoids for 1 month and assessed as completely resolved in 50 days.

Reviewer comment: Most corneal transplant rejections occur in the first year after transplant, but have been reported to occur many years out, and in association with influenza vaccination.[14] Neither the Sponsor nor the investigator provided any evidence to support an alternative cause of this corneal transplant rejection.

- Subject 6907, a 63 year old male presented with right sided abdominal pain and was diagnosed with cecitis following exploratory surgery on Day 143 following two doses of Q-Pan. Pathology revealed inflammatory changes and thickening of the cecum. The event was assessed as resolved 8 days later.

Reviewer comment: Insufficient evidence is provided to rule out a diagnosis of inflammatory bowel disease and no alternate plausible cause was postulated.

PREGNANCIES

A total of 22 pregnancies, of which 17 received Q-Pan H5N1 and 5 received placebo, occurred through Day 364 follow-up. Of the 22 pregnancies, 3 occurred between Day 0 and Day 42. Two of those pregnancies (in Q-Pan H5N1 recipients) ended in elective abortions and one (in a placebo recipient) resulted in the home-birth of a healthy, full term baby, who was subsequently admitted to the hospital for bacterial pneumonia. Between Days 43 and 182 an additional 9 subjects became pregnant: 6 delivered healthy, full-term infants, 1 elected to terminate the pregnancy and 2 were lost to follow-up. Between Days 183 and 364, 10 subjects became pregnant: 4 subjects delivered healthy, full-term infants; 1 subject delivered a healthy infant after experiencing an SAE of pre-eclampsia; 2 subjects had spontaneous abortions; and 1 subject was lost to follow-up. Brief narratives for the subject with pre-eclampsia and the subjects experiencing spontaneous abortions are below. All three of these subjects received Q-Pan H5N1.

- Subject 2281 (Case ID B0565647A), a 20-year-old female with a history of migraines, had a spontaneous abortion on Day 311 (10 months) following 2 doses of active study vaccine. The subject refused to provide data sufficient to estimate the duration of gestation. The event was considered resolved the same day.
- Subject 5272 (Case ID B0559035A), a 32-year-old female with a history of obesity, asthma, smoking, 2 previous spontaneous abortions and 1 full term pregnancy (with cesarean section) with normal birth, had a last menstrual period approximately 6 months after the second of two doses of active vaccine. An obstetrical ultrasound showed no abnormalities 11 months after vaccine, but she developed gestational diabetes and subsequently experienced pre-eclampsia on Day 435 (>12 months post vaccine) following 2 doses of active study vaccine and was hospitalized. At approximately 37 weeks gestation, 15 months after dose 2 of the study drug, labor was induced with oxytocin and the subject vaginally delivered a healthy male infant.
- Subject 8080 (Case ID B0556034A), a 38-year-old female with a history of one previous full term pregnancy, had a spontaneous abortion after 8 weeks of pregnancy on Day 272 (9 months) following 2 doses of active study vaccine. The event was considered resolved the same day.

Reviewer comment: A similar proportion of subjects became pregnant in each of the treatment groups during the study. Most subjects delivered healthy, full-term babies. The three subjects who experienced adverse events during pregnancy all received Q-Pan H5N1. However, the narratives of Subject 8080 and 5272 suggest that these subjects were at least at somewhat increased risk for these common complications of pregnancy because of age and other co-morbid medical conditions, respectively. Subject 2281 did not provide enough information to make any assessment about her case. Based on the information provided, the events appear to be unrelated to the vaccine.

6.2.12.5 Adverse Events of Special Interest (AESI)

A theoretical concern exists that novel, immunostimulatory adjuvants may precipitate autoimmune disorders. In light of this concern adverse events of special interest/potentially immune-mediated disorders (AESI/pIMDs) defined as a subset of AEs including known autoimmune diseases as well as other inflammatory and/or neurologic disorders which may or may not have autoimmune etiologies were sought by querying the safety database for MedDRA Preferred Terms corresponding to the diagnoses among the following categories:

- Neuroinflammatory disorders (optic neuritis, multiple sclerosis, demyelinating disease, transverse myelitis, Guillain-Barre syndrome, myasthenia gravis, encephalitis, neuritis, Bell's palsy)
- Musculoskeletal disorders (systemic lupus erythematosus (SLE), cutaneous lupus, Sjogren's syndrome, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis, juvenile rheumatoid arthritis, polymyalgia rheumatica (PMR), reactive arthritis, psoriatic arthropathy, ankylosing spondylitis, spondylarthropathy)
- Gastrointestinal disorders (Crohn's disease, ulcerative colitis, celiac disease)
- Metabolic diseases (autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto thyroiditis, insulin-dependent diabetes mellitus [IDDM], Addison's disease)
- Skin disorders (psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases)
- Others (autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, antiphospholipid syndrome, vasculitis, temporal arteritis, Behcet's syndrome, pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune glomerulonephritis, autoimmune uveitis, autoimmune cardiomyopathy, sarcoidosis, Stevens-Johnson syndrome).

The WHO Global Advisory Committee on Vaccine Safety's (GACVS) has developed generally established criteria underpinning vaccine AE causality assessment for vaccine safety[15]. The criteria include consistency, strength of the association, specificity, temporal relation and to a lesser degree biological plausibility. GSK evaluated each of the AESI/pIMDs by applying the two GACVS criteria considered potentially applicable to individual cases specificity (a distinctive association with the vaccine rather than its occurring frequently, spontaneously or commonly in association with other external stimuli or conditions) and temporal relation (GSK defined as > 7days post vaccination).

A total of 15 subjects (14 Q-Pan H5N1 subjects, 1 placebo group) reported 16 AESI/pIMDS. Table 22 presents these cases with an assessment by GSK and this reviewer as to the existence of an alternate plausible cause.

Table 22: AESI/pIMDs by treatment group Q-Pan-002

Treatment	Diagnosis	Subject Age, Gender and Significant Past Medical History	AESI Onset Days Post Last Vaccine Dose	Dose	Alternate Plausible Cause per GSK	Alternate Plausible Cause per CBER	Additional Comments
Q-Pan H5N1	4th Nerve Palsy	77 y.o. M w/ hypertension	22	2	Y	N	GSK considered hypertension a likely cause. CBER considered a hyperinflammatory vaccine response a likely cause.
Q-Pan H5N1	PMR	84 y.o. F w/ leg pain.	82	2	_	N	PI considered fibromyalgia plausible after the data base lock though subject had new onset back pain 2 days after initial vaccine and new onset neck and shoulder pain and elevated ESR with a formal diagnosis of PMR.
Q-Pan H5N1	Autoimmune hepatitis (AIH)	28 y.o. M	40	2	Y	N	Mild to mod ↑liver enzymes, TBili – 2.6 post dose 2. AntiSMA+ 1:5120, Bx suggestive of AIH. Baseline sera tested after diagnosis and found to be antiSMA + at 1:320 with normal liver enzymes. The possibility that receipt of Q-PAN H5N1 may have precipitated AIH in a subject predisposed to develop this condition cannot be ruled out.
Q-Pan H5N1	Psoriasis	48 y.o. F	5	2	N	N	

Treatment	Diagnosis	Subject Age, Gender and Significant Past Medical History	AESI Onset Days Post Last Vaccine Dose	Dose	Alternate Plausible Cause per GSK	Alternate Plausible Cause per CBER	Additional Comments
Q-Pan H5N1	Erythema Nodosum	35 y.o. F	40	2	N	N	
Q-Pan H5N1	Facial Palsy	62 y.o. F	78	2	N	N	
Q-Pan H5N1	SLE*	54 y.o. F	137	2	N	-	Osteoporosis and hypothyroidism diagnosed on the same date
Q-Pan H5N1	Vasculitis* cutaneous	50 y.o. F	22	1	N	-	
Q-Pan H5N1	PMR Temporal arteritis	72 y.o. F w/ long standing hip pain	81 196	2 2	Y N	Y N	Hip pain symptoms unchanged post vaccination. New diagnoses of PMR applied. New symptoms diagnosed as temporal arteritis.
Q-Pan H5N1	Crohn's	36 y.o. F w/ abdominal pain and diarrhea	271	2	Y	Y	Symptoms antedated vaccine by 6 months
Q-Pan H5N1	Lumbar radiculitis	74 y.o F w/ vertebral disc disease	325	2	Y	Y	
Q-Pan H5N1	RA	44 y.o. F w/ Hashimotio's	277	2	Y	Y	RA is a common secondary autoimmune disease with Hashimoto's
Q-Pan H5N1	Psoriasis	37 y.o. F	39	2	Y	Y	Guttate psoriasis 8 days post streptococcal pharyngitis
Q-Pan H5N1	Rheumatoid Lung	72 y.o. F w/ rheumatoid arthritis	?	2	Y	Y	
Q-Pan H5N1	Celiac disease	49 y.o. F	161	2	Y	Y	
Placebo	Psoriasis	68 y.o. M	226	2	N	N	

*Disputed diagnoses, so no alterative plausible cause considered by GSK.
Source: Table generated by CBER clinical reviewer from information in BLA 125419/0, Module 5.3.5.1 D364 CSR pps 72-74 and D182 WUNSOL analysis data set,

None of the AESI/pIMD events were considered vaccine related by the investigator.

Reviewer comment: The case of SLE and cutaneous vasculitis were found in the D182 WUNSOL dataset and in the respective subject's CRF, but not in the -002 Clinical Study Reports or the D364 WUNSOL dataset. GSK reports that these diagnoses were later deleted (in the case of SLE) or changed (in the case of cutaneous vasculitis) by the investigator. However, this reviewer finds this explanation unsatisfactory without further supporting documentation or medical evidence given that:

- ***these are serious, chronic illnesses that generally require extensive clinical and laboratory evaluations often including biopsy, prior to making a diagnosis. Therefore, these diagnoses are less likely to be given presumptively, without convincing evidence of their existence***
- ***these diagnoses were changed 4 and 9 months respectively after they were made without comment.***

Source data for both subjects were requested as part of the CR letter.

