BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125419/39
CBER Received Date	November 12, 2015
PDUFA Goal Date	September 11, 2016
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Darcie Everett, MD, MPH
Review Completion Date / Stamped Date	
Supervisory Concurrence	Meghan Ferris, MD, MPH, Team Leader
	Andrea Hulse, MD, Branch Chief
Applicant	ID Biomedical Corporation of Quebec dba GlaxoSmithKline Biologicals (GSK)
Established Name	Influenza A (H5N1) Virus Monovalent Vaccine
(Proposed) Trade Name	<No Proprietary Name>
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Each 0.25 mL pediatric dose contains 1.9 mcg hemagglutinin (HA) H5N1, 2.5 mcg thimerosal, 5.35 mg squalene, 5.93 mg DL-α-tocopherol, and 2.43 mg polysorbate 80.
Dosage Form(s) and Route(s) of Administration	An emulsion for intramuscular injection supplied as 2 separate vials: 1) H5N1 antigen and 2) AS03 adjuvant that are combined prior to administration
Dosing Regimen	Children (aged 6 months through 17 years): Two doses (0.25-mL each) administered 21 days apart
Indication(s) and Intended Population(s)	Prophylaxis of influenza A (H5N1) in children (6 months and older) and adults
Orphan Designated (Yes/No)	No

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GLOSSARY

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP-I	according to protocol cohort for immunogenicity
BARDA	Biomedical Advanced Research and Development Authority
BLA	biologics license application
BUN	blood urea nitrogen
CBC	complete blood count
CMC	chemistry, manufacturing, and controls
CSR	complete study report
DHHS	Department of Health and Human Services
D-Pan	Influenza A Virus Monovalent Vaccine, Adjuvanted, manufactured in Dresden
HA	hemagglutinin
Hgb	hemoglobin
HI	hemagglutination inhibition
ISE	integrated summary of efficacy
ISS	integrated summary of safety
MedDRA	Medical Dictionary for Regulatory Activities
MGI	mean geometric increase
OBE	Office of Biostatistics and Epidemiology
PeRC	Pediatric Review Committee (CDER)
PI	package insert
pIMD	potential immune-mediated disease
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
Q-Pan	Influenza A Virus Monovalent Vaccine, Adjuvanted, manufactured in Quebec (refers to H5N1 vaccine unless otherwise stated)
SAE	serious adverse event
sBLA	supplement biologics license application
SCR	seroconversion rate
SPR	seroprotection rate
TVC	total vaccinated cohort
ULN	upper limit of normal
US	United States
VRR	vaccine response rate
WBC	white blood cell count

1. Executive Summary

Influenza A (H5N1) virus monovalent vaccine, adjuvanted (also referred to as Q-Pan H5N1 throughout this document), is approved for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained the vaccine. Currently it is approved for use in adults at increased risk for exposure to the H5N1 subtype contained in the vaccine. This clinical reviewer is recommending extending approval for use in persons 6 months through 17 years of age. This recommendation is based on review of the immunogenicity and safety data submitted by ID Biomedical dba GlaxoSmithKline (also referred to as GSK or the Applicant throughout this review) in support of the efficacy supplement to the Biologic Licensing Application (BLA) 124519/39. No clinical endpoint efficacy data exist for Q-Pan H5N1 in the pediatric or

adult populations, and such studies are not feasible in the absence of an H5N1 pandemic.

Influenza is an acute respiratory illness caused by infection with influenza viruses. Influenza A virus circulates in the human population, causing yearly outbreaks. It is also capable of causing pandemics, which can occur when a new subtype of influenza A virus emerges through antigenic shift to which the population has not been exposed and to which it has little or no immunity. The H5N1 virus subtype is a highly pathogenic avian influenza virus that has caused the largest and most severe poultry outbreaks ever recorded. H5N1 is not currently capable of efficient human-to-human transmission, but has resulted in approximately 50% mortality when it has infected adults and children. If an H5N1 influenza virus were to acquire the ability to easily transmit from one person to another through genetic reassortment, a catastrophic pandemic could be anticipated, given the severity of the virus and the lack of immunity in the worldwide population.

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. Each adult dose of Q-Pan H5N1 contains 3.75 µg H5N1 antigen combined with AS03 adjuvant. The immune response elicited by the adjuvant allows for a lower dose of antigen to achieve levels of hemagglutination inhibition (HI) antibody titers anticipated to provide protection from influenza, based on seasonal influenza data. A lower antigen concentration enables GSK to manufacture more doses of vaccine, which would be desirable in the event of a pandemic. The stockpiled vaccine will be distributed by the US government in the event of an H5N1 pandemic.

Q-Pan H5N1 received traditional approval for the prevention of disease caused by the influenza strain in the vaccine for use in adults in November 2013. Approval was based on safety and immunogenicity data from two pivotal trials of the vaccine in 3,574 subjects who received the final formulation of Q-Pan H5N1. The trials demonstrated 1) the vaccine's ability to induce target levels of HI antibody titers based on the proportion of subjects with a four-fold rise in baseline HI titers and geometric mean titer (GMT) ratios, and 2) the need for two doses of vaccine to reach these levels. These trials also showed imbalances in the proportion of adult subjects reporting certain serious adverse events (SAEs) and selected neuroinflammatory, musculoskeletal, gastrointestinal, metabolic, skin and autoimmune disorders referred to as potential immune mediated diseases (pIMDs), though the overall risk benefit profile was favorable.

The Pediatric Research Equity Act (PREA) mandated pediatric assessment was deferred at the time of the initial Q-Pan H5N1 approval. The deferred pediatric assessment included four required studies spanning the entire pediatric age group. Q-Pan-021 was the first required pediatric assessment for Q-Pan H5N1. The study, conducted in the United States, Canada, and Thailand, was a pivotal, phase 2/3, multi-center, observer-blind, placebo controlled trial to evaluate the immunogenicity and safety of Q-Pan H5N1 in subjects 6 months through 17 years of age. Subjects were divided into three age groups and were randomized 8:3 to receive vaccine at half the adult dose (1.9 µg H5N1 antigen and $AS03_B$) or placebo as a two-dose series 21 days apart. Following completion of the controlled portion of the study, subjects who had received placebo,

were offered Q-Pan H5N1 at the same dose and schedule in an uncontrolled cross-over study to evaluate safety.

A total of 838 subjects were enrolled in the study and received at least one vaccination, 607 received Q-Pan and 231 received placebo. Study completion rate was 93%. In Year 2, 155 subjects from the Placebo Group received Q-Pan.

Immunogenicity analysis at Day 42, 21 days following the second dose of vaccine, demonstrated that ≥ 99% of subjects who received Q-Pan in each age group achieved a level of hemagglutination inhibition (HI) titers possibly indicative of protection from disease (≥ 1:40) compared to 0.5% of subjects who received placebo. This met immune response targets agreed upon by GSK and CBER and consistent with the 2007 CBER Pandemic Influenza Guidance.[1] Immunogenicity analyses at Day 21 demonstrated that two doses of vaccine were necessary to meet the targets.

The vaccine was reactogenic in children. Pain was the most frequently reported local solicited reaction in all age groups, reported by 47% of subjects 6 through 35 months, 71% of subjects 3 through 8 years, and 82% subjects 9 through 17 years. In the placebo group, injection site pain was reported in 30%, 38%, and 23% of subjects in these age groups, respectively. Injection site erythema and swelling were also commonly reported. The most frequently reported systemic solicited reactions were irritability in subjects younger than six years of age (reported by 51% of subjects 6 through 35 months, and 30% of subjects 3 through 5 years) and myalgias in subjects six years of age and older (reported by 35% in 6 through 8 years, and 42% in 9 through 17 years). In the placebo group, irritability was reported in 40%% and 22%, respectively; myalgias were reported in 19% and 15%, respectively. Other common systemic reactions included drowsiness, loss of appetite, and fever in children younger than 6 years of age and arthralgias, fatigue, headache, sweating, shivering, and fever in those older than 6 years of age. No clear dose-dependent increase in solicited adverse reactions following the second dose was observed. There were no clinically significant differences between Q-Pan H5N1 and placebo recipients in rates of unsolicited adverse events reported in the 42 days following the first vaccination.

Subjects in Q-Pan-021 were monitored for safety for one year following the second vaccination for the following reasons: 1) the theoretical risk of an immune-stimulating adjuvant contributing to autoimmunity, 2) reports of immune-mediated events of narcolepsy and autoimmune hepatitis in association with GSK's related, AS03-adjuvanted H1N1 pandemic influenza vaccine (D-Pan H1N1), and 3) imbalances noted in the original BLA review in certain chronic inflammatory and pIMDs. During the Q-Pan-021 study period, medically-attended adverse events (MAAEs), SAEs, and pIMDs were reported. There were no differences in medically attended adverse events or SAEs between study groups. Two pIMDs were reported during the one-year safety follow-up period – alopecia in a Q-Pan-recipient and type 1 diabetes mellitus in a placebo-recipient. The safety results of the uncontrolled crossover study generally corroborated the results in Year 1; no pIMDs were reported in the crossover study.

In support of licensure in the pediatric population, CBER reviewed additional pediatric safety data from a trial of a related non-US licensed vaccine. Study Q-Pan-035 was a Phase 3, randomized, observer-blind, active-controlled, multi-center, trial evaluating a related vaccine, Q-Pan H1N1 with and without AS03 adjuvant, in children 6 months through 9 years of age. Approximately 6000 subjects were randomized 1:1:1 to receive

one dose of the adjuvanted vaccine, two doses of the adjuvanted vaccine, or two doses of the unadjuvanted vaccine. One death due to pneumonia and sepsis occurred within the 42-day primary study period in a subject who received adjuvanted vaccine. SAEs were reported at similar rates in subjects receiving the adjuvanted and unadjuvanted vaccines at Day 42 (0.4% in both of these groups) and 385 (3.5% and 3.3%, respectively). Potential immune-mediated diseases were reported at the same rate in subjects receiving the adjuvanted vaccine as subjects receiving the unadjuvanted vaccine (0.2% in both groups).

The submitted data supported expanding use to the pediatric population. Q-Pan H5N1 is recommended for approval in children and adolescents 6 months – 17 years of age based upon a favorable risk-benefit profile. Release from two PREA postmarketing requirements (PMRs) is recommended because the reactogenicity and immunogenicity demonstrated in Q-Pan-021 make further dose-finding studies unnecessary. A study to evaluate Q-Pan H5N1 in infants less than 6 months of age will be initiated in the event of an H5N1 pandemic.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Three age groups were evaluated in Year 1 of Study Q-Pan-021, 6 to < 36 months, 3 to < 9 years, and 9 to < 18 years. Subjects were evenly split between these age groups in both the Q-Pan Group and the Placebo Group. Proportionally fewer females were in the group that received Q-Pan (47%) than the group that received placebo (50%). The study population was composed of White – Caucasian/Europeans (45%), Asians (36%), African/African Americans (15%), American Indian/Alaskan Native (0.4%), White – Arabic/North African Heritage (0.4%), and Other races (3.5%). Hispanics made up 11% of the study population. Relative to the US population, Asians were over-represented (5% US) and White – Caucasian/Europeans were under-represented (77% US population). Enrollment of African/African Americans (13% US) and Hispanics (18% US) was representative of the US population based on 2015 census data.[2]

The primary study endpoint was the proportion of subjects achieving an immune response that has the potential to be protective (hemagglutination inhibition antibody titer ≥ 1:40) in each age group. Antibody level (geometric mean titer) was a secondary endpoint. Two doses of Q-Pan were required in all age groups to reach the target immune response. Antibody levels decreased over time and decreased more dramatically in the older age groups, declining to below target levels by Day 182 in subjects 9 to < 18 years of age and by Day 385 in subjects 3 to < 9 years of age. In the youngest age group, 6 to < 36 months, they were still above target levels at Day 385. While small differences in immune response by sex were observed, with females showing a greater immune response, none of these differences were statistically significant. No statistically significant differences were seen by race. The clinical significance of any differences is unknown.

Reporting of adverse reactions solicited on subject diary cards following any vaccination with Q-Pan varied by age. Most notably, injection site pain increased with age (47% of subjects 6 through 35 months, 71% of subjects 3 through 8 years, and 82% subjects 9 through 17 years) and fever decreased with age (22% of subjects 6 through 35 months, declining to 3% of subjects 9 through 17 years). Adverse events that were not solicited were reported at lower rates in older age groups at study Day 42 in both the Q-Pan and Placebo Groups. There were no clear clinically significant differences based on sex in

local or systemic reactions solicited in the first seven days following vaccination or in unsolicited adverse events reported in the 42-day primary study period. In general, subjects of White – Caucasian/European geographic ancestry, and to a lesser extent South East Asian ancestry, reported statistically significantly more local and systemic reactogenicity and unsolicited adverse events compared to Africans/African Americans. However, differences adverse event reporting noted by geographic ancestry may be confounded by other factors, such as age. Similar trends were also seen in the Placebo Group.

2. Clinical and Regulatory Background

The candidate vaccine, Influenza A (H5N1) virus monovalent vaccine, adjuvanted (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 and AS03 adjuvant yields multiple doses 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 10µg/mL of thimerosal as a preservative.

Q-Pan H5N1 was approved by the U.S. FDA in 2013 for the prevention of disease caused by the Influenza H5N1 subtype contained in the vaccine in adults at increased risk of exposure to Influenza A H5N1 virus (STN: 125419/0). The vaccine is being stockpiled for distribution in the event of an H5N1 pandemic. This Biologics Licensure Application (BLA) efficacy supplement considers expansion of use to the pediatric population.

2.1 Disease or Health-Related Condition(s) Studied

Influenza is an acute respiratory illness caused by infection with influenza viruses. Outbreaks of variable extent and severity occur 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 hemagglutinin (HA) and neuraminidase (NA). In total, 18 HA antigenic subtypes (H1-H16) and 11 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 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.[3] The 1918-19 H1N1 pandemic virus, the most lethal of the 20th century, resulted in about 50 million deaths worldwide.[4]

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 850 humans in 16 countries with a mortality rate of greater than 50%.[5] While instances of human-to-human transmission have been rare to date, the potential for a pandemic outbreak exists should these viruses acquire enhanced transmissibility by reassortment or mutation.

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 an antigen sparing H5N1 influenza virus vaccine. Q-Pan H5N1 is stockpiled and will be distributed by the US government in the event of an H5N1 pandemic. The vaccine was initially licensed in the US in November 2013 for use in adults 18 years of age and older.

As part of the approval for licensure, GSK is required to evaluate Q-Pan H5N1 in persons younger than 18 years of age in post-marketing clinical studies. Based upon current knowledge, H5N1 is also highly pathogenic in children. In an epidemiologic study of 193 children less than 18 years of age with confirmed H5N1 infections from 13 countries, the case-fatality rate was 48.7% for all pediatric age groups. The case-fatality rate was higher in older children (80.4% in children 12-17 years of age and 52.2% in children 6-11 years of age) compared to younger children (27.5% in children younger than 5 years of age).[6]

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

Currently, there are two vaccines approved for prevention of pandemic influenza H5N1 in adults – the candidate vaccine, GSK's A/H5N1/Indonesia/05/2005 (STN 125419/0) and Sanofi's A/H5N1/Vietnam/2004 vaccine (STN 125244/0). No vaccines are currently licensed for the prevention of pandemic influenza H5N1 in children.

Four US licensed antiviral agents (amantadine, oseltamivir, peramavir, rimantadine, and zanamavir) are available for prophylaxis and treatment of influenza disease in adults and in children of specific ages. However, since 2005, emerging resistance to one or more of these licensed antivirals has complicated recommendation for their use. H5N1 resistance to antiviral agents has been reported, including resistance to oseltamivir both in association with oseltamivir treatment and spontaneously.[7, 8, 9]

2.3 Safety and Efficacy of Pharmacologically Related Products

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 and FluLaval Quadrivalent process. FluLaval is GSK's unadjuvanted, seasonal, trivalent influenza virus vaccine that was originally licensed in 2006 under Accelerated Approval for use in adults and granted Traditional Approval in 2013. FluLaval Quadrivalent is GSK's unadjuvanted, seasonal, quadrivalent influenza virus vaccine, which was licensed in the U.S. in 2013 for use in persons $\geq$ 3 years of age based on an efficacy study in subjects 3 – 8 years of age. Pandemrix H1N1 is an AS03 adjuvanted vaccine manufactured by GSK in Dresden,

Germany, using the Fluarix manufacturing process. Fluarix is another GSK unadjuvanted, seasonal, trivalent influenza virus vaccine that is currently US licensed for use in persons ≥ 3 years of age. Approximately 173 million doses of Pandemrix H1N1 were distributed during the 2009 pandemic and an estimated 31 million people received the vaccine. Approximately 171 million doses of Arepanrix H1N1 were distributed during the 2009 pandemic and an estimated 59 million people received the vaccine. The European Medicines Agency (EMA) marketing authorization for Pandemrix has since expired and the EMA marketing authorization for Arepanrix has since been withdrawn by GSK.

There are theoretical concerns of potential autoimmunity associated with Q-Pan H5N1 and other vaccines containing a potent immune stimulator, such as AS03. GSK conducted a variety of analyses on the spontaneously reported postmarketing safety reports received for Pandemrix H1N1 and Arepanrix H1N1 to assess for safety signals. A brief summary is provided here. Please see the clinical review of the original BLA for further details.

Narcolepsy

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, with a bimodal peak age of diagnosis: 14 years and 35 years. The mechanisms underlying narcolepsy are not fully understood, but the disease may be due to an autoimmune process triggered by environmental factors in susceptible individuals leading to significant loss of hypocretin-secreting neurons in the hypothalamus. Narcolepsy is strongly associated with HLA DQB1*0602, which has been found in > 90% of patients with narcolepsy with cateplexy.[10,11] Narcolepsy with cataplexy has also been associated with an autoantibody against tribbles homologue 2 (Trib2).[12, 13]

As of November 5, 2012, GSK reported in the original BLA review via electronic mail that over 800 spontaneous reports of narcolepsy associated with Pandemrix use had been reported to them. Based upon the PVP, GSK estimates at least 31 million doses of Pandemrix have been administered. In Finland and Sweden, increases in the rate of narcolepsy were noted in children following the immunization campaign. Some follow-up studies showed increases in risk associated with the vaccine. The estimated risk in these studies (relative risk, odds ratio, or incidence rate ratio) ranged from 2 to 16 and was primarily seen in children.[14] In the PVP, GSK states that 14 reports of narcolepsy were reported following distribution of Arepanrix. Narcolepsy has not been reported in association with Q-Pan H5N1.

Based on the increased rate of reporting of narcolepsy cases, additional epidemiologic studies are ongoing in countries where Arepanrix and Pandemrix were distributed. In countries where Pandemrix had marketing approval, narcolepsy was added to the warning section of Pandemrix product labeling, and use in persons less than 20 years of age was restricted to situations only when seasonal influenza vaccine was unavailable. 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 AS03 adjuvant to the narcolepsy signal. Narcolepsy is mentioned in the Q-Pan H5N1 package insert as part of the post-marketing experience with related products.