Further, GSK and this reviewer disagreed on two cases associated with Q-Pan H5N1 use with regard to the presence of an alternate plausible cause, and GSK deferred to the judgment of the principal investigator (PI) in one case (which was in disagreement with this reviewer's assessment). Otherwise, for the remainder of the cases GSK and this reviewer agreed that either no alternative plausible cause existed (4 Q-Pan H5N1 cases, 1 placebo case) or an alternative plausible cause did exist (7 Q-Pan H5N1 cases). Even when alternate causes are considered, an imbalance persists in the Q-Pan H5N1 group that is out of proportion to the trial's 3:1 randomization: 10:1 if this reviewer's assessment of cases is considered; 4:1 if GSK/PI's assessment of cases is considered.

Of note, no cases of narcolepsy were reported in Q-Pan-002. However, two cases of hypersomnia were reported in subjects who received Q-Pan H5N1. In reviewing the Case Report Forms (CRFs) for these events, both subjects were found to be elderly women who experienced one day of "increased sleep". One was reported as severe intensity, occurring 19 days after the initial vaccination, and resolved without sequelae in 1 day; and the other was reported as mild intensity, occurring 21 days after the initial vaccination, and resolved without sequelae in 1 day.

Reviewer comment: These cases of hypersomnia are unlikely to be undiagnosed narcolepsy given the older age of the subjects, the transient nature of the symptoms and lack of reported recurrence of symptoms. However, in Q-Pan H5N1 002 insomnia occurred in Q-Pan subjects at a rate nearly 5 times that of placebo subjects, albeit at a relatively low frequency in both study groups (0.4% vs 0.09%). Additionally, new onset convulsions occurred in three subjects (0.08%) in the Q-Pan H5N1 arm versus no convulsions in the placebo arm (please refer to Sections 6.2.12.2 and 6.2.12.4 for further discussion of these events). Of note, both insomnia and convulsion can be early presentations of narcolepsy.

6.2.12.6 Clinical Test Results

No clinical laboratory evaluations were performed during this study.

Vitals signs were checked on Day 0, 21 and 42. No clinically relevant trends were observed in association with vaccination.

6.2.12.7 Dropouts and/or Discontinuations

Considering the entire study period (Day 0 to Day 379), 5 Q-Pan H5N1 subjects (0.1%) and 10 Placebo subjects (0.9%) experienced SAEs resulting in study discontinuation. The majority of discontinuations were due to fatal outcomes (4 out of 5 Q-Pan H5N1 subjects and 7 of 10 placebo subjects died). Table 23 presents the SAEs leading to withdrawal by treatment and subject.

Table 23: SAEs leading to withdrawal by subject and treatment group, Q-Pan-002

Subject ID	Treatment	SAE	Outcome
4253	Q-Pan H5N1	MI	Fatal
1663	Q-Pan H5N1	Ovarian CA w/ liver metastases	Fatal
6568	Q-Pan H5N1	Exacerbation of pre-existing liver disease and diabetes mellitus	Fatal
1041	Q-Pan H5N1	Septic arthritis, acute PE, lower spinal abscess and spinal cord compression	
4308	Q-Pan H5N1	Carcinoma	Fatal
6307	Placebo	Musculoskeletal pain	
6120	Placebo	Brain neoplasm	Fatal
3701	Placebo	Pneumococcal pneumonia	
6567	Placebo	Cardiomegaly secondary to COPD	Fatal
7937	Placebo	CVA and left carotic artery dissection	
3548	Placebo	Cardiac disorder	Fatal
5514	Placebo	Death NOS	Fatal
2856	Placebo	Gunshot wound	Fatal
7304	Placebo	Malignant neoplasm of the tongue	Fatal
8078	Placebo	Pneumonia	Fatal

Source: Table generated by CBER clinical reviewer from information in BLA 125419/0, Module 5.3.5.1 D364 CSR pps 69-70.

Reviewer comment: In both treatment groups, the number of withdrawals due to AEs was small, and the majority of withdrawals were due to fatalities deemed unrelated to vaccine. Overall these withdrawals have little impact on the safety assessment of the vaccine.

In conclusion, Q-Pan-H5N1-002, met its primary immunogenicity outcomes; the antigen sparing dose of 3.8 µg of HA H5N1 combined with $AS03_A$ elicited an immune response that fulfilled the CBER recommended criteria in both the younger (18-64 years) and older

(>64 years) age strata. Additionally, three consecutive lots of H5N1 antigen and three consecutive lots of AS03 adjuvant were shown to elicit consistent immunogenicity.

Regarding interim safety results, solicited local and general adverse reactions were reported at significantly higher frequencies by the Q-Pan H5N1 subjects than the placebo subjects. Similar to Q-Pan-H5N1-001 results, pain at the injection site was the most commonly reported solicited adverse reaction and was more commonly severe in the Q-Pan H5N1 subjects. Although rates of unsolicited AEs and SAEs were similar in both treatment groups, imbalances were noted with regard to specific events being reported at higher rates or exclusively in the Q-Pan H5N1 arm. Additionally, AESI/pIMDs were reported at a higher frequency in the Q-Pan H5N1 arm. Deaths were disproportionately reported within the placebo group. However, the subjects were elderly with several reported comorbidities making this imbalance likely a chance finding.

6.3 Trial #3

FLU Q-PAN H1N1-AS03-049 DB (116528) (Van Buynder) "A Test-negative Case-Control Study to Evaluate the Effectiveness of GSK Biologicals' Adjuvanted Monovalent Inactivated H1N1 Influenza Vaccine (Arepanrix) in Young Children (6 months to < 10 years of age)

6.3.1. Objectives

The primary objective was to evaluate the effectiveness of adjuvanted monovalent inactivated H1N1 influenza vaccine in young children (6 months to < 10 years of age) through the reduction in relative risk of laboratory-confirmed (via reverse transcriptase-polymerase chain reaction (RT-PCR)) influenza illness.

The secondary objective was to evaluate the effectiveness of partial vaccination with adjuvanted monovalent inactivated H1N1 influenza vaccine in young children (6 months to < 10 years of age) through the reduction in relative risk of laboratory-confirmed (via RT-PCR) influenza illness.

Reviewer comment: Although the vaccine assessed in this study contained the 2009 H1N1 pandemic influenza strain, this study provided an opportunity to assess the effectiveness of an adjuvanted pandemic influenza vaccine manufactured using the same process as that used to manufacture Q-Pan H5N1 prior to a licensing decision.

6.3.2 Design Overview

FLU Q-PAN H1N1-AS03-049 DB (from here on referred to as VanBuynder, et al study)[16] was a case-control test-negative, retrospectively designed, vaccine effectiveness (VE) observational study conducted by Dr. Van Buynder, et al. It was a community-based study comprising all children throughout New Brunswick, Canada, 6 months to less than 10 years of age, who had been tested for H1N1 infection at the central provincial laboratory. The study was conducted to determine the effectiveness of a single 0.25 mL dose of 1.9 mcg H1N1 vaccine adjuvanted with $AS03_B$ in children 36 months of

age and older. The study also sought to determine the need for a second dose of vaccine in children under 36 months of age.

The parents of all children, 6 months to <10 years of age in New Brunswick, Canada who were tested for H1N1, were contacted for a direct telephone interview to collect information on age, gender, hospitalization, indigenous status, prematurity, immunosuppression, coexisting medical conditions, previous seasonal flu vaccination, and recent pandemic vaccination. The study started on November 16, 2009 (3 weeks after the H1N1 vaccination campaign commenced to allow 14 days for the vaccine to take effect) and ended on December 2, 2009.

Reviewer comment: Please refer to Dr. Hector Izurietta's and Dr. Tsai-Lien Lin's, from the Office of Biostatistical Evaluation, epidemiological and statistical reviews for a comprehensive assessment of the strengths and weaknesses of this study design in general and the results of this study specifically in estimating the effectiveness of GSK's AS03 adjuvanted H1N1 vaccine.

Briefly, the case control test-negative design appears to be an appropriate and often used observational study design for estimating influenza vaccine effectiveness. However, the Van Buynder, et al study was retrospectively designed, which may have contributed to additional biases being introduced into the study e.g. not capturing the time between symptom onset and patient sample testing, which could have impacted the test results and consequently the study outcome. In theory, a prospectively designed trial might allow for additional time between the trial concept and trial conduct to thoroughly consider the data that need to be collected to more completely inform outcomes and endpoints.

6.3.3 Population

The study population included all children, 6 months to less than 10 years of age, throughout New Brunswick, who were tested for influenza from October 26, 2009 up to December 2, 2009.

Immunosuppressed children were excluded.

6.3.4 Study Treatments or Agents Mandated by the Protocol

AS03 adjuvanted Monovalent Inactivated H1N1 Influenza vaccine for 2009 pandemic H1N1 influenza (GSK's Arepanrix); 0.25 mL (1.9 mcg hemagglutinin), intramuscular administration.

Reviewer comment: Vaccination was provided as a public health intervention in response to the 2009 H1N1 influenza pandemic, independent of the study by Van Buynder, et al.

6.3.5 Directions for Use

Healthy subjects 36 months to < 10 years of age were to receive Arepanrix administered as a single 0.25 mL intramuscular dose (IM) equivalent to 1.9 mcg HA + $AS03_B$. Subjects 6 months to 35 months of age were to receive two IM doses (not less than 21 days apart), as were those 36 months to < 10 years with chronic medical conditions.

6.3.6 Sites and Centers

Not applicable. This was a case-control observational study.

6.3.7 Surveillance/Monitoring

Not applicable. This was a case-control observational study. No interventions occurred.

6.3.8 Endpoints and Criteria for Study Success

Laboratory confirmed influenza was the primary outcome and H1N1 vaccination status the primary exposure to assess VE after a single 0.25 mL dose.

Reviewer comment: The study assessed VE only. No safety or immunogenicity outcomes were assessed.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Reviewer comment: Please refer to Dr. Tsai-Lien Lin's review for a comprehensive discussion of the Statistical considerations and Statistical Analysis Plan (SAP).

Children were classified as "cases" if their respiratory sample was RT-PCR positive for H1N1 and "controls" if their respiratory sample was RT-PCR negative.

Children were considered "vaccinated" if they received Arepanrix at least 14 days prior to the onset of symptoms and "partially vaccinated" if they received Arepanrix at least 10 days prior to the onset of symptoms.

6.3.10 Study Population and Disposition

During the study period, a total of 116 children in the target age group were tested for H1N1 infection (Table 24). Of these, 25 subjects were excluded from the analysis due to inability to contact by phone (17 subjects), non-compliance with study inclusion/exclusion criteria (4 controls failed to meet the ILI qualification and 1 subject had immunosuppressive treatment), or refusal to participate (3 subjects).