Autoimmune hepatitis

Reports of autoimmune hepatitis (AIH) have occurred in clinical trials in association with D-Pan and Q-Pan H5N1 and in the post-marketing setting in association with Pandemrix. GSK reports that approximately 32,836 subjects have received at least one dose of GSK's H5N1+AS03 or H1N1+AS03 vaccines during clinical trials. Two cases of AIH were reported in clinical studies – one in a 3 year-old girl enrolled in a trial of 300 children evaluating D-Pan H5N1 and another in the pivotal trial for Q-Pan H5N1 in adults, Q-Pan-002. GSK reports an additional case of exacerbation of AIH in a post-marketing safety study. As per the PVP, eight spontaneous post-marketing reports of AIH following vaccination with Pandemrix H1N1 had been reported to GSK by September 29, 2014. GSK reports that, according to the International Autoimmune Hepatitis Group diagnostic criteria, one case met the criteria for definite AIH, one case met the criteria for probable AIH, and the remaining cases did not meet diagnostic criteria for AIH. Three additional post-marketing reports of hepatitis with no identified cause and not meeting the diagnostic criteria of AIH have been spontaneously reported. Based upon the PVP, GSK estimates at least 31 million doses of Pandemrix have been administered. No AIH cases have been spontaneously reported following Arepanrix H1N1 vaccination. The estimated incidence of AIH is 1-2/100,000 per person per year, respectively.[15]

Reviewer comment: Please see the Clinical Review of the original BLA for details of the two cases reported in pre-marketing clinical trials. As per that document, both cases appeared to have been at least exacerbated by the vaccine. The safety monitoring for Q-Pan-021 includes laboratory evaluations of liver function tests. Per the November 22, 2013 Approval Letter for the original BLA, GSK is required to report cases of AIH as 15-day expedited reports to the Vaccine Adverse Event Reporting System (VAERS).

Solid Organ Transplant Rejection

The FDA clinical review for the original BLA for Q-Pan in adults (BLA 125419/0), noted that GSK had 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. An additional subject in the Q-Pan-002 adult pivotal trial reported a corneal rejection 18 years following transplant.

At that time, based on these reports and a paper from Schaffer, et al.[16] 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. However, it was not clear if GSK's analysis specifically considered the background reporting rate of patients with long-term (> 10 years) graft survival, and therefore if their conclusion of not higher-than-expected reporting was generalizable to this patient population.

The issue was included as a potential risk in the EMA's Risk Management Plan but not in the U.S. Pharmacovigilance Plan (PVP) Version 4. In reviewing the current PVP for this BLA supplement, Dr. Maria Said, the Pharmacovigilance Reviewer, reviewed the literature as well as the GSK-sponsored study EPI-FLU-H1N1-012, titled "Risk of solid organ transplant rejection following vaccination with Pandemrix in the United Kingdom. Based on review of the literature and the GSK study and supported by the fact that the EMA has decided to remove solid organ transplant rejection as a potential risk from its Risk Management Plan, the Office of Biostatistics and Epidemiology Reviewer (OBE), Dr. Maria Said, determined that addition of this issue to the U.S. Pharmacovigilance Plan was not needed. Please see Dr. Said's review for further details.

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

Q-Pan H5N1 was licensed in the U.S. on November 22, 2013. Please refer to clinical review of Dr. Andrea Hulse for related details. GSK received a marketing authorization for Q-Pan H5N1 by the European Medicines Agency (EMA) on April 3, 2011 under the trade name Pumarix. There is no post-marketing human experience 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

- March 2, 2012 Study Q-Pan-021 protocol submission
- November 22, 2013 approval of original BLA supporting an indication of Q-Pan H5N1 for use in adults; approval letter included PMRs for four pediatric studies including Q-Pan-021 as PMR #1
- September 8, 2014 CBER and GSK Meeting to discuss overall pediatric study plan. CBER indicated that, based on preliminary safety results of study Q-Pan-021 that did not identify any new safety issues further dose-finding studies may not be necessary and that it may be acceptable to postpone the study to evaluate Q-Pan H5N1 in infants < 6 months of age until the time of a pandemic
- July 30, 2015 GSK proposed submission of study Q-Pan H1N1 AS03-035 in the sBLA.
- September 18, 2015 CBER agreed study Q-Pan H1N1 AS03-035 would provide relevant, supportive safety data and requested submission of the final clinical study report (CSR), relevant datasets, and serious adverse event (SAE) and potential immune mediated disease (pIMD) narratives.
- November 12, 2015 sBLA submitted, including safety and efficacy data from study Q-Pan-035. GSK suggested the data from Q-Pan-035 be included in the Summary Basis of Regulatory Action (SBRA).
- March 24, 2016 CBER informed GSK that efficacy data from study Q-Pan H1N1-035 will not be included in the SBRA (see below for CBER's rationale).
- July 27, 2016 Q-Pan H5N1 pediatric assessment presented to the Pediatric Review Committee (PeRC). CBER recommends release from PMR's #2 and 3, and change to PMR#4 dates

<u>Review of Safety Data from Study Q-Pan-035</u>
In an amendment submitted to IND 13413 on July 30, 2015, and e-mail communications on August 17-24, 2015, GSK proposed to submit study Q-Pan H1N1-035 in the sBLA for Q-Pan H5N1. The study enrolled approximately 6000 infants and children ages 6 months through 9 years and was conducted during a declared H1N1 pandemic. Two

formulations of H1N1 vaccine containing the A/California/07/2009 (H1N1pdm) strain, manufactured using the same process as Q-Pan H5N1, with and without AS03 adjuvant, were evaluated. Because the study evaluated a vaccine containing the same ASO3 adjuvant as Q-Pan H5N1 in the pediatric population, CBER agreed that the study would provide relevant safety data and requested submission of the final clinical study report, relevant datasets, and Serious Adverse Event (SAE) and potential immune-mediated disorder (pIMD) narratives.

In the sBLA submission, GSK included a CSR and safety data for study Q-Pan H1N1-035, as requested. They also submitted efficacy data for the study. The efficacy data do not contribute to the basis for the regulatory action for this pediatric supplement because the study evaluated a different product (antigen to a different influenza virus subtype.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The sBLA was well organized, with all sections accessible and organized appropriately. CBER issued several information requests (IRs) for additional information and analyses. Please see section 5.2 and sections throughout this document pertinent to the IRs for the details of these IRs and GSK's responses.

3.2 Compliance With Good Clinical Practices And Submission Integrity

GSK states that Study Q-Pan-021 was conducted in accordance with good clinical practice (GCP) and all applicable regulatory requirements. Written informed consent from subjects or each subject's parent/guardian/legally authorized representative and informed assent from subjects, as appropriate, was obtained prior to the performance of any study-specific procedures.

The Bioresearch Monitoring (BIMO) Branch issued inspection assignments for three clinical investigators/study sites in the pivotal study Q-Pan-021, representing approximately 46% of the enrolled subjects. Study sites 85912, 85917, and 87086 were chosen based on several factors, including subject enrollment, previous inspectional history, geographic location, and a reported potential immune-mediated disease with an unclear diagnosis. No Forms FDA 483 were issued as a result of these inspections, nor were any issues identified that might adversely impact the data submitted in the application.

Study Q-Pan H1N1-035 was conducted (not under IND) exclusively in foreign countries. A distinct but related, non-U.S.-licensed vaccine, pandemic strain A/H1N1 vaccine adjuvanted with AS03 was evaluated in pediatric subjects 6 months to < 9 years of age. BIMO did not inspect any of the -035 study sites because this study was only supportive of the results of the pivotal trial with the candidate vaccine.

Review comment: Please refer to Ms. Haecin Chun's review for complete details of the inspection findings.

3.3 Financial Disclosures

Covered clinical study (name and/or number): Study 114464, Q-Pan-021		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 17 principal investigators, 155 total		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

Covered clinical study (name and/or number): Q-Pan-035		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 19 Principal Investigators (including 1 former Principal Investigator), 128 total		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

GSK reports having financial disclosure information from all investigators at study outset. After exercising due diligence, they were unable to obtain financial disclosure information from nine subinvestigators in study Q-Pan H5N1-021 and four subinvestigators in study Q-Pan H1N1-035 at the conclusion of the study.

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.

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

4.1 Chemistry, Manufacturing, and Controls

No new information submitted. Refer to Drs. Hana Golding and Surrender Khurana's chemistry, manufacturing, and controls (CMC) reviews of the original BLA.

4.2 Assay Validation

Please see Drs. Hana Golding's and Rong Fu's review of the [redacted] assay and validation, which was used as a secondary endpoint in study Q-Pan-021.

4.3 Nonclinical Pharmacology/Toxicology

No new information was submitted.

4.4 Clinical Pharmacology

Not applicable.

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 definitively correlated with efficacy, but HI antibody titers have been used as a measure of vaccine immune response. 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.[17]

The mechanism of action of AS03 is also not well understood. Please refer to Dr. Hana Golding's review of the original BLA 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 induction of cytokine secretion by AS03. Several studies have shown that the addition of α - tocopherol to AS03 results in a higher immune response. However, the mechanism of action of α-tocopherol and how it exerts this added adjuvant effect is unknown.

4.5 Statistical

Please see Dr. Rong Fu's Biostatistical review.

4.6 Pharmacovigilance

Please refer to Dr. Maria Said's review for a comprehensive assessment of the Q-Pan H5N1 pharmacovigilance plan.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

GSK submitted the results of two studies, Q-Pan H5N1-021 and Q-Pan H1N1-035, in support of this sBLA. Study Q-Pan-021 is considered pivotal and is reviewed in this document in detail for immunogenicity and safety outcomes. The safety outcomes of study Q-Pan-035, specifically SAEs, pIMDs, and other unsolicited adverse events (AEs) are reviewed in section 8. An Integrated Summary of Safety was not provided by GSK and is not included in section 8 of this review. The two studies are not appropriate to integrate as they evaluate different vaccines with different antigens.

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 1 BLA components reviewed by the clinical reviewer

Module	Section/Study
5.3.5.1	Clinical study report and supportive documents for Q-Pan-021
5.3.5.1	Protocol for proposed study Q-Pan-025
5.3.5.4	114000 Flu Q-Pan H1N1-035: CSR and supporting materials pertinent to safety data and analyses (Case Report Forms and Data Analysis Data)

In addition, this reviewer reviewed Financial Disclosure information (Module 1.3.4), the Correspondence Regarding Meetings (1.6), the Request for Deferral of Pediatric Studies (Module 1.9.2.), Labeling (Module 1.14), the Risk Management Plan (Module 1.16), Clinical Overview (Module 2.5), Summary of Clinical Efficacy (Module 2.7.3), Summary of Clinical Safety (Module 2.7.4), and Literature References (5.4). The protocol for study Q-Pan-021 was located in 125419/18 (Module 5.3.5.1) and was reviewed.

This reviewer also reviewed the data submitted in response to clinical information requests (IRs)and those pertinent to the clinical review in amendments to the BLA (125419/39.1 received 2/5/16; 125419/39.2 received 2/12/16; 125419/39.3 received 2/25/16; 125419/39.4 received 3/1/16; 125419/39.8 received 6/10/16; 125419/39.12 received 6/30/16; 125419/39.14 received 7/1/16; 125419/39.16 received 7/19/16; 125419/39.19 received 8/2/16; 125419/39.21 received 8/10/16; 125419/39.22 received 8/17/2016; 125419/39.23 received 8/24/2016; communications regarding the deferred pediatric study (125419/39.7, 39.9, 39.10, 39.11, 39.15, and 39.21); and all amendments pertaining to labeling negotiations (125419/39.20 received on 8/5/16; 125419/39.24 received on 8/29/16). Description of individual clinical IRs can be found in the section(s) of this document to which they pertain.

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.

5.3 Table of Studies/Clinical Trials

Table 2 Overview of clinical studies reviewed, pivotal and supportive for licensure of Q-Pan H5N1 in a pediatric population

Study ID Study Year	Countries	Design	Objectives	Population (age) Schedule of vaccination	Study groups	Number of subjects	
						Immunogenicity ATP Cohort – Day 42	Safety TVC cohort
FLU Q-PAN H5N1-AS03-021 Year 1 (NCT01310413) Pivotal	United States, Canada, Thailand	Phase II/III, randomized, controlled, observer-blind	Immunogenicity Reactogenicity/ safety	Healthy children 6 months to < 18 years of age 2 doses (Day 0, Day 21)	Q-Pan H5N1 vaccine (1.9 µg HA, A/Indonesia strain+ $AS03_B$) Placebo (phosphate buffered saline)	562 211	607 231

FLU Q-PAN H5N1-AS03-021 Year 2 (NCT01310413)	United States, Canada, Thailand	Open-label	Reactogenicity/ safety	Eligible Year 1 placebo recipients 2 doses (DayU0, Day U21)	Q-Pan H5N1 vaccine (1.9 µg HA, A/Indonesia strain+ $AS03_B$)	Not applicable	155
FLU Q-PAN H1N1-AS03-035 (NCT01051661)	Australia, Brazil, Colombia, Costa Rica, Mexico, Philippines, Singapore, Thailand	Phase III, randomized, controlled, observer-blind	Efficacy Immunogenicity Reactogenicity/safety (Study reviewed for safety)	Healthy children 6 months to < 10 years of age 2 doses (Day 0, Day 21)	Q-Pan H1N1 vaccine (1.9 µg HA A/California strain + $AS03_B$), 2 doses Q-Pan H1N1 vaccine (1.9 µg HA A/California strain + $AS03_B$), 1 dose followed by 1 dose of placebo (saline) Unadjuvanted Q-Pan H1N1 vaccine (7.5 µg or 15 µg HA, depending on subject age, A/California strain), 2 doses	Not applicable to this review	2048 2048 2049

Source: Adapted from - sBLA 125419/039; Synopsis of Individual Studies
Day U0 = Unblinded Visit 1 of Year 2; Day U21 = Unblinded Day 21 visit of Year 2
ATP According to Protocol
TVC Total Vaccinated Cohort
HA hemagglutinin

5.4 Consultations

No outside consultations were obtained.

5.4.1 Advisory Committee Meeting

CBER consulted the Vaccines and Related Biological Products Advisory Committee (VRBPAC) during the review of the original BLA (please refer to the original clinical review for details of that discussion). CBER determined that a VRBPAC meeting was not necessary for this supplement.

5.4.2 External Consults/Collaborations

No external consults were obtained.

5.5 Literature Reviewed

[1] Food and Drug Administration Center for Biologics Evaluation and Research (CBER). Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines. May 2007. Available at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074786.htm.

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1920 “Spanish” influenza pandemic. Bulletin of the History of Medicine. 2002; 76:105-115.
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[7] de Jong MD, Thanh TT, Khanh TH, et al. Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection. N Engl J Med 2005; 353 :2667-72.
[8] Earhart KC, Elsayed NM, Saad MD, et al. Oseltamivir resistance mutation N294S in human influenza A(H5N1) virus in Egypt. Journal of Infection and Public Health 2009; 2: 74-80.
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[12] Cvetkovic-Lopes V, Bayer L, Dorsaz S, Maret S, et al. Elevated Tribbles homolog 2-specific antibody levels in narcolepsy patients. J Clin Invest. 2010; 120(3): 713.
[13] Kawashima M, Lin L, Tanaka S, et al. Anti-Tribbles homolog 2 (TRIB2) autoantibodies in narcolepsy are associated with recent onset of cataplexy. Sleep. 2010; 33(7): 869-74.
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[15] Boberg KM. Prevalence and epidemiology of autoimmune hepatitis. Clinics in Liver Disease 2002; 6: 635-647.
[16] Schaffer SA, Husain S, Delgado DH, Kavanaugh L, Ross HJ. Impact of adjuvanted H1N1 vaccine on cell-mediated rejection in heart transplant recipients. Am J Transplant 2011; 11: 2751-4.
[17] Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J Hyg (Lond). 1972; 70: 767–777.
[18] Committee for Human Medicinal Products (CHMP). Note for guidance on harmonisation of requirements for influenza vaccines. 12 March 1997. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003945.pdf. Accessed 18 June 2016.
[19] De Serres G, Rouleau I, Skowronski DM, et al. Paresthesia and sensory disturbances associated with 2009 pandemic vaccine receipt: Clinical features and risk factors. Vaccine 2015; 33: 4464-71
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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

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

Study (Year 1) dates
Initiation (first subject enrolled): March 7, 2011
Completion (last subject last visit): July 4, 2012
Study (Year 2) dates
Initiation (first subject enrolled): November 1, 2012
Completion (last subject last visit): January 26, 2014
Data lock point (Date of database freeze) for integrated analysis: April 23, 2014
Date of report: Report (Integrated) Final: May 20, 2015

6.1.1 Objectives

The study objectives, as defined by GSK are stated below.

Primary objective

- To assess whether two doses of H5N1 antigen in association with AS03 elicits an immune response, measured by post-immunization vaccine-homologous virus HI titers, that met or exceeded Center for Biologics Evaluation and Research (CBER)/Committee for Medicinal Products for Human Use (CHMP) young adult targets for proportion of subjects attaining postimmunization reciprocal HI titers ≥40 against A/Indonesia/5/2005 virus.

GSK defines seroprotection rate (SPR) as the proportion of subjects with reciprocal HI titers ≥ 40 against the vaccine homologous virus (A/Indonesia/5/2005 virus). This level is based upon the 2007 Center for Biologics Evaluation and Research (CBER) pandemic vaccine Guidance and Committee for Medicinal Products for Human Use (CHMP) young adult criteria.[1, 18] The CBER criterion recommends a lower bound of the 95% confidence interval around the proportion of subjects with HI titers ≥ 1:40 to be ≥ 70%; the CHMP criterion recommends a point estimate >70%. GSK notes that HI titers ≥ 1:40 refer to what may be protective levels of antibody based on extrapolation from seasonal influenza data.

Reviewer comment: Objectives were agreed upon by CBER and GSK prior to study implementation. As GSK indicates, both the HI titer of ≥ 1:40 as a surrogate marker of protection from influenza and the CBER criterion for evaluating immunogenicity response to influenza vaccination are based on seasonal influenza data.

Secondary objectives

- To describe at different time points the immunogenicity of the vaccine regimen in three age strata [6 to < 36 months, 3 to <9 years, and 9 to < 18 years] in terms of HI titers specific for the vaccine-homologous virus the following parameters: seropositivity rate, geometric mean titer (GMT), seroconversion rate (SCR), SPR, and mean geometric increase (MGI) in terms of point estimates and 95% confidence interval (CI). In particular:
    - To assess whether the SPR meets or exceeds CBER/CHMP guidance targets (≥ 70%) in the various active treatment groups 21 days after the first dose of vaccine (Day 21).
    - To assess whether the SCR meets or exceeds CBER/CHMP guidance targets (≥ 40%) in the various active treatment groups 21 days after the first and second doses of vaccine (Days 21 and 42). [SCR is defined as the proportion of subjects who have either a pre-vaccination reciprocal HI titer < 10 and a post-vaccination reciprocal titer ≥ 40, or a pre-vaccination reciprocal HI titer ≥ 10 and at least a 4-fold increase in post vaccination reciprocal titer against the vaccine virus.]
    - To assess whether H5N1 antigen in association with AS03 elicits an immune response, measured by post-immunization vaccine-homologous virus HI titers, that meets or exceeds the CHMP guideline target for MGI in young adults (>2.5) in the various active treatment group 21 days after the first and second doses (Days 21 and 42).
    - To describe the immunogenicity of the vaccine in terms of seropositivity rate, GMT, SCR, SPR, and MGI in terms of point estimates and 95% CI, 6 months (182 days) and 12 months (385 days) following the first dose of vaccine.
    - To further describe the immunogenicity of the vaccine regimen in terms of [redacted] titers specific for the vaccine-homologous virus and for one or more drift-variant viruses.
- To describe the safety of Q-Pan H5N1 compared with placebo in pediatric subjects 6 months to <18 years of age in terms of clinical laboratory abnormalities, as assessed in Year 1.
- To describe the safety of Q-Pan H5N1 in terms of solicited local and general reactogenicity events, unsolicited adverse events (AEs), medically attended adverse events (MAEs), potential immune mediated diseases (pIMDs), and serious adverse events (SAEs) compared with placebo in pediatric subjects 6 months to <18 years of age, as assessed in Years 1 and 2.