Table 24: Study Population

Total Number of Children in New Brunswick (age 0 < 10 yrs)	~73,310
Total tested for H1N1 infection (~% of total population)	116 (0.16%)
Not contactable	17
Contactable	99
Excluded from the Contactable group	8
Included in the analysis	91
Cases	28
Controls	63

Source: BLA 125419, Module 5.3.5.4.3 CSR for FLU Q-PAN H1N1-AS03-049 DB (116528) (Van Buynder), Figure 1

Reviewer comment: The high rate of subjects excluded for undocumented reasons represented an important weakness in this study.

6.3.10.1 Populations Enrolled/Analyzed

The demographics and baseline characteristics of the study subjects are shown in Table 25.

Table 25: Summary of demographic characteristics (cohort for analysis of vaccine effectiveness)

Characteristic/Demographic	Subgroup	H1N1 Positive N=28 (%)	H1N1 Negative N=63 (%)
Age	6-35 months	9 (32.1)	28 (44.4)
	36-59 months	9 (32.1)	7 (11.1)
	60-119 months	10 (35.7)	28 (44.4)
Gender	Male	14 (50.0)	33 (52.4)
First Nation/Aboriginal	Yes	4 (14.3)	5 (7.9)
Hospitalized	Yes	5 (17.9)	21 (33.3)
Pre-existing medical condition	Yes	4 (14.3)	15 (23.8)
Received a dose of H1N1 vaccine pre-diagnosis	< 10 days	6 (21.4)	8 (12.7)
	< 14 days	7 (25.0)	13 (20.6)
	14 days or more	0 (0.0)	24 (38.1)
	Vaccinated after onset*	1 (3.6)	8 (12.7)
	No valid immunizations**	21 (75.0)	26 (41.3)
Received seasonal influenza vaccine in 2009	Yes	5 (17.9)	12 (19.0)

* Immunization date is after onset date, range of these immunizations was between 3 to 36 days post-diagnosis
** Either no immunizations or invalid immunization (i.e., vaccinated after onset), the number of H1N1 positives with no immunizations was 20, the number of H1N1 negatives with no immunizations was 18.
§ Fisher's exact test
Source: BLA 125419, Module 5.3.5.4.3 CSR for FLU Q-PAN H1N1-AS03-049 DB (116528) (Van Buynder), Table 1

Reviewer comment: A comparison of cases versus controls showed that the 36-59 month age group was more likely to have cases than controls (32.1% vs. 11.1% respectively), and that controls had a higher hospitalization rate (33.3%) than the cases (17.9%). Cases and controls appeared to be similar with respect to all other demographic and baseline characteristics.

6.3.11.1 Analyses of Primary Endpoint(s)

Overall, 26% (24/91) of study subjects were vaccinated at least 14 days prior to symptom onset. All these subjects were controls. No case subjects were vaccinated at least 14 days before symptom onset, resulting in a VE of 100%. The proportion of case subjects regarded as vaccinated is 0% versus 38.1% (24/63) in control subjects. VE is statistically significant for subjects overall (100%, CI 79.5–100%), and for subjects 6 months to <5 years of age (100%, CI 44–100%) and 5 to <10 years of age (100%, CI 56.6–100%), considered separately. The small number of subjects marginally prevented a statistically significant vaccine effectiveness estimate to be reached for subjects 6 months to <3 years of age (VE = 100%, CI -25.7 to 100%) but did permit one for subjects 3 to <10 years of age (VE = 100%, CI 75.5–100%).

Estimated VEs for subjects vaccinated at least 14 days prior to disease onset for all study subjects and for different age groupings are presented in Table 26.

Table 26: Van Buynder et al. study: vaccine effectiveness (for subjects vaccinated at least 14 days prior to disease presentation)

Age	Vaccination status	*H1N+	*H1N1-	Point Estimate	Vaccine Effectiveness (VE) 95% CI & P-value
Children 6 months to < 10 years	Vaccinated Not vaccinated Total	0 28 28	24 39 63	VE = 100%	79.5–100% (P =0.0001)
Children 6 months to < 5years	Vaccinated Not vaccinated Total	0 18 18	10 25 35	VE = 100%	44.0–100% (P <0.01)
Children 5 years to <10 years	Vaccinated Not vaccinated Total	0 10 10	14 14 28	VE = 100%	56.6–100% (P =0.004**)
Children 6 months to < 3 years	Vaccinated Not vaccinated Total	0 9 9	8 20 28	VE = 100%	-25.7–100% (P =0.08**)
Children 3 years to < 10 years	Vaccinated Not vaccinated Total	0 19 19	16 19 35	VE = 100%	75.5–100% (P <0.001**)

* H1N1+ (presence of H1N1 infection) and H1N1- (absence of H1N1 infection) by RT-PCR assay.
** Fisher's exact one-sided test statistic used as an expected cell size <5 present. Other probabilities were computed with the chi-square test.

Source: BLA 125419, Module 5.3.5.4.3 CSR for FLU Q-PAN H1N1-AS03-049 DB (116528) (Van Buynder), Table 2

A second analysis looking at VE when partially vaccinated subjects (at least 10 days prior to symptom onset) were included resulted in an additional case in each of the study arms making it a total of 1 case in the vaccinated arm and 29 cases in the unvaccinated arm. This resulted in a VE of 95%, 95% CI = 66-99.4%.

Reviewer comment: Based on the reported results, a single dose of 0.25 mL of Arepanrix appears to be effective against H1N1 virus. However, Drs. Lin and Izurietta outline a number of limitations of this study in their reviews including methodologic design issues that may introduce selection bias and fail to provide critical information, small sample size and a large percentage (22%) of subjects excluded from analysis for reasons that were unlikely to occur at random. These limitations result in a high degree of uncertainty about the estimated VE against H1N1. In addition, this reviewer has concerns that even a well designed, well conducted H1N1 efficacy trial of an H1N1 vaccine would not be suitable as the pivotal study on which to base an inference of H5N1 vaccine effectiveness given the inherent, important differences between H1N1 and H5N1.

7. INTEGRATED OVERVIEW OF EFFICACY

Reviewer Comment: As previously stated, no efficacy trials of Q-Pan H5N1 have been or can be conducted given that H5N1 virus is not currently widely circulating and only rarely causes human disease. The two pivotal Q-Pan H5N1 immunogenicity and safety studies and the proposed Q-Pan H1N1 vaccine effectiveness study are presented and discussed individually above in Section 6. The Sponsor, as agreed upon in consultation with CBER, did not provide an Integrated Summary of Efficacy.

7.1.11 Efficacy Conclusions

Reviewer comment: The immunogenicity data from the two pivotal trials, Q-Pan-H5N1-001 and Q-Pan-H5N1-002, demonstrated that an antigen sparing dose of 3.75 ug of Q-Pan H5N1 vaccine achieved an adequate HI antibody response (based on CBER's suggested immunogenicity criteria[1]) after two doses of vaccine. Based on these data and these assumptions about HI antibody titers, this vaccine is reasonably likely to be effective against disease caused by the specific strain contained in the vaccine. No data are currently available, however, nor are there likely to be any data prior to an H5N1 pandemic that will provide direct evidence that this vaccine will be effective against the actual pandemic H5N1 virus.

8. INTEGRATED OVERVIEW OF SAFETY

GSK performed two Integrated Summaries of Safety (ISS). Table 27 gives an overview of the studies included in both ISS-1 and ISS-2.

Table 27: Overview of studies included in ISS-1 and ISS-2

All listed studies were included in ISS-2. Studies included in ISS-1 are designated with a double asterisk (**).

Study number(s) (Country)	Study period (FSFV-LSLV)	Age range (years)	Majority race	Blinding	Influenza Vaccines Utilized* (N vaccinated)	Control (N vaccinated)
Q-Pan-H5N1-001 (United States)**	3.75 formulations: 02 Aug 2007 21 Mar 2008 1.9 formulations: 08 Apr 2008 24 Oct 2008	18-64	White/ Caucasian	Observer-blind	Q H5N1 3.75 $AS03_B$ 2D (21d) = 151 D H5N1 3.75 $AS03_B$ 2D (21d) = 148 Q H5N1 3.75 $AS03_A$ 2D (21d) = 152 D H5N1 3.75 $AS03_A$ 2D (21d) = 151 Q H5N1 1.9 $AS03_B$ 2D (21d) = 50 Q H5N1 1.9 $AS03_A$ 2D (21d) = 50	Q H5N1 3.75 2D (21d) = 78
Q-Pan-H5N1-002 (United States)**	28 Jan 2008 19 Mar 2009	≥ 18	White/ Caucasian	Observer-blind	Q H5N1 3.75 $AS03_A$ 2D (21d) = 3422	Saline Placebo = 1139
Q-Pan-H5N1-005 (United States)	15 Jul 2008 18 Feb 2009	≥ 18	White/ Caucasian	Observer-blind	Q H5N1 3.75 $AS03_B$ 1D = 239 Q H5N1 3.75 $AS03_A$ 1D = 119 Q H5N1 7.5 $AS03_B$ 1D = 241 Q H5N1 7.5 $AS03_A$ 1D = 122	Saline Placebo = 120
Q-Pan-H5N1-009 (Canada)	5 Jun 2008 9 Jan 2009	18-64	White/ Caucasian	Open	Q H5N1 3.75 $AS03_A$ 2D (21d) = 78 Q H5N1 3.75 $AS03_A$ 2D (14d) = 78 Q H5N1 3.75 $AS03_A$ 2D (7d) = 78 Q H5N1 3.75 $AS03_A$ 2D (0d) = 78	None
Q-Pan-H5N1-011 (Japan)	1 Sep 2008 7 Mar 2009	20-64	Asian	Open	Q H5N1 3.75 $AS03_A$ 2D (21d) = 100	None
D-Pan-H5N1-002/030** (Hong Kong, Singapore, Taiwan, Thailand)	24 Mar 2007 10 June 2008	18-60	Asian	Observer-blind	D H5N1 3.75 $AS03_A$ 2D (21d) = 961	D H5N1 3.75 2D (21d) = 245
D-Pan-H5N1-007** (Belgium)	27-Mar-2006 15-Jun-2006	18-60	White/ Caucasian	Observer-blind	D H5N1 30 $AS03_A$ 2D (21d) = 49 D H5N1 15 $AS03_A$ 2D (21d) = 50 D H5N1 7.5 $AS03_A$ 2D (21d) = 50 D H5N1 3.75 $AS03_A$ 2D (21d) = 51	D H5N1 30 2D (21d) = 50 D H5N1 15 2D (21d) = 50 D H5N1 7.5 2D (21d)= 50 D H5N1 3.75 2D (21d) = 50
D-Pan-H5N1-008/011** (Estonia,France, Germany)**	02 May 2006 21 Feb 2007	≥ 18	White/ Caucasian	Observer-blind	D H5N1 15 $AS03_A$ 2D (21d) = 3801	*Fluarix*/saline placebo = 1269