6.1.2 Design Overview

Study Year 1 was a randomized, double-blind, placebo-controlled study to evaluate the immunogenicity and safety of Q-Pan H5N1 in children aged 6 months to 17 years. Planned enrollment was 825 subjects randomized 8:3 to receive two doses of Q-Pan H5N1 (600 subjects) or placebo (225 subjects) given 21 days apart. The randomization algorithm used a minimization procedure accounting for center, age strata (approximately 1:1:1 for 6 to < 36 months, 3 to < 9 years, and 9 to < 18 years), and

history of seasonal influenza vaccination (Yes or No) in the current and prior two seasons, including pandemic strain A/H1N1 vaccine. Duration of the study for each subject was 385 days. At the end of Study Year 1, following the database freeze, unblinding occurred. Year 2 was a crossover, open-label study to evaluate the safety of the same dose and schedule of Q-Pan H5N1 in Year 1 placebo recipients who remained eligible and elected to receive the vaccine. Study Year 2 had an additional study duration of 385 days per subject.

The original study protocol dated June 3, 2010, was amended four times.

Reviewer comment: Prior to study initiation, independent data monitoring committee oversight was added. Revisions following study initiation were generally minor and did not significantly or differentially affect study conduct for subjects. The study design was adequate to assess immunogenicity of Q-Pan H5N1. The planned enrollment of 825 subjects, 600 receiving the candidate vaccine, limits the ability to detect rare safety signals. Consequently, additional safety data in the pediatric population from Year 2 of this study and from study Q-Pan-035, which evaluated a related, non-US licensed vaccine with AS03 adjuvant (Q-Pan H1N1), were viewed by CBER as supplemental safety evaluations for this small population.

The study design was reviewed and agreed upon by CBER. The randomization and blinding procedures were deemed adequate by the statistical reviewer.

6.1.3 Population

Relevant eligibility criteria included:

- Healthy children ≥ 6 months and <18 years of age at the time of first vaccination. Age requirement applied to Year 1 only.
- No prior receipt of H5N1 vaccine, seasonal influenza vaccine within 14 days (inactivated vaccine) or 30 days (live vaccine), any other vaccine up to 42 days from baseline
- No significant acute or chronic uncontrolled illness
- No history of allergy to influenza
- Temperature < 38°C (< 100.4°F) at baseline
- No cancer diagnosis within previous 3 years
- No immunosuppressive or immunodeficient conditions
- No receipt of systemic glucocorticoids within 1 month, cytotoxic or immunosuppressive drugs within 6 months, or immunoglobulins within 3 months of the start of study and throughout the study

Reviewer comment: Subjects who had previously received AS03 were not excluded from study enrollment. As Arepanrix, an AS03-adjuvanted H1N1 vaccine, was available in Canada during the 2009 H1N1 pandemic, it is possible that subjects who had previously received AS03 were enrolled in the study. It does not appear that prior receipt of vaccine containing AS03 was collected by GSK. Due to the potential for immune response interference with prior influenza vaccination, there was a minimization procedure based on prior influenza vaccine. This procedure accounted for year, but did not account for type of vaccine. Therefore, an individual subject's exposure to AS03 may be greater than that defined by this study and is unknown.

The eligibility criteria were identical in Year 2, except that Year 1 subjects who received placebo and had aged beyond the pediatric category at the start of Year 2 were eligible to be enrolled if all other criteria were met. There was no requirement to complete all study visits in Year 1 to enroll in Year 2.

Female subjects who were pregnant or lactating were not allowed to participate. A negative urine pregnancy test was required for all female subjects at least 9 years of age at the time of each dose of study vaccine.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Each 0.25 mL pediatric dose of active vaccine consisted of 0.125 mL of antigen (15 µg/mL = 1.9 µg hemagglutinin (HA) of the influenza virus strain A/Indonesia/05/2005 (H5N1)), 2.5 µg thimerosal) and 0.125 mL of AS03 adjuvant (47.4 mg/mL = 5.93 mg DL-α-tocopherol, 5.35 mg squalene, and 2.43 mg polysorbate 80).

Subjects received either active vaccine or 0.25 mL of phosphate buffered saline, administered intramuscularly (IM), on Days 0 and 21. Q-Pan H5N1 and placebo were not identical in appearance. Consequently, individuals who prepared and administered vaccine and placebo did not participate in any study evaluations.

The following lot numbers were used in the study:
Year 1
- Q-Pan H5N1 Antigen: DFLPA606A
- Q-Pan H5N1 Adjuvant: AA03A209C
- Placebo: PFLSA003A

Year 2
- Q-Pan H5N1 Antigen: DFLPA659A
- Q-Pan H5N1 Adjuvant: AA03A209C

6.1.5 Directions for Use

Vaccine preparation required mixing of multiple components, instructions for which were provided in the Study Procedures Manual. Study sites were instructed to store vaccine at +2 to +8°C in a safe and locked place.

For subjects at one year of age and older, the first injection of the two-dose series was preferably given in the deltoid region of the dominant arm and the second in the non-dominant arm. For subjects less than one year of age, the first injection was given in the left anterolateral thigh and the second in the right anterolateral thigh.

6.1.6 Sites and Centers

This study was conducted by 17 investigators at 17 centers, including 11 in the United States (US), 5 in Canada, and 1 in Thailand.

Table 3 Participating clinical sites with number of subjects enrolled by study group into the Total Vaccinated Cohort, Study Q-Pan-021

Site #	Location	Country	Q-Pan Group	Placebo Group	Total Enrolled	%
85650	Hamilton, Ontario	Canada	14	4	18	2.1%
85651	Sudbury, Ontario	Canada	28	14	42	5.0%

Site #	Location	Country	Q-Pan Group	Placebo Group	Total Enrolled	%
85652	Sherbrooke, Québec	Canada	10	2	12	1.4%
85653	Sherbrooke, Québec	Canada	10	3	13	1.6%
85654	Coquitlam, British Columbia	Canada	9	2	11	1.3%
85911	Newton, Kansas	US	23	7	30	3.6%
85912	Bardstown, Kentucky	US	34	11	45	5.4%
85913	San Angelo, Texas	US	21	11	32	3.8%
85914	Henderson, Nevada	US	35	12	47	5.6%
85915	Sacramento, California	US	23	9	32	3.8%
85916	Paramount, California	US	24	8	32	3.8%
85917	Fort Worth, Texas	US	34	12	46	5.5%
85988	Omaha, Nebraska	US	56	21	77	9.2%
85989	Metairie, Louisiana	US	37	12	49	5.8%
85990	Cleveland, Ohio	US	17	12	29	3.5%
86640	St. Louis, Missouri	US	22	9	31	3.7%
87086	Khon Kaen	Thailand	210	82	292	34.8%

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 37, p.119
Total proportions may not add up to 100% due to rounding of proportions at individual sites.

Reviewer comment: The site in Khon Kaen, Thailand enrolled the most subjects (35%); the site in Omaha, Nebraska was the second highest enrolling site (9%). The remaining sites enrolled a median of 3.8% of the total vaccinated cohort.

6.1.7 Surveillance/Monitoring

Screening evaluations were completed up to 28 days prior to Day 0 or on Day 0. During Year 1, all subjects had visits at Day 0, 7, 21, 28, and 42. Year 1 subjects were randomly assigned either to a Day 182 study visit and Day 385 telephone contact, or to a Day 182 telephone contact and Day 385 study visit.

Immunogenicity blood draws were performed at baseline, on Day 21 (prior to receiving the second dose), 42, 182 (50% of subjects), and 385 (50% of subjects). All assessments supporting primary and secondary objectives (including safety laboratory assessments, see below) were performed using standardized and validated procedures by a GSK Biologicals' designated laboratory that was blinded to subject treatment assignment. In each age group, three sets of 40 subjects in the study vaccine group and 10 subjects in the placebo group were randomly selected to be tested by [redacted] assay at one of the following three groups of time points: 1) Days 0, 21, and 42; 2) Day 182; and 3) Day 385.

Safety laboratory assessments consisted of complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), bilirubin (total and direct) and creatinine. They were performed on Days 0, 42, 182 (50% of subjects), and 385 (50% of subjects). Clinically significant laboratory abnormalities were followed until they had returned to normal, or a satisfactory clinical explanation had been provided.

All subjects were followed for local injection site reactions (pain, redness, and swelling) and general symptoms (drowsiness, fever, irritability/fussiness, and loss of appetite for children younger than 6 years of age; fatigue, fever, gastrointestinal symptoms, headache, joint pain, muscle aches, shivering (chills), and increased sweating for children 6 years of age and older), which were solicited on diary cards on the day of vaccination and the following six days. All unsolicited adverse events were recorded on diary cards for 21 days following each vaccination (through study Day 42). Concomitant medications, including prophylactic medications and vaccines, and excluding vitamins and dietary supplements, were collected through 21 days following the second vaccination (Day 42).

Following Day 42, all subjects were followed for serious adverse events (SAEs), potential immune-mediated diseases (pIMDs), and medically attended adverse events (MAAEs) for one year following the second vaccination. Potential immune-mediated diseases (pIMDs) include both clearly autoimmune diseases and other inflammatory and/or neurologic disorders which may or may not have an autoimmune etiology (See 125419/39, CSR, Table 9, pg. 67). All concomitant medications were collected during the primary study period (through Day 42); those used to treat an SAE were collected during the entire study period (through Day 385). Any pregnancy occurring from Day 0 through Day 385 was to be reported to the Sponsor and followed until its conclusion.

Reviewer comment: The pIMD list is appropriate with the exception that narcolepsy and morphea are not included in the protocol-specified list, but are currently listed as pIMDs by CBER. This is possibly due to the evolution in CBER's thinking on pIMDs. From Day 42 through Day 385, only concomitant medications used to treat an SAE were collected. As pIMDs arising at least in part secondary to vaccination, may not manifest or be diagnosed within this short time frame (21 days following the second vaccination), concomitant medication information may be of limited value in assisting with identifying pIMDs that were not categorized as such by investigators.

In Study Year 2, subjects had visits on Days 0, 21, and 42, and telephone contacts on Days 7, 28, 182, and 385. Procedures for collection of solicited AEs, unsolicited AEs, MAEs, pIMDs, SAEs, and concomitant medications were identical to Year 1. No immunogenicity or safety laboratory assessments were performed in Year 2.

An independent Data Monitoring Committee (DMC), consisting of three physicians, one in each country in which the study was conducted, and a statistician, periodically reviewed safety data to ensure continued safety of the study participants throughout the study.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoints, as specified by GSK, were:

- Serum homologous H5N1 HI antibody titers on Day 42
- SPR on Day 42

The study would meet its success criterion if the lower limit of the 98.3% confidence bound for the proportion of subjects achieving HI titer ≥ 1:40 on Day 42 met or exceeded 70% for any vaccine group. The 98.3% CI was used as this criterion was evaluated independently in 3 age groups: 6 to < 36 months, 3 to < 9 years, and 9 to < 18 years of age.

Reviewer comment: As noted above, GSK defines SPR to be proportion of subjects achieving HI titer ≥ 1:40, which they note may be a protective level of antibody based upon extrapolation from seasonal influenza data. The protective effect of this level is not known.

The secondary immunogenicity endpoints assessed for all subjects on Days 0, 21, and 42, for 50% of subjects on Day 182, and for the remaining 50% of subjects on Day 385 were:

- For the vaccine-homologous strain:
  - Serum H5N1 HI antibody titers on Days 0, 21, 42, 182, and 385
  - Serum H5N1 [redacted] antibody titers on Days 0, 21, 42, 182, and 385
  - SPRs and GMTs assessed by HI on Days 0, 21, 42, 182, 385; assessed by [redacted] on Days 0, 21, 42, 182, and 385
  - Seroconversion rate (SCR) assessed by HI on Days 21, 42, 182, 385
  - Mean geometric increase (MGI) assessed by HI on Days 21, 42, 182, 385
  - Vaccine response rate (VRR) assessed by [redacted] on Days 21, 42, 182, and 385
- For the drift variant strain A/Vietnam/1194/2004 (H5N1):
  - Serum [redacted] antibody titers on Days 0, 21, 42, 182, and 385
  - Seropositivity rates and GMTs: assessed by [redacted] on Days 0, 21, 42, 182, and 385
  - VRR assessed by [redacted] on Days 21, 42, 182, and 385

GSK uses the following definitions, in addition to their above noted definition of SPR:

- SCR - The proportion of subjects who have either a pre-vaccination reciprocal HI titer <10 and a post-vaccination reciprocal titer ≥ 40, or a pre-vaccination reciprocal HI titer ≥10 and at least a 4-fold increase in post vaccination reciprocal titer against the vaccine virus.
- MGI - The geometric mean of the within-subject ratios of the post-vaccination reciprocal hemagglutination inhibition (HI) titer to the pre-vaccination reciprocal HI titer for the vaccine virus.
- VRR - The proportion of vaccinees with a 4-fold increase in post-vaccination reciprocal titer relative to Day 0.

There was no assessment of immune response in Study Year 2.

Reviewer comment: Assessments based upon HI titers were evaluated using the entire according to protocol for immunogenicity (ATP-I) cohort for the appropriate time point. Assessments based upon [redacted] titers were evaluated using a randomly selected subgroup of subjects*. As the A/Indonesia/5/2005 strain and the A/Vietnam/1194/2004 strain are of different clades, CBER prefers to refer to A/Vietnam/1194/2004 as the heterologous strain. This review focuses on the primary immunogenicity endpoint, which is the data used to support licensure. Secondary endpoint analyses are only briefly discussed.*

For Study Year 1 and 2, separate but identical safety analyses were conducted (except no blood samples were taken in Study Year 2). The secondary safety endpoints tabulated for each study year, unless otherwise specified, were:

- The occurrence of solicited local and general signs and symptoms during the 7-day follow-up period after each vaccine administration, and overall per subject

- Number and percentage of subjects with abnormal clinical laboratory results at Days 0, 42, 182, and 385 (Study Year 1 only)
- The occurrence of all unsolicited AEs during a 21-day follow-up period for each vaccine administration, as well as overall
- The occurrence of SAEs, MAEs, and pIMDs throughout the study
- Occurrence and relationship to vaccination of adverse pregnancy outcomes throughout the study

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Calculation

The sample size calculation was based on the primary endpoint proportion of subjects with HI titer ≥ 1:40 at Day 42 for each age group (6 to < 36 months, 3 to < 9 years, and 9 to < 18 years). The applicant used a potential SPR reference value of 82%, the lower bound of the 95% confidence interval (CI) for adults in study Q-Pan-001 who received $AS03_B$. A significance level of 0.0167 (98.3% CI) was used for assessment in each age group, making the overall type I error 5%. Assuming 20% of subjects would not be evaluable, each age group individually had a power of 83.3%.

Demographic Assessments

Descriptive statistics were used to characterize the demographics of each study group in the total vaccinated cohorts (TVC) for Years 1 and 2 and in the ATP-I.

Immunogenicity Assessments and Sample Size Calculation

The primary immunogenicity analysis was conducted on the ATP-I for Day 42. As was pre-specified in the statistical analysis plan, the analysis was also performed on the TVC because the percentage of vaccinated subjects excluded from the ATP-I analysis was > 5% in Study Year 1. The secondary immunogenicity analyses were conducted on the ATP-I cohorts for the appropriate Day (21, 42, 182, or Day 385). See Section 6.1.10.1 for definitions of study populations.

Hypotheses were tested for each age group, 6 months to < 36 months, 3 to < 9 years, and 9 to <18 years, separately. For each treatment group, vaccine-homologous virus antibody response, as demonstrated by the proportion of subjects with HI titer ≥ 1:40 at Day 42 were evaluated with the following hypotheses:

- Null hypothesis: proportion of subjects with HI titers ≥ 1:40 ≤70%
- Alternative hypothesis: potential SPR >70% for subjects in the Q-Pan H5N1 vaccine group, 21 days after the second dose

Statistical tests of the primary immunogenicity endpoint were performed at an overall level of 0.05 type I error. Thus, for each age group, the 98.3% CI was constructed to evaluate the primary objective. If the lower bound of the 98.3% CI for the proportion of subjects with HI titer ≥ 1:40 was ≥70% for any age group, the study primary immunogenicity objective was met.

In this study, the cut-off for seropositivity was set at 1:10 for the HI assay. Antibody titers below the cut-off of the assay were given an arbitrary value of half the cut-off for the purpose of geometric mean titer (GMT) calculation.

Safety Assessments

Safety assessments were based on the TVC. All TVC analyses were performed per vaccine actually administered at the first dose.

The analysis of safety was performed separately for Study Year 1 and Study Year 2 on the TVCs. In each year of the study:

- The incidence of solicited local and general symptoms that occurred during the solicited follow-up period (Days 0-6 after each dose) was tabulated with exact 95% CIs for each treatment group and age stratum. The same calculations were performed for symptoms of any intensity, those with intensity Grade ≥ 2, and those with intensity of Grade 3.
- The percentage of subjects with at least one unsolicited adverse event (AE) classified by Medical Dictionary for Regulatory Activities (MedDRA) preferred term up to 21 days after each vaccination and for 42 days following initial vaccination was tabulated with exact 95% CIs for each treatment group and age stratum. The same tabulations were performed for Grade 3 unsolicited AEs and for unsolicited AEs considered related to vaccination.
- The percentage of subjects with at least one report of an unsolicited SAE and pIMD classified by MedDRA preferred term up to 21 days after each vaccination and for 42 days following initial vaccination was tabulated with exact 95% CIs for each treatment group and age stratum.
- SAEs, pIMDs, medically attended AEs (MAAEs) and withdrawals due to AEs were described through Day 385.

The clinical laboratory results (obtained only in Year 1) were summarized by descriptive statistics and graphs. The incidence of abnormal clinical laboratory values were tabulated with exact 95% CIs for each treatment group at each Year 1 time point.

Missing Data

Missing or non-evaluable immunogenicity measurements were not replaced. Therefore, immunogenicity analyses excluded subjects with missing or non-evaluable measurements. For the analysis of solicited symptoms, missing or non-evaluable measurements were not replaced. Therefore, the analysis of the solicited symptoms based on the TVC includes only vaccinated subjects and doses with documented safety data (i.e., symptom diary returned). For analysis of unsolicited AEs, including SAEs and pIMDs, all vaccinated subjects were considered, and subjects who did not report the event were considered as subjects without the event.

Provisional Analyses

GSK performed subject-level blinded analyses at several time points, providing results to CBER in a main study report with several annexes. For the complete study report submitted for this sBLA, all analyses were repeated on the final, clean immunogenicity and safety dataset (data lock point April 23, 2014). Data released in previous study reports might have been updated or corrected. Additionally, in the final dataset there were changes related to changes in MedDRA coding version.

Reviewer comment: The final CSR submitted to this sBLA is the formal response to PMR#1. Other study reports are viewed as preliminary and have no regulatory intent.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The protocol pre-specified the populations for the immunogenicity and safety analyses.

The primary and secondary immunogenicity analyses were based on the ATP-I cohort for the appropriate time point. The ATP-I during the specified interval included all subjects who:

- met all eligibility criteria
- complied with study procedures defined in the protocol with no elimination criteria during the analysis interval
- did not have his or her treatment assignment unblinded (specified in the CSR, not the protocol)
- received the vaccine or placebo doses during the specified interval per protocol treatment assignment
- did not receive immunoglobulins, blood products, or forbidden medication during the analysis interval
- had assay results available for antibodies against the vaccine-homologous H5N1 antigen for the blood sample taken at baseline (Day 0)
- and had assay results available for antibodies against the vaccine-homologous H5N1 antigen for the blood samples taken during the specified analysis interval.