Study number(s) (Country)	Study period (FSFV-LSLV)	Age range (years)	Majority race	Blinding	Influenza Vaccines Utilized* (N vaccinated)	Control (N vaccinated)
D-Pan-H5N1-010/021** (Belgium, Italy)	02 Mar 2007 06 Mar 2008	> 60	White/ Caucasian	Open	D H5N1 7.5 AS03$_A$ 2D (21d) = 159 D H5N1 3.75 AS03$_A$ 2D (21d) = 165	D H5N1 7.5 2D (21d)= 52 D H5N1 3.75 2D (21d) = 61
D-Pan-H5N1-012 (Germany)**	05 Feb 2007 20 Oct 2008	18-60	White/ Caucasian	0pen	D H5N1 3.75 AS03$_A$ 2D (21d) = 512	None
D-Pan-H5N1-041 (Germany)	15 Nov 2008 08 Nov 2007	18-60	White/ Caucasian	Observer-blind	D H5N1 3.75 AS03$_A$ 2D (21d) = 320	None
Q-Pan-H1N1-001 (US, Canada)	19 Oct 2009 07 Dec 2010	>18	White/ Caucasian	Observer blind	Q H1N1 3.75 AS03$_A$ 2D (21d) = 222 Q H1N1 3.75 AS03$_A$ 1D = 221 Q H1N1 1.9 AS03$_B$ 2D (21d) = 114 Q H1N1 1.9 AS03$_B$ 1D = 112	Q H1N1 15 1D = 223 Q H1N1 7.5 2D (21d) = 115 Q H1N1 7.5 1D = 111 Q H1N13.75 2D (21d) = 222
Q-Pan-H1N1-002 (US, Canada)	13 Nov 2009 01 Feb 2011	>18	White/ Caucasian	Observer blind	Q H1N1 3.75 AS03$_A$ 1D = 2025	Q H1N1 15 1D = 2023
Q-Pan-H1N1-016 (Japan)	13 Oct2009 19 Apr 2010	20 - 64	Asian	Open	Q H1N1 3.75 AS03$_A$ 2D (21d) = 100	None
Q-Pan-H1N1-019 (US, Canada)	28 Oct 2009 29 Dec 2010	19 - 40	White/ Caucasian	Observer blind	*FluLaval* followed by 2D of Q H1N1 3.75 AS03$_A$ (21d) = 104 *FluLaval* + Q H1N1 3.75 AS03$_A$ followed by 1D of Q H1N1 3.75 AS03$_A$ (21d) = 100 2D of Q H1N1 3.75 AS03$_A$ (21d) followed by *FluLaval* = 102	2D of Q H1N1 15 (21d) followed by *FluLaval* = 101 *FluLaval* + Q H1N1 15 followed by 1D of Q H1N1 15 (21d) = 102 *FluLaval* followed by 2D of Q H1N1 15 (21d) = 102
D-Pan-H1N1-007 (Belgium)	08 Sep 2009 28 Sep 2010	18 - 60	White/ Caucasian	Open	D H1N1 3.75 AS03$_A$ 2D (21d) = 64	D H1N1 15 2D (21d) =66
D-Pan-H1N1-008 (Belgium)	08 Sep2009 23 Sep 2010	>18	White/ Caucasian	Open	D H1N1 3.75 AS03$_A$ 2D (21d) = 138 D H1N1 3.75 AS03$_A$ 1D = 102	None
D-Pan-H1N1-017 (Germany, France)	12 Oct 2009 04 Nov 2010	18 - 60	White/ Caucasian	Double blind	Q H1N1 3.75 AS03$_A$ 2D (21d) = 167 D H1N1 3.75 AS03$_A$ 2D (21d) = 167	None

Study number(s) (Country)	Study period (FSFV-LSLV)	Age range (years)	Majority race	Blinding	Influenza Vaccines Utilized* (N vaccinated)	Control (N vaccinated)
D-Pan-H1N1-018 (Sweden)	12 Sep 2009 23 Sep 2010	> 60	White/ Caucasian	Open for the H1N1 vaccine,observer-blind for *Fluarix*/saline placebo	D H1N1 3.75 AS03$_A$ 2D (21d) + *Fluarix* at dose 1/saline placebo at dose 2 = 84 D H1N1 3.75 AS03$_A$ 2D (21d) + saline placebo at dose 1/*Fluarix* at dose 2 = 84	None
D-Pan-H1N1-020 (Denmark)	08 Sep 2009 08 Oct 2010	> 60	White/ Caucasian	Single blind	D H1N1 3.75 AS03$_A$ 2D (21d) then *Fluarix* = 72 *Fluarix* then D H1N1 3.75 AS03$_A$ 2D (21d) = 73	None
D-Pan-H1N1-021 (Germany)	11 Aug 2009 30 Aug 2010	18-60	White/ Caucasian	Observer blind	D H1N1 3.75 AS03$_A$ 2D (21d) = 64	D H1N1 15 2D (21d) =66
D-Pan-H1N1-022 (France)	14 Sep 2009 30 Apr 2010	>18	White/ Caucasian	Open	D H1N1 1.9 AS03$_A$ 2D (21d) = 184 D H1N1 1.9 AS03$_A$ 2D (6m) = 122	None
D-Pan-H1N1-024 (Germany)	14 Oct 2009 09 Nov 2010	>18	White/ Caucasian	Double blind (with respect to D H1N1 lots)	D H1N1 3.75 AS03$_A$ 2D (21d) = 148 D H1N1 3.75 AS03$_A$ 1D = 152	None
D-Pan- H1N1-033 (Belgium)	07 Oct 2009 26 Oct 2010	18-60	White/ Caucasian	Observer-blind	D H1N1 3.75 AS03$_A$ 2D (21d) = 65	D H1N1 3.75 2D (21d) =66

Source: BLA 125419, Module 5.3.5.3.28, Integrated summry of safety (H5N1+H1N1) Table 1

8.1 Safety Assessment Methods

In both the Q-Pan and D-Pan programs, the principal tool for collection of safety data was the diary card. A diary card was provided to each subject to record specific solicited events for 7 days following each vaccination. Unsolicited events and MAEs were collected during site visits or phone interviews for various lengths of time but for no longer than 6 months and SAEs were collected through 6 months.

Reviewer comment: For products with novel adjuvants CBER has been requesting safety follow-up of SAEs, MAEs and AESI/pIMDS for at least 1 year post the last vaccination. This is due to the concern that novel adjuvants, which may non-specifically stimulate the immune system, may either induce or exacerbate autoimmunity that may initially present non-specifically leading to a time lag between initial symptoms and definitive diagnosis. Ideally, any integrated safety assessments would evaluate at least one year worth of safety data. However, given the various study designs of the trials included in the ISS-1 assessment, only six months of data were available for subjects enrolled in some of the studies. This is a limitation of this integrated safety analysis.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The initial ISS (ISS-1) was conducted in 2009 in which data from 8 D-Pan H5N1 or Q-Pan H5N1, controlled and uncontrolled adult studies including 12,281 participants were pooled. A total of 9,873 subjects in the pooled dataset received an H5N1+AS03 vaccine while 2,408 subjects received either an active (Fluarix or unadjuvanted H5N1) or saline placebo control. ISS-1 was further divided into Analysis 1 which included the 2 large, saline placebo or Fluarix controlled studies, Q-Pan-H5N1-002 and D-Pan-H5N1-008, and Analysis 2 which included all the ISS-1 studies designated in Table 27.

ISS-2 was conducted to extend the data on less common and more medically serious events (MAEs, SAEs and pIMDs) through the evaluation of all available data from adult recipients of GSK's adjuvanted D-Pan and Q-Pan H5N1 and H1N1 vaccines. Subjects included in ISS-1 also were included in ISS-2. Safety data from 24 Q-Pan and D-Pan H5N1 and H1N1 controlled and uncontrolled studies (Table 28) were pooled including 22,521 adult subjects. A tiered approach was taken in the ISS-2 evaluation: expanding from the most relevant and clean data (controlled, adjuvanted H5N1 trials) to uncontrolled H5N1 plus H1N1 data. GSK performed multiple pre-planned and *post hoc* analyses. A total of 16,160 received H5N1 or H1N1 + AS03 vaccine and 6,361 received an active (unadjuvanted H5N1, Fluarix, or Flulaval) or saline placebo control. GSK also examined data from booster studies involving 3,158 subjects. However, because of widely varying conditions and treatments in these booster studies the results of the analysis are confined to description of the pIMDs in these subjects.

Tables 28 and 29 presents the safety follow-up periods for all of the studies included in the ISS-1 and -2 analyses.

Table 28: Follow-up periods for adverse events in each of the primary vaccination trials included in the Q-PAN and D-PAN integrated summary of safety

Study number(s)	MAEs	SAEs	pIMDs *	AESIs *
Q-PAN-H5N1-001/010	D0-D182	D0-D182	-	-
Q-PAN-H5N1-002	D0-D384	D0-D384	-	-
Q-PAN-H5N1-005	D0-D182	D0-D182	D0-D182	-
Q-PAN-H5N1-009	D0-D182	D0-D182	-	-
Q-PAN-H5N1-011	D0-D182	D0-D182	-	-
D-PAN-H5N1-002/030	D0-D51	D0-D182**	-	-
D-PAN-H5N1-007	D0-D51	D0-D182	-	-
D-PAN-H5N1-008/011	D0-D51	D0-D182	-	-
D-PAN-H5N1-010	D0-D51	D0-D182	-	-
D-PAN-H5N1-012	D0-D51	D0-D182	-	-
D-PAN-H5N1-041	D0-D51	D0-D182	-	D0-D182
Q-PAN-H1N1-001	D0-D385	D0-D385	D0-D385	-
Q-PAN-H1N1-002	D0-D385	D0-D385	D0-D385	-
Q-PAN-H1N1-016	D0-D84	D0-D182	D0-D182	-
Q-PAN-H1N1-019	D0-D406	D0-D406	D0-D406	-
D-PAN-H1N1-007	D0-D84	D0-D364	D0-D364	-
D-PAN-H1N1-008	D0-D84	D0-D364	D0-D364	-
D-PAN-H1N1-017	D0-D84	D0-D364	D0-D364	D0-D364
D-PAN-H1N1-018	D0-D84	D0-D364	D0-D364	-
D-PAN-H1N1-020	D0-D84	D0-D364	D0-D364	D0-D364
D-PAN-H1N1-021	D0-D84	D0-D364	D0-D364	D0-D364
D-PAN-H1N1-022	D0-D84	D0-D364	D0-D364	D0-D364
D-PAN-H1N1-024	D0-D84	D0-D364	D0-D364	D0-D364
D-PAN-H1N1-033	D0-D84	D0-D364	D0-D364	-

* When specific follow-up for pIMDs or AESIs was not planned in the protocol (studies indicated as "-"), the database was queried within the same interval as MAEs.
** follow-up time for the control test article recipients was limited to 182 days; adjuvanted vaccine recipients were divided into 3 cohorts: the first received a booster 6 months after the primary course, the second at 24 months after the primary course and the third at 36 months after the primary course; thus the follow-up period for some adjuvanted vaccine recipients extended to 36 months.
Source: BLA 125419/0, Module 5.3.5.3.28 Integrated Summary of Safety, Table 4

Table 29: Follow-up periods for adverse events in each of the booster vaccination trials included in the Q-PAN and D-PAN integrated summary of safety

Study number(s)	MAEs	SAEs	pIMDs *	AESIs *
Q-PAN-H5N1-005	D0-D182**	D0-D909	D0-D909	D0-D909
Q-PAN-H5N1-010	D0-D182	D0-D182	-	-
D-PAN-H5N1-012	D0-D50	D0-D182	–	–
D-PAN-H5N1-015	D0-D51	D0-D182	-	-
D-PAN-H5N1-030	D0-D51	D0-D182	-	-
D-PAN-H1N1-038	D0 D29	D0-D1095	D0-D1095	D0-D1095

*When specific follow-up for pIMDs or AESIs was not planned in the protocol (studies indicated as "-"), the database was queried within the same interval as MAEs.
**Study period until the next vaccination
Source: BLA 125419/0, Module 5.3.5.3.28 Integrated Summary of Safety, Table 5

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The demographics of the pooled safety populations resembled that of the pivotal clinical trials consisting of predominately white (82%) and female (56%) subjects with a mean age of 43 years. Unlike the pivotal trials, the predominant non-white racial group was of Asian descent (as opposed to black) due to the inclusion of more than 1,000 subjects from study D-Pan-H5N1-002/030 conducted exclusively in Asia.

8.2.3 Categorization of Adverse Events

All verbatim terms for spontaneously reported AE were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the resulting system organ class (SOC) and preferred terms (PTs) were used for tabulation of incidence rates.

Reviewer comment: In general, MedDRA tends to "split" closely related events likely leading to greater specificity around an event but less sensitivity (e.g., abdominal pain is split into upper abdominal pain, lower abdominal pain, right upper quadrant abdominal pain, etc) and applicants tend to code in accordance with this splitting. For the purposes of this review and analysis of events "split" events were "lumped" and assessed for trends. None were noted.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The ISS analyses have several recognized limitations including pooling data from studies with:

- Vaccines manufactured by different processes.
- Vaccines containing different HA antigen subtypes (H5N1 and H1N1)
- Randomization ratios that result in 2.5 – 4 times as many subjects receiving H5N1 or H1N1 adjuvanted vaccine as compared to subjects receiving placebo or control vaccine.
- Different antigen content (1.9 to 30 µg) and adjuvant content (half-dose $AS03_B$) from the to-be-licensed formulation used in a limited number of subjects.
- Variable safety follow-up periods.

Reviewer comment: The goal of the ISS analyses was to gather as much safety data on AS03 adjuvanted monovalent pandemic vaccines as possible recognizing all the above limitations and the likelihood that background noise and limited long-term follow-up might falsely dilute or fail to identify a safety signal.

8.4 Safety Results

Safety findings from ISS-1:

- Local reactogenicity, especially pain, was increased in recipients of H5N1+AS03. The rates of other local events and general solicited symptoms were increased as well in recipients of H5N1+AS03, but not as commonly as pain. Mild temperature elevations were experienced by twice as many H5N1+AS03 recipients as compared to control subjects.
- Objective lymphadenopathy was clinically mild and reported at a similar low rate in both the H5N1+AS03 and control groups.
- MAEs and SAEs were reported at similar rates by both H5N1+AS03 and control groups.
- H5N1+AS03 recipients reported more unsolicited AEs (preferred terms)
    - In Analysis 1 (controlled H5N1+AS03 studies) these events were: injection site reaction, injection site warmth, injection site pruritus, malaise, nausea, cystitis and insomnia. The rates and relative risks are presented in the table below.

Table 30: Analysis 1 - Percentage of subjects reporting the occurrence of unsolicited adverse events classified by MedDRA Primary System Organ Class and Preferred Term from Day 0 to Day 50 after the first dose or from Day 0 to Day 29 after second dose and estimated relative risks (Total vaccinated cohort, ISS-1)

Primary System Organ Class	Preferred Term	H5N1/AS03 N=7,224 % (95% CI)	Control N=2,408 % (95% CI)	Relative Risk H5N1/AS03 over control (95% CI)
Gastrointestinal disorder	Nausea	2.4 (2.1, 2.8)	1.5 (1.0, 2.1)	1.62 (1.13, 2.39)
General disorders and administration site conditions	Injection site pruritus	1.8 (1.5, 2.1)	0.6 (0.3, 1.0)	3.12 (1.79, 5.86)
General disorders and administration site conditions	Injection site reaction	0.8 (0.6, 1.0)	0.2 (0.1, 0.5)	3.06 (1.32, 8.69)
General disorders and administration site conditions	Injection site warmth	1.7 (1.4, 2.0)	0.2 (0, 0.4)	10.09 (3.84, 37.61)
General disorders and administration site conditions	Malaise	1.0 (0.8, 1.2)	0.2 (0.1, 0.5)	3.89 (1.70, 10.97)
Infections and infestations	Cystitis	0.3 (0.2, 0.4)	0 (0, 0.2)	6.67 (1.07, 276.54)
Psychiatric disorders	Insomnia	0.5 (0.4, 0.7)	0.1 (0, 0.4)	4.22 (1.34, 21.39)

Source: BLA 125419/0, Module 5.3.5.3.28 Integrated Summary of Safety (H5N1), Table 16

- In Analysis 2, which included controlled and uncontrolled H5N1+AS03 studies, cystitis was no longer observed at an increased incidence over control (RR < 1), and one additional PT was added, dizziness.

Table 31: Analysis 2 - Percentage of subjects reporting the occurrence of unsolicited adverse events classified by MedDRA Primary System Organ Class and Preferred Term from Day 0 to Day 50 after the first dose or from Day 0 to Day 29 after second dose and estimated relative risks (Total vaccinated cohort, ISS-1)

Primary System Organ Class	Preferred Term	H5N1/AS03 N=9,873 % (95% CI)	Control N=2,408 % (95% CI)	Relative Risk H5N1/AS03 over control (95% CI)
Gastrointestinal disorder	Nausea	2.4 (2.1, 2.7)	1.5 (1.0, 2.1)	1.62 (1.13, 2.39)
General disorders and administration site conditions	Injection site pruritus	1.6 (1.4, 1.9)	0.6 (0.3, 1.0)	3.12 (1.79, 5.86)
General disorders and administration site conditions	Injection site reaction	0.7 (0.6,0.9)	0.2 (0.1, 0.5)	3.06 (1.32, 8.69)
General disorders and administration site conditions	Injection site warmth	1.3 (1.1, 1.6)	0.2 (0, 0.4)	10.09 (3.84, 37.61)
General disorders and administration site conditions	Malaise	0.9 (0.7, 1.1)	0.2 (0.1, 0.5)	3.89 (1.70, 10.97)
Nervous system disorders	Dizziness	1.5 (1.3, 1.7)	1.0 (0.6, 1.4)	1.56 (1.00, 2.54)
Psychiatric disorders	Insomnia	0.5 (0.4, 0.7)	0.1 (0, 0.4)	4.15 (1.34, 20.77)

Source: BLA 125419/0, Module 5.3.5.3.28 Integrated Summary of Safety (H5N1), Table 17

Reviewer comment: Injection site reactions, nausea and malaise, which are solicited adverse reactions, are expected and were reported at increased rates relative to controls in the pivotal clinical trials.

Both dizziness and insomnia, though unexpected adverse events, were reported to have onsets clustered around the time of vaccination (the day of or 1-2 days post vaccination) and were also reported at similarly increased rates in Q-Pan-H5N1-002. Additionally, insomnia is an AE of interest given the narcolepsy signal associated with Pandemrix use and the fact that insomnia can be an early presentation of narcolepsy.

Cystitis was only observed in analysis 1, was only observed in female subjects, appeared to occur randomly throughout the follow-up period and had only a slightly elevated relative risk (lower bound 95% CI, 1.06). All of these observations make it less likely that observed cases of cystitis are related to receipt of the AS03 adjuvanted vaccine.

The other imbalances, both expected and unexpected, appear to have the criteria of temporal relation to the vaccine and consistency of increased reporting rate with the vaccine as criteria increase the likelihood that the vaccine is causally related to the event.

- All reported pIMDs were in the H5N1+AS03 group (n=17)
  - Five of these events were captured in Q-Pan-H5N1-002: PMR (n=2) and 1 each cranial nerve IV palsy, psoriasis, and erythema nodosum.
  - Twelve events were unique to the ISS-1 and included facial palsy (n=3), PMR (n=2), and 1 case each of Grave's disease, uveitis, facial paresis, neuritis, multiple sclerosis (MS), scleroderma and psoriasis.