Reviewer comment: In the CSR, GSK initially included one subject who did not have Day 0 immunogenicity results in their analysis of proportion of subjects with HI titers ≥ 1:40. They also included that subject and 11 additional subjects with Day 21 immunogenicity results, but missing Day 42 results, in their analysis of demographics and subject disposition for the ATP-I Day 42. In Amendment 39.21, in response to an IR requested July 21, 2016, they submitted the reanalyzed data, which are presented below.

Because the percentage of vaccinated subjects with serological results excluded from the ATP cohort for analysis of immunogenicity was more than 5%, a second immunogenicity analysis based on the TVC was also presented. The TVC for immunogenicity in Year 1 (TVC-I) included all vaccinated subjects for whom immunogenicity endpoint measures were available.

The analysis of safety was based on the TVC. The TVC for each study year was defined as all subjects who received at least one study vaccination in that year.

6.1.10.1.1 Demographics

The following tables show the demographic characteristics of subjects in the TVC.

Table 4 Age distribution in months for the Total Vaccinated Cohort, Year 1, Study Q-Pan-021

Study Group	N	Mean	Standard deviation	Median	Range
Q-Pan	607	85.7 (7 years)	61.81	74 (6 years)	6 - 215
Placebo	231	82.8 (7 years)	60.29	64 (5 years)	7 - 215
Total	838	84.9 (7 years)	61.37	71 (5 years)	6 – 215

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 19, p.86
N number of subjects in Study Group

Table 5 Demographics for the Total Vaccinated Cohort, Year 1, Study Q-Pan-021

Demographic	Category	Q-Pan n = 607	Placebo n = 231	Total n = 838
Age	6 to < 36 months	199 (32.8%)	75 (32.5%)	274 (32.7%)
	3 to < 9 years	198 (32.6%)	76 (32.9%)	274 (32.7%)
	9 years to <18 years	210 (34.6%)	80 (34.6%)	290 (34.6%)
Gender	Female	285 (47.0%)	116 (50.2%)	401 (47.9%)
	Male	322 (53.0%)	115 (49.8%)	437 (52.1%)
Geographic Ancestry	African/ African American	93 (15.3%)	35 (15.2%)	128 (15.3%)
	American Indian/Alaskan Native	2 (0.3%)	1 (0.4%)	3 (0.4%)
	Asian*	214 (35.3%)	84 (36.4%)	298 (35.6%)
	Native Hawaiian/Other Pacific Islander	0	0	0
	White – Arabic/North African	3 (0.5%)	0	3 (0.4%)
	White – Caucasian/ European	271 (44.6%)	106 (45.9%)	377 (45.0%)
	Other	24 (4.0%)	5 (2.2%)	29 (3.5%)
Ethnicity	Hispanic or Latino	68 (11.2%)	25 (10.8%)	93 (11.1%)
	Not Hispanic or Latino	539 (88.8%)	206 (89.2%)	745 (88.9%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 19, p.86
* Asian includes Central/South, East, Japanese, and South East Asian Heritage

The Q-Pan Group was slightly older than the Placebo Group based upon the mean and median ages of the study groups. A majority of subjects in the Q-Pan Group were male, while the Placebo Group was evenly split male: female. White – Caucasian/European and South East Asian were the dominant geographic ancestry.

Demographic analyses for the ATP-I Day 42 were similar, with the exception that there were slightly more females than males in the Placebo Group (51%:49%) and the proportion of Asians was approximately 41% in both study groups (not shown).

The mean age by age group for the ATP-I Day 42 is presented in the package insert (PI) and is as follows: 22 months for 6 to < 36 months, 6 years for 3 to < 9 years, and 13 years for 9 to <18 years.

Reviewer comment: In reference to Table 3, the older age of the Q-Pan Group appears to be driven by older females in the Q-Pan Group (mean age 88 months vs. 84 months for males) and younger females in the Placebo Group (mean age 81 months vs. 85 months in males) (data not shown). Given that randomization followed a minimization procedure based on age, and the difference is small, it is unlikely to be clinically significant. Other than small differences in age and sex, demographics are similar between study groups in both the TVC and ATP-I Day 42. The racial or ethnic groups of African/African Americans, Asians, White – Caucasian/Europeans, and Hispanics each comprise at least 10% of the study population. The overwhelming majority of Asian subjects were South East Asian.

Year 2
Subjects were 27 months to 19 years old (mean 8 years; median 7 years) at the time of the first vaccination with Q-Pan in study Year 2. The following table shows the demographic characteristics of subjects in the TVC in Year 2.

Table 6 Demographics for the Total Vaccinated Cohort, Year 2, Study Q-Pan-021

Demographic	Category	Q-Pan n = 155
Age at Dose 1 Year 1	6 to < 36 months	50 (32.3%)
	36 months to < 9 years	48 (31.0%)
	9 years to <18 years	57 (36.8%)
Age at Dose 3 (Year 2)	6 to < 36 months	7 (4.5%)
	36 months to < 9 years	79 (51%)
	9 years to <18 years	64 (41.3%)
	≥ 18 years	5 (3.2%)
Gender	Female	80 (51.6%)
	Male	75 (48.4%)
Geographic Ancestry	African/ African American	17 (11.0%)
	American Indian/ Alaskan Native	0
	Asian*	75 (48.4%)
	Native Hawaiian/ Other Pacific Islander	0
	White – Arabic/ North African	0
	White – Caucasian/ European	60 (38.7%)
	Other	3 (1.9%)
Ethnicity	Hispanic or Latino	12 (7.7%)
	Not Hispanic or Latino	143 (92.3%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 20, p.87
* Asian includes Central/South, East, Japanese, and South East Asian Heritage

Subjects who participated in Year 2 were evenly distributed between the age groups from Year 1, but only a small number of subjects were in the youngest age strata (6 months - < 3 years) at the time of their first dose of Q-Pan. In Year 2, a majority of subjects were female and not Hispanic or Latino. The dominant geographic ancestry was Asian in Year 2.

Reviewer comment: Due to the very small number of subjects in the youngest age group at the time of Year 2 vaccination, it will be particularly difficult to draw conclusions from the reactogenicity data in this age group.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
GSK did not provide an analysis of baseline medical history. The protocol specified subjects enrolled were to be free of any significant acute or chronic uncontrolled illness.

Reviewer comment: The reviewer conducted an analysis of proportion of subjects with baseline medical conditions reported in each study group by age group. While the overall rates of reporting a baseline condition were similar between groups (38% in Q-Pan vs. 41% in Placebo), a lower proportion of subjects in the youngest age strata in the Q-Pan Group reported a baseline condition (31%) compared to the Placebo Group (41%). A majority of baseline conditions in this age group were either indicative of common infections or other common conditions. Placebo Group subjects in this age

group (6 months to 36 years) reported notably more skin and subcutaneous tissue disorders (8% Q-Pan, 19% Placebo), immune system disorders (9% Q-Pan, 15% Placebo), ear and labyrinth disorders (5% Q-Pan, 9% Placebo), cardiac disorders (0 Q-Pan, 1.3% Placebo – 1 subject), musculoskeletal disorders (0.5% Q-Pan, 1.3% Placebo – 1 subject each), and eye disorders (0.5% Q-Pan, 1.3% Placebo – 1 subject each). It is difficult to determine how, if at all, this lower reported rate of baseline conditions in the Q-Pan group might impact the safety. One possible theory is that subjects reporting a higher rate of baseline conditions (placebo group) might be more likely to experience/report adverse events during the treatment period and subjects reporting less baseline conditions (Q-Pan group) less likely.

GSK provided an analysis of the proportion of subjects who had received prior influenza vaccine (45.4%) and influenza vaccine in each influenza season 2008-2011. GSK provided a descriptive statistical analysis of subject vital signs at baseline.

Reviewer comment: A similar proportion of subjects in the Q-Pan and Placebo Groups received at least one prior influenza vaccine by age strata. There were small differences noted when comparing vaccine receipt in individual seasons between the study groups. Specifically, in the 6 – < 36 months age group, 3% of Q-Pan vs. 6.7% of placebo recipients reported influenza vaccination in 2008-2009. In the 9 – < 18 year age group, 36.2% of Q-Pan vs. 30% of placebo reported vaccination in 2009-2010 and 21.4% of Q-Pan vs. 16.3% of Placebo in 2010-2011. Please see section 6.1.11.5 for a discussion of the differences in immune response based on prior influenza vaccination. There were no clinically significant differences in baseline vital signs between study groups.

6.1.10.1.3 Subject Disposition

Overall subject disposition, Year 1

Eight hundred eighty-one subjects were screened for enrollment into Q-Pan-021; forty-one subjects were screen failures. In amendment 39.23, submitted in response to an IR sent on August 17, 2016, GSK specified the reasons for screen failures: eligibility criteria not fulfilled (21 subjects), baseline blood sample not obtained (8 subjects), subject lost to follow-up prior to vaccination (5 subjects), consent withdrawn prior to vaccination (4 subjects), age group closed to enrollment at the site (2 subjects), and SAE of pyelonephritis prior to vaccination (1 subject).

840 subjects met eligibility criteria and were randomized to either Q-Pan or placebo. One subject in each group was randomized but did not receive vaccine. In amendment 39.23, GSK also clarified that the two subjects that were randomized but did not receive vaccine, did so because a baseline blood sample was unable to be obtained. Therefore, 838 subjects were included in the TVC. The table below shows subject disposition in study Year 1.