Table 32 presents the ISS-1 AESI/pIMDs with an assessment of alternative plausible cause by GSK and this reviewer.

Table 32: ISS-1 AESI/pIMDs

Treatment	Diagnosis	Subject Age, Gender and Significant Past Medical History	AESI Onset Days Post Last Vaccine Dose	Dose	Alternate Plausible Cause per GSK	Alternate Plausible Cause per CBER	Comments
Q/D-Pan+AS03	Facial paresis	38 y.o. F w/ h/o HA on the day of vaccination	0 (8 hrs)	1	Y	N	GSK believes time to event too short and patient successfully rechallenged. Subject continued to have symptoms for 39 days (19 days post Dose 2) i.e up to and through the second dose, which is inconsistent with a s a positive rechallenge
Q/D-Pan+AS03	Neuritis	48 y.o. F no relevant PMH	0	1	Y	N	Severe arm pain within hrs of injection. Persisted for 83 days. CBER considered the diagnosis as compatible with brachial plexus neuritis
Q/D-Pan+AS03	PMR	59 y.o. F w/ h/o fibromyalgia	13	2	N	N	Qualitatively worse symptoms, ↑CRP, ↑ESR. Treated w/ steroids w/ relief of symptoms
Q/D-Pan+AS03	PMR	70 y.o. F w/out h/o rheumatic dz	38	2	N	N	New onset scapular and pelvic girdle pain
Q/D-Pan+AS03	Grave's Disease	40 y.o. F w/ h/o Chronic Hep C and depression	33	2	N	N	Antithyroglobulin ab were positive 22 months post diagnoisis. Tx'd w/ total thyroidectomy.
Q/D-Pan+AS03	Uveitis	47 y.o. F no relevant PMH	91	2	N	N	
Q/D-Pan+AS03	PMR	59 y.o. F w/ h/o fibromyalgia	13	2	N	N	Qualitatively worse symptoms, ↑CRP, ↑ESR. Treated w/ steroids w/ relief of symptoms

Treatment	Diagnosis	Subject Age, Gender and Significant Past Medical History	AESI Onset Days Post Last Vaccine Dose	Dose	Alternate Plausible Cause per GSK	Alternate Plausible Cause per CBER	Comments
Q/D-Pan+AS03	PMR	70 y.o. F w/out h/o rheumatic dz	38	2	N	N	New onset scapular and pelvic girdle pain
Q/D-Pan+AS03	Grave's Disease	40 y.o. F w/ h/o Chronic Hep C and depression	33	2	N	N	Antithyroglobulin antibodies were positive 22 months post diagnosis. Treated w/ total thyroidectomy.
Q/D-Pan+AS03	Uveitis	47 y.o. F no relevant PMH	91	2	N	N	

Source: Table generated by CBER clinical reviewer from information in BLA 125419/0, Module 5.3.5.3.28 Integrated Summary of Safety (H5N1), Section 4.3.2, pps 43-52

Reviewer comment: This reviewer found no evidence of an alternate plausible cause for any of the 12 unique AESI/pIMDs identified in ISS-1 associated with the H5N1 + AS03 group. This suggests that, in these subjects, receipt of AS03-containing H5N1 vaccines may have been responsible for precipitating or exacerbating possible immune-mediated diseases.

In the ISS-2 there were an additional 36 AESI/pIMDs identified in the AS03 group for a total of 53 pIMD events in the ISS compared to a total of 8 reported pIMDs in the ISS control groups (Table 33).

Table 33: All pIMDs identified in the ISS - 2 (ISS1 included)

Primary SOC	Preferred Term	N	# AS03	# Control	GSK # of AS03 cases without alternate plausible cause	CBER # of AS03 cases without alternate plausible cause
Blood and lymphatic system disorders	Thrombocytopenia	3	3	0	1	1
Endocrine disorders	Autoimmune thryoiditis	3	3	0	1	1
	Basedow's disease	1	1	0	1	1
Eye disorders	Uveitis	2	1	1	1	1
	Optic neuritis	1	1	0	0	1
Gastrointestinal disorders	Celiac disease	3	2	1	0	0
	Ulcerative colitis	2	2	0	2	2
	Crohn's disease	1	1	0	0	0
Hepatobiliary disorders	Autoimmune hepatitis	1	1	0	0	1
Immune system disorders	Systemic Lupus Erythematosus	1	1	0	1	1
Musculoskeletal and connective tissue disorders	Ankylosing spondylitis	1	1	0	1	1
	Rheumatoid arthritis	1	1	0	1	1
Nervous system disorders	Polymyalgia rheumatica	7*	6	1	3	4
	Scleroderma	1	1	0	1	1

Primary SOC	Preferred Term	N	# AS03	# Control	GSK # of AS03 cases without alternate plausible cause	CBER # of AS03 cases without alternate plausible cause
	Facial paresis	2	1	1**	1	1
	CN III palsy	1	1	0	1	1
	CN IV palsy	1	1	0	0	1
	CN VI palsy	1	1	0	0	1
	Multiple sclerosis	3	2	1**	1	1
	Neuritis	1	1	0	0	1
	Radiculitis	3	2	1	0	0
	CN VII palsy	5	5	0	3	4
Skin and subcutaneous tissue disorders	Erythema nodosum	1	1	0	1	1
	Stevens-Johnson syndrome	1	1	0	0	0
	Psoriasis	5	3	2	2	2
Vascular disorders	Raynaud's phenomenon	1	1	0	1	1
	Temporal arteritis	1	1	0	1	1
Total		54*	46	8	24	31

* One PMR case was withdrawn by the PI without rationale after the database lock in favor of a diagnosis of fibromyalgia. GSK therefore considered that there were only 53 pIMD cases, CBER considers that there are 54.
** Control subjects for which an alternate plausible cause could not be determined.
Source: Table generated by CBER clinical reviewer from information in BLA 124519/0, Module 2.7.4, Section 7.2.2, p 99 – 116; Module 5.3.5.3 ISS Supplement 2 p 107-139.

Reviewer comment: Regardless of whether there are 24 or 31 AS03 associated pIMD cases without an alternate plausible cause (per GSK or this reviewer, respectively), there appears to be an imbalance in the number of pIMD cases in the AS03 group as compared to the control group because only 2 pIMD cases without alternate plausible causes were identified in the control arm. With the 2.5:1 randomization one might expect there to be at least 10 - 12 pIMD events without an alternate plausible cause in the control group. Given the rarity of many of these immune mediated events, the relatively small number of subjects considered, and the limitations of the pooled assessment noted above, it is difficult to draw any definitive conclusions from these imbalances. However, , the possibility that exposure to vaccines containing AS03 may have contributed to this imbalance cannot be excluded, and must be taken into account in any assessment of risks and benefits in using these vaccines.

8.4.1 Deaths

A total of 33 deaths were captured in the ISS: 24 (0.1%) in the AS03 group and 9 (0.1%) in the control group.

Table 34: Fatal SAEs in the Integrated Summaries of Safety

Study	Subject ID	Age	Gender	Treatment	Dose	Day of Onset	SAE
Q-Pan-H5N1-002	4253	59	M	AS03	1	17	MI
	1663	78	F	AS03	1	168	Ovarian CA w/ liver metastases
	6568	53	M	AS03	1		Exacerbation of pre-existing liver disease and diabetes mellitus
	4308	69	F	AS03	1	179	Carcinoma
	3548	80	M	Placebo	1	265	Cardiac disorder
	5514	89	F	Placebo	1	292	Death NOS
	6120	73	M	Placebo	1	63	Brain neoplasm
	2856	60	M	Placebo	1	317	Gunshot wound
	6567	60	M	Placebo	1	50	Cardiomegaly secondary to COPD
	7304	69	M	Placebo	1	295	Malignant neoplasm of the tongue
	8078	85	M	Placebo	1	183	Pneumonia
Q-Pan-H5N1-005	1155	51	M	AS03	1	157 207	GI bleed Metastatic adenoCA
	1156	18	M	AS03	1	224	Suicide
	196	85	F	AS03	1	237	CVA
	524	74	M	AS03	1	687	Cholecystitis and septic shock
Q-Pan-H5N1-009	222	51	M	AS03	1	75	Blunt injury
D-Pan-H5N1-002	204	27	M	AS03	1	14	Accidental death
	3222	37	M	AS03	2	460	Acute MI leading to hypoxic encephalopathy and acute renal failure
D-Pan-H5N1-008	2640	41	F	AS03	1	101	Therapeutic abortion of fetus with trisomy 21
	6871	65	F	AS03	1	109	Ovarian CA
D-Pan-H5N1-010	251	63	M	AS03	1	81	Congestive heart failure
	80	69	M	AS03	1	141	CVA
	270	72	M	Control	1	162	Ventricular fibrillation
	318	84	F	Control	1	130	Heart block
D-Pan-H5N1-012	118	18	F	AS03	1	41	Traumatic brain injury
Q-Pan-H1N1-001	2373	77	F	AS03	1	76	Acute MI
	2379	45	F	AS03	1	65	Pancreatic CA
	1318	84	F	AS03	1	380	Failure to thrive
Q-Pan-H1N1-002	12691	62	F	AS03	1	138	Suicide
	127	85	F	AS03	1	116	Malignant right groin tumor
	12910	72	F	AS03	1	357	MI
	269	57	M	AS03	1	47	Acute coronary syndrome (MI)
	2843	74	M	AS03	1	314	Metastatic melanoma

Source: Table generated by CBER clinical reviewer from information in BLA 125419/0, Module 5.3.5.3.28 Integrated Summary of Safety (H5N1+H1N1), Supplement 5

Reviewer comment: The overall death rate is very similar in the two groups.

8.4.2 Nonfatal Serious Adverse Events

See Section 8.4

8.4.3 Study Dropouts/Discontinuations

Study dropouts were not a part of the ISS analyses.

8.4.4 Common Adverse Events

See Section 8.4

8.4.5 Clinical Test Results

Clinical evaluations were not considered in the ISS.

8.4.6 Systemic Adverse Events

See Section 8.4

8.4.7 Local Reactogenicity

See Section 8.4

8.4.8 Adverse Events of Special Interest

See Section 8.4

8.5 Additional Safety Evaluations

Post-hoc safety analyses were performed at CBER's request based on age (stratified by cohorts: 18-40 years, 41-64 years and ≥ 65 years), gender and race.

8.5.3 Product-Demographic Interactions

Similar to the demographic make-up of the pivotal trials, subjects in the ISS analyses were predominately female, Caucasian and 18-40 years of age. Review of the post-hoc safety analyses revealed no new or product-demographic specific safety signals.

8.6 Safety Conclusions

The pooled D-Pan/Q-Pan H5N1 safety data in nearly 10,000 recipients of D-Pan or Q-Pan H5N1 revealed a higher rate of all solicited adverse events, most notably pain, as compared to the controls. These results were consistent with what was observed in the pivotal clinical trials. Additionally, the unsolicited AEs of nausea, injection site pruritus,

injection site reaction, injection site warmth, malaise, insomnia and dizziness were reported in the H5N1 + AS03 vaccinees at a higher incidence, in close temporal relation to the vaccine and are consistent with events observed in Q-Pan-H5N1-002. Lastly, 17 AESI/pIMDs (5 previously identified in -002 and 12 newly identified) were reported exclusively by the H5N1+AS03 vaccinees.

The imbalance in AESI/pIMD reporting persisted in the pooled D-Pan/Q-Pan H5N1 and H1N1 safety data with 0.3% of test vaccine recipients reporting a pIMD versus 0.1% of controls and 0.1 – 0.2% of test vaccine recipients having no alternate plausible cause for the reported pIMD versus 0.03% of controls.

Reviewer comment: The totality of the integrated safety data demonstrates that GSK's AS03 adjuvanted influenza vaccines are associated with an increased rate of expected, solicited local and systemic adverse reactions as well as suggests an increased rate of unexpected, unsolicited AEs and potentially immune mediated diseases.

Given the high degree of morbidity and mortality associated with H5N1 disease, the plans to have the government stockpile and control the use of Q-Pan H5N1, no plans for GSK to market the vaccine for general use in the inter-pandemic period and the restricted usage in adults at increased risk of exposure to H5N1 or during a pandemic all combined for an overall favorable risk/benefit profile for approval of Q-Pan H5N1.for this limited indication against a virus capable of precipitating a potentially catastrophic pandemic. Any use outside of that previously mentioned will require a much larger safety database to further assess these safety signals.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Please see Section 6.1.12.4 and 6.2.12.4 for specific pregnancy outcomes in the pivotal trials. Overall, 17 subjects exposed to Q-Pan H5N1 + $AS03_A$ became pregnant after vaccine exposure. None of these pregnancies resulted in reports of untoward vaccine-related outcomes.

A reproductive and development toxicity study has been performed in female rats at dose approximately 80 times the human dose (on a mcg/kg basis) and according to the Sponsor showed no evidence of impaired fertility or harm to the fetus. The effect of Q-Pan was also evaluated on embryo-fetal and pre-weaning development in rats. Animals were administered Q-Pan IM prior to gestation, during the period of organogenesis (gestatation days 7,9 and 12), later in pregnancy (gestation day 16) and during lactation (day 7), 0.2 mL/dose/rat (approximately 80-fold excess relative to the projected human dose on a body weight basis). According to the Applicant no adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were also no reported vaccine-related fetal malformations or other evidence of teratogenesis.

9.1.2 Use During Lactation

No human data exist on whether or not this vaccine is excreted in milk. The label will reflect this lack of data and provide a cautionary statement regarding administering this vaccine to a nursing woman.

9.1.3 Pediatric Use and PREA Considerations

GSK submitted a Pediatric Plan requesting deferral of all pediatric age groups (birth through 17 years of age) on the grounds that the candidate vaccine is ready for approval in the adult population. The original request for deferral was submitted with the original BLA on February 22, 2012. However, during a telephone conference between GSK and CBER on May 9, 2012, where the specifics of the pediatric plan were being discussed, GSK indicated that further studies evaluating lower antigen and adjuvant doses were being contemplated in an effort to determine if the degree of reactogenicity observed with AS03 adjuvanted influenza vaccines (especially in the youngest age group studied to date, 6 – 35 months) could be reduced. Subsequent to this conversation an amended Pediatric Plan was submitted to the BLA on July 19, 2012.

GSK's amended Pediatric Plan contained four proposed studies, the results of which will be submitted as a supplement to this original BLA in accordance with the Pediatric Research Equity Act requirement. All proposed studies are immunogenicity and safety studies. Table 35 briefly describes the proposed studies.

Table 35: Ongoing and Planned Pediatric Studies for Q-Pan H5N1

Study Number	Population	Final Protocol (Submission Date)	Study Completion (Date)	Final Study Report (Submission Date)
Q-Pan H5N1=AS03-021	6 months to <18 years	March 2, 2012	November 2013	June 2014
Q-Pan-023	6 to <36 months	December 2013	March 2016	September 2016
Q-Pan-024[a]	6 months to <18 years	August 2015	July 2017	December 2017
Q-Pan-025[b]	<6 months	August 2016	October 2018	March 2019

aStudy Q-Pan-024 will be conducted only if study Q-Pan-023 identifies a pediatric dose different than the current 1.9 µg HA +AS03B.
bThe dates provided for study Q-Pan-025 assume that study Q-Pan-024 will be conducted. If the current dose, 1.9 µg HA +AS03B, is confirmed by study Q-Pan-023, study Q-Pan-024 will not be conducted and the timing for Q-Pan-025 will change.
Source: BLA 125419/0.5, Module 1.9.2, Request for Deferral of Pediatric Studies, Table 1

CBER presented GSK's Pediatric Plan to the Pediatric Review Committee (PeRC) on September 26, 2012. PeRC agreed with the plan as presented to defer pediatric studies for all pediatric age groups.

Reviewer comment: During the BLA review process GSK and CBER had further discussions as additional information regarding narcolepsy became available. The end result of these discussions was GSK and CBER agreed that pediatric studies will be further deferred until the results of planned and ongoing studies designed to provide additional information regarding this narcolepsy signal are available for review.

The revised Pediatric Plan submitted on March 1, 2013 (amendment 31) includes the new deferral dates and removal of the proposed booster dose in Study -023 (Table 36).

Table 36: Ongoing and Planned Pediatric Studies for Q-Pan H5N1 (BLA Amendment 31)

Study Number	Population	Final Protocol (Submission Date)	Study Completion (Date)	Final Study Report (Submission Date)
Q-Pan H5N1=AS03-021	6 months to <18 years	March 2, 2012	March 2014	October 2014
Q-Pan-023	6 to <36 months	February 2015	December 2016	June 2017
Q-Pan-024[a]	6 months to <18 years	June 2016	April 2018	October 2018
Q-Pan-025[b]	<6 months	October 2017	July 2019	December 2019

aStudy Q-Pan-024 will be conducted only if study Q-Pan-023 identifies a pediatric dose different than the current 1.9 µg HA +AS03B.
bThe dates provided for study Q-Pan-025 assume that study Q-Pan-024 will be conducted. If the current dose, 1.9 µg HA +AS03B, is confirmed by study Q-Pan-023, study Q-Pan-024 will not be conducted and the timing for Q-Pan-025 may change.
Source: BLA 125419/0.31, Module 1.9.2, Request for Deferral of Pediatric Studies, Table 1

Reviewer comment: The changes to the Pediatric Plan are acceptable.

9.1.4 Immunocompromised Patients

Immunocompromised subjects were not included in these clinical trials.

9.1.5 Geriatric Use

A total of 1,118 subjects 65 years and older received the candidate vaccine in the two pivotal studies. Immunogenicity results although less robust than in younger subjects still met all pre-specified immunogenicity endpoints. Regarding safety outcomes, the older age cohort appeared to tolerate the vaccine at least as well as the younger cohort and with

regard to local and general adverse reactions they appeared to tolerate the vaccine somewhat better.

10. CONCLUSIONS

The pivotal studies submitted in support of Q-Pan H5N1 provided

- Q-Pan H5N1 immunogenicity data that demonstrated
  - an adequate HI antibody response in adults (ages 18-64 years and >64 years) based on CBER's suggested immunogenicity criteria after two doses of vaccine.
  - the ability to reduce the antigen dose down to 3.75 µg HA with the addition of AS03 adjuvant.
  - lot-to-lot consistency of Q-Pan H5N1 consisting of 3 H5N1 antigen lots and 3 consecutive AS03 adjuvant lots.
- Q-Pan H5N1 safety data that demonstrated
  - Increased frequency and severity of solicited, local and general (systemic) adverse reactions
  - Slightly higher rates of unsolicited adverse event reported overall with a significantly higher rate of both expected, injection site reactions and unexpected events such as dizziness and insomnia.
  - Similar rates of SAEs as control subjects. However, in -002 SAEs occurred that were either temporally associated or found in more than one subject exclusively in the Q-Pan H5N1 arm and had no other identified alternative plausible cause.
  - An imbalance in the rate of AESI/pIMDs reported.

The integrated summary of safety assessments provided safety data in approximately 10,000 subjects, who received H5N1+AS03 and approximately 16,000 subjects, who received H5N1+AS03 or H1N1+AS03. The results of these assessments produce findings similar to the pivotal trials:

- Increased solicited local and general adverse reactions.
- Increased incidence and relative risk of expected, unsolicited AEs as well as unexpected, unsolicited AEs.
- Increased rate of AESI/pIMDs

Reviewer comment: The information submitted in response to the CR may impact the final numbers and rates of adverse events including AESI/pIMDs.

A safety signal of narcolepsy in persons < 20 years of age was identified in association with Pandemrix (GSK's Dresden manufactured AS03 adjuvanted H1N1 vaccine) from spontaneous post-marketing reports. An elevated risk of narcolepsy has been confirmed by an independent epidemiologic study conducted in multiple European countries (the VAESCO study[7]), in addition to other less rigorously conducted epidemiologic studies and has resulted in the use of Pandemrix being restricted. A similar safety signal has not been confirmed for Arepanrix (GSK's Quebec manufactured AS03 adjuvanted H1N1 vaccine), which is made using the same process as Q-Pan H5N1. Spontaneous

postmarketing reports following use of Arepanrix include febrile convulsions, autoimmune hepatitis and solid organ transplant rejection. Only the safety signal of febrile convulsions has resulted in a safety labeling change for Arepanrix in countries where it is marketed.