Table 7 Subject disposition at screening and at the conclusion of Year 1, Q-Pan-021

	Q-Pan	Placebo	Total
Planned	600	225	825
Screened	-	-	881
Screen Failures	-	-	41 (4.7%)*
Screen Passes/ Randomized	608	232	840 (95.3%)*
TVC	607	231	838 (95.1%)*

	Q-Pan	Placebo	Total
Completed the study	565 (93.1%)	217 (93.9%)	782 (93.3%)
Withdrawn	42 (6.9%)	14 (6.1%)	56 (6.7%)
Reason Withdrawn			
Consent withdrawn, not due to an AE	7 (1.2%)	4 (1.7%)	11 (1.3%)
Moved from the study area	7 (1.2%)	2 (0.9%)	9 (1.1%)
Lost to follow-up	24 (4.0%)	8 (3.5%)	32 (3.8%)
- Subject didn't complete vaccination	7 (1.2%)	2 (0.9%)	9 (1.1%)
- Subject completed vaccination	17 (2.8%)	6 (2.6%)	23 (2.7%)
Other†	2 (0.3%)	0	2 (0.2%)
Unknown	2 (0.3%)	0	2 (0.2%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 13 and 15, p.81 and 82
TVC = Total Vaccinated Cohort
* % of screened
† Two subjects discontinued due to "Unavailable"

The rate of study completion was 93-94% in both study groups. There were no notable differences between study groups in reasons for study withdrawal. GSK reports that no subjects discontinued the study due to an SAE or AE. Of all subjects vaccinated, 97.7% of the Q-Pan Group and 97.0% of the Placebo Group received both vaccinations; 2.3% of the Q-Pan Group and 3.0% of the Placebo Group dropped out prior to completing the two-dose vaccine series (Table 8).

Reviewer comment: The rate of study completion was acceptable and similar between the two study groups. Two subjects in the Q-Pan Group completed the Day 182 visit, then have no specified reason for not completing the Day 385 visit (listed as "Unknown" in the table above). Neither of these subjects reported unsolicited adverse events which could have reasonably led to study discontinuation, in the opinion of this clinical reviewer.

More children in the youngest age stratum, 6 months to < 3 years of age, withdrew from the study (35 subjects, 12.8%) compared with children in the older age strata. This was seen in both the Q-Pan (27 subjects withdrew, 13.6%) and the Placebo (8 subjects, 10.7%) Groups. The most common reason for withdrawal in the youngest age stratum was loss to follow-up following completion of vaccination, which occurred at a similar rate in both the Q-Pan (13 subjects, 6.5%) and Placebo (4 subjects, 5.3%) Groups.

Reviewer comment: Rates of study discontinuation and reasons for discontinuation were similar between study groups and acceptable. Subjects in the Q-Pan Group did not discontinue for any reason, discontinue due to consent withdrawal, or discontinue due to loss to follow-up prior to completing vaccination at a clinically significantly greater rate than the Placebo Group.

Safety analysis population disposition, Year 1
All subjects who were vaccinated were evaluable for safety.

Immunogenicity analysis population disposition, Year 1
The ATP-I for Day 42 immunogenicity analysis was used for evaluation of the primary objectives. The table below presents a summary of subjects from the TVC, who were excluded from the ATP-I and the reasons for exclusion. Please see section 6.1.10.1 for

the list of requirements for subjects to be included in the ATP-I cohort during the relevant analysis interval (for example, for Day 42). As more than 5% of subjects from the TVC were excluded from the ATP-I (7.8%), the Applicant provided immunogenicity results using both study populations, the ATP-I and the TVC.

Table 8 Number of subjects excluded from the According to Protocol Cohort for Immunogenicity Day 42 and the reasons for exclusion, Year 1, Study Q-Pan-021

	Q-Pan	Placebo	Total
TVC	607	231	838
Completed vaccination*	593 (97.7%)	224 (97.0%)	817 (97.5%)
Completed study Year 1	565 (93.1%)	217 (93.9%)	782 (93.3%)
ATP-I Day 42	562 (94.8%†, 92.6% of TVC)	211 (94.2%†, 91.3% of TVC)	773 (94.6%†, 92.2% of TVC)
Number in TVC but excluded from ATP-I Day 42	45 (7.4% of TVC)	20 (8.7% of TVC)	65 (7.8% of TVC)
Completed vaccination but excluded from ATP-I Day 42*	31 (5.2%†)	13 (5.8%†)	44 (5.4%†)
Reason excluded			
- Administration of forbidden vaccine	3	0	3
- Randomization failure‡	0	1	1
- Underlying forbidden medical condition	1	0	1
- Non-compliance with vaccine schedule	7	4	11
- Non-compliance with blood sampling	9	3	12
- Essential serologic data missing	25	12	37

Source: Adapted from - sBLA 125419/039/021, Table 1, p.3
If subjects had more than one reason for elimination, only the primary reason for elimination is shown
* Based upon the Clinical Reviewer's analysis, not presented by GSK
† % of those that completed vaccination
‡ One subject was randomized to the Placebo Group, but inadvertently received Q-Pan for the second vaccination.
TVC Total Vaccinated Cohort
ATP-I According to Protocol cohort for Immunogenicity

There was a trend toward more subjects completing both doses of vaccine in the older age strata, which was more noticeable in the Q-Pan Group (95.5% of subjects 6 - < 36 months, 98.0% of subjects 3 - <9 years of age, 99.5% of subjects 9 - < 17 years of age) compared to the Placebo Group (96.0% of subjects 6 months - < 3 years, 97.4% of subjects 3 - <9 years of age, 97.5% of subjects 9 - < 17 years of age).

Reviewer comment: The number of subjects included in the ATP-I at Day 42 is acceptable and similar between study groups. The one randomization failure was a Placebo Group subject who inadvertently received Q-Pan at the second dose. This subject was analyzed with the group of the first vaccination the subject received, the Placebo Group, in safety analyses as was specified in the protocol. The subject reported irritable bowel syndrome 27 days and conjunctivitis 28 days following Dose 2 (Q-Pan), as well as Bartholin gland cyst, constipation, and hemorrhoids later. These events did not significantly change any safety assessments.

Year 2

Of the 231 subjects In the Placebo Group, 155 (67.1%) were eligible and chose to enroll in Year 2; 76 (32.9%) did not enroll. The most common reason for not enrolling in Year 2 was subject declined participation (38%); all reasons for not enrolling are shown in the table below. Subjects were not required to complete all study visits in Year 1 in order to be enrolled in Year 2. Consequently, this table includes 13 of the 14 subjects who discontinued the study in Year 1 and reasons for discontinuation in Year 1 may have been different than reasons for non-participation in Year 2. One subject who was lost to follow-up in Year 1 was vaccinated in Year 2 and is not included in the table.

Table 9 Placebo subjects who did not participate in Year 2, Study Q-Pan-021

Reason	**N = 76**
Consent withdrawn, declined participation	29 (38.2%)
Moved from the study area	6 (7.9%)
Lost to follow-up	15 (19.7%)
Eligibility criteria not fulfilled	3 (3.9%)
Other	10 (13.2%)
Unknown	13 (17.1%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 14, p.82

The completion rate in Year 2 was 98.1%. Three subjects (1.9%) discontinued the study in Year 2. Two (1.3%) were lost to follow-up following administration of both vaccinations and one (0.6%) withdrew consent for a reason other than an adverse event after one vaccination.

Reviewer comment: Few subjects discontinued the study in Year 2 after receiving one vaccination. The information the Applicant provides that is presented in Table 9 is not informative because 1) subjects who discontinued the study in Year 1 are included in Table 9, 2) some subjects who discontinued the study in Year 1 reported a different reason for discontinuing in Year 2, and 3) 17% of subjects had an unknown reason for not participating in Year 2 due to a technical error with the web-based reporting system. In the opinion of the reviewer, Year 2 was a convenience sample. While it has the potential to add important information, particularly concerning SAEs and pIMDs, it is difficult to draw definitive conclusions from this uncontrolled data and results are not directly comparable to Year 1.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The protocol specified that the primary immunogenicity analysis (proportion of subjects with HI titers ≥ 1:40, possibly indicative of protection) was to be conducted on the ATP-I Day 42, which required subjects to have an immunogenicity assessment at Day 0 and Day 42. GSK initially presented the immunogenicity results including subjects who were not part of the ATP-I cohort(s). They provided an analysis excluding these subjects in Amendment 21, in response to an IR requested on July 21, 2016. These results are presented below. 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 as specified in the statistical analysis plan on all members of the TVC with immunogenicity data.

Table 10 Number and proportion of subjects with Day 42 HI titers against the A/Indonesia/05/2005 virus strain ≥ 1:40 in the According to Protocol cohort for immunogenicity Day 42, Year 1, Q-Pan-021

Study Group	Age	N	n	% subjects with HI titer ≥ 1:40	98.3% CI
Q-Pan	**6 to < 36 months**	175	175	100	97.3, 100
	3 to < 9 years	184	183	99.5	96.3, 100
	9 to <18 years	203	201	99.0	95.8, 99.9
Placebo	**6 to < 36 months**	64	0	0	0, 7.2
	3 to < 9 years	71	0	0	0, 6.5
	9 to <18 years	76	1	1.3	0, 8.6

Source: sBLA 125419/039/021, Table 3, p. 5
GSK considered the proportion of subjects with HI titer ≥ 1:40 to be equivalent to seroprotection rate (SPR).
Baseline, Day 21, and Day 42 results were analyzed on protocol-defined ATP-I cohort at Day 42.
N number of subjects in each group with immunogenicity results available
n number of subjects with hemagglutination inhibition titer ≥ 1:40
HI hemagglutination inhibition
CI confidence interval
GMT geometric mean titer

Reviewer comment: The primary immunogenicity outcomes were met, with a lower bound of the confidence interval around the proportion of subjects with HI titers ≥ 1:40 > *70% in each age strata. Proportion of subjects with HI antibody titer ≥ 1:40 and GMT based on HI titer in the TVC were nearly identical to results in the ATP-I (data not shown).*

6.1.11.2 Analyses of Secondary Endpoints

Important secondary endpoints, proportion of subjects with HI titers ≥ 1:40 and GMTs at all study time points in the Q-Pan Group, are shown in the table below.

Table 11 Number and proportion of subjects with Day 42 HI titers against the A/Indonesia/05/2005 virus strain ≥ 1:40 and Geometric mean titers for all study time points by age group in the Q-Pan