The aggregate safety data from controlled clinical trials and post-marketing studies and spontaneous reports suggest that GSK's AS03 adjuvanted influenza vaccines (Q-Pan and D-Pan) may be associated with an increased risk of certain unexpected AEs, some of which are known to be inflammatory/immune in nature (e.g. narcolepsy and autoimmune hepatitis) and others for which the nature of the event is unknown (e.g. insomnia and dizziness). However, the safety database for Q-Pan is not large enough to evaluate reliably the rates of uncommon or rare events, such as autoimmune disease.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Influenza pandemics are unpredictable, recurring events. • Little human immunity exists to influenza strains with pandemic potential. • H5N1 influenza virus is a highly pathogenic avian influenza virus that currently causes limited human disease. • When H5N1 has caused human disease it has resulted in ~60% mortality. • If H5N1 virus acquires genes that make it easily transmissible from human-to-human, it has great potential to be a severe pandemic virus.	• An H5N1 pandemic will likely have globally devastating morbidity and mortality.
Unmet Medical Need	• Q-Pan H5N1 will be the second pandemic H5N1 vaccine licensed in the U.S. • The currently licensed H5N1 vaccine requires a large amount of antigen (90µg x 2 vaccinations) to produce what is considered a meaningful HI antibody response. Based on the currently available stockpiled bulk vaccine there is not enough vaccine to vaccinate the US population. • Q-Pan H5N1 requires less antigen (3.75µg) due to the addition of AS03 adjuvant. • The applicant states that antigen dose sparing and manufacturing capacity will allow the production of an estimated ---(b)(4)--- doses in 6 months.	• Q-Pan H5N1 meets an unmet medical need.
Clinical Benefit	• Two pivotal clinical trials in adults were conducted and submitted in the BLA. • Immunogenicity was demonstrated based on seroconversion rates and using a surrogate HI titer of 1:40, which is borrowed from seasonal influenza immunogenicity studies. • Avian H5N1 influenza virus is not currently circulating and human disease is infrequent. Therefore, clinical efficacy of Q-Pan H5N1 cannot be established at this time. Vaccine effectiveness can only be determined during an actual H5N1 pandemic event.	• Immunogenicity data support accelerated approval of this vaccine based on a surrogate endpoint that is reasonably likely to predict clinical benefit (21CFR 601.41). • Clinical benefit cannot be confirmed until use of the product during an actual H5N1 pandemic. All other studies only lend support to the likelihood that the vaccine is effective.
Risk	• The most substantial risks of vaccination with Q-Pan H5N1 are associated with local and systemic reactions. Pain, erythema, swelling, myalgias, arthralgias, fatigue, headache, sweating, shivering and pain are common with this vaccine. • Majority of subjects experience mild local and systemic reactions lasting 2 -3 days. • Severe pain preventing school or work attendance occurred in up to 6% of subjects. • AESIs/pIMDs occurred more frequently in association with Q-Pan H5N1. • A 6 -13 fold increased risk of narcolepsy has been observed in persons < 20 years of age in association with a related AS03 adjuvanted influenza vaccine (Pandemrix)	• Q-Pan H5N1 vaccination leads to an intense, short term local and likely systemic inflammatory response. • The complete mechanism of action of AS03 is unknown and reported immune mediated events are biologically plausible and have been temporally associated with AS03 adjuvanted influenza vaccines.
Risk Management	• Q-Pan H5N1 will be held in a stockpile and owned and distributed by the US government. • Q-Pan H5N1 is intended for use in persons at increased risk of exposure to H5N1 (e.g. laboratory workers) or for use during an H5N1 pandemic. • GSK has a pharmacovigilance plan that involves both passive and active safety surveillance	• Q-Pan H5N1's government ownership and restricted intended use will help balance the expected benefit of the vaccine with the safety concerns associated with the AS03 adjuvant. • GSK has committed to work closely with the government to assess the safety of Q-Pan H5N1.

11.2 Risk-Benefit Summary and Assessment

Based on the immunogenicity data submitted in the Q-Pan H5N1 BLA, the vaccine produces a robust immune response leading to a statistically significant rise in HI antibody titer, a surrogate endpoint for influenza vaccine effectiveness, that is reasonably likely to predict clinical benefit.

Q-Pan H5N1 is commonly associated with transient local injection-site and general, systemic adverse reactions with pain at the injection site being the most common adverse reaction. The aggregate safety data suggest that there may also be an association with rarer, chronic inflammatory or immune mediated adverse events. The clinical trial safety database is not large enough to evaluate reliably rare adverse events such as autoimmune events.

Given the high degree of morbidity and mortality associated with H5N1 disease, plans to have the government stockpile and control the use of Q-Pan H5N1, no plans for GSK to market the vaccine and the restricted usage in adults at increased risk of exposure to H5N1 or during a pandemic all combined results in an overall favorable risk/benefit profile for Q-Pan H5N1.

11.3 Discussion of Regulatory Options

Based on the immunogenicity data submitted in the BLA the biological product has an effect (as described above) on a surrogate endpoint (HI antibody titer, which is borrowed from seasonal influenza studies) that is reasonably likely to predict clinical benefit. The Accelerated Approval pathway requires that the Applicant study the biological product further to verify and describe its clinical benefit, and that these studies should be carried out with due diligence. The options for confirming the benefit of Q-Pan H5N1 include:

- using efficacy data generated with a US-licensed, seasonal influenza virus vaccine made according to the same manufacturing process (i.e. Flulaval-006, a study of a quadrivalent, unadjuvanted seasonal influenza vaccine in children) or
- conducting an effectiveness study (or studies) during an H5N1 influenza virus pandemic or outbreak.

Reviewer comment: Please also refer to Sections 5.4.1. for additional discussion regarding the approval pathway.

Avian H5N1 influenza virus is not currently circulating and only rarely causes isolated cases of human disease. Therefore, confirming the benefit of this vaccine will likely only be done during an actual H5N1 pandemic. Waiting for a pandemic to occur to confirm benefit would mean that this product could remain under accelerated approval indefinitely. FDA has approved two products under Accelerated Approval where the confirmation of clinical benefit of the product was left to be conducted during an event.

- ***Cipro® received Accelerated Approval for post-exposure inhalational anthrax prophylaxis in August 2000 and Bayer's Post Marketing Requirement under***

Subpart H Accelerated Approval regulations stated that Bayer was required to: "Cooperate with U.S.-based public health agencies in evaluating data on the use of Cipro® brand of ciprofloxacin in a large U.S. population for inhalational anthrax (post-exposure), should an exposure occur."[17]

- ***During the 2001 anthrax bioterroist attacks CDC conducted a PEP effectiveness study with Cipro® and Bayer "cooperated" per the approval letter agreement.***
- ***In 2004 Bayer submitted a supplemental NDA including the results of the CDC's effectiveness study, which satisfied the Accelerated Approval requirement for a confirmatory study.***
- ***Bayer was granted Traditional Approval of Cipro® for post-exposure prophylaxis of inhalational anthrax on January 7, 2005.***

- ***Ortho-Mc-Neil/Johnson & Johnson's received a similar PEP inhalational anthrax indication in 2004 for Levaquin®.[18]***
  - ***Levaquin® remains under Accelerated Approval indefinitely in the absence of another bioterroist attack with aerosolized anthrax.***

Both of these examples and the approach taken to traditional approval with these products, are directly applicable to the Q-Pan H5N1 scenario: In both the case of pandemic influenza and inhalational anthrax, disease has yet to occur and therefore the opportunity to verify the benefit of the product through controlled clinical trials does not exist.

- ***Although the Accelerated Approval regulations specify that the Applicant is to conduct the confirmatory study with "due diligence" (21 CFR 314.510; 21 CFR 601.41) in both the case of Cipro® and Levaquin® the Agency has accepted that, where the disease in question is not exigent and where an outbreak of the disease in question would be so threatening as to necessitate governmental leadership in the conduct of clinical studies occurring during such an outbreak, a statement by the Applicant of its willingness to cooperate with the government in such endeavors is sufficient (see approval letters for both Cipro® and Levaquin®).***
- ***Levaquin® has been under Accelerated Approval since 2004 providing precedent for leaving a product under Accelerated Approval potentially indefinitely where a definitive efficacy study cannot be conducted given the lack of exigency of the disease in question.***

It could be argued that conducting field studies during a geographically isolated bioterrorist attack is different than conducting field studies during a global influenza pandemic. Even if that were true, the feasibility, or lack thereof, of conducting a definitive efficacy study during a pandemic should not compel the Agency to accept data that is less rigorous than generally accepted under the regulations for determining the effectiveness of a product, and also lacks product specificity, in an attempt to rapidly fulfill a regulatory requirement that does not impact how the product is ultimately manufactured, procured or used. In the case of pandemic influenza, intrapandemic observational or case-control studies have been shown to be feasible, albeit challenging to execute, as is evidenced by the Arepanrix study conducted by Van

Buynder, et al., as well as other studies evaluating vaccine effectiveness conducted during the H1N1 pandemic.[19,20]

For all of the aforementioned reasons this reviewer recommends that Q-Pan H5N1's clinical benefit be confirmed by a prospective, effectiveness study conducted during an H5N1 pandemic or outbreak. In lieu of an H5N1 pandemic or outbreak, Q-Pan H5N1, if approved under Accelerated Approval regulations, should remain under Accelerated Approval indefinitely.

11.4 Recommendations on Regulatory Actions

BLA 125419 received a CR letter on March 22, 2013 (please refer to Section 3.1 for details.)

11.5 Labeling Review and Recommendations

At the time this review was finalized, labeling negotiations with the Applicant were still ongoing. Major changes recommended or areas of ongoing negotiation for the Q-Pan H5N1 proposed package insert (PI) included:

- Changing the proposed proper name, Influenza A (H5N1) virus monovalent vaccine, to add "adjuvanted" to the end. This came as the result of an internal discussion where the decision was made to add the word "adjuvanted" to all vaccine containing novel adjuvants.
- Adding relevant safety data from related AS03 adjuvanted influenza products, Arepanrix and Pandemrix including narcolepsy.
- Inclusion of AESIs and SAEs that were temporally associated with Q-Pan H5N1 vaccination, including the contested case of SLE and cutaneous vasculitis that are part of the CR letter.

11.6 Recommendations on Postmarketing Actions

To be determined at the time of approval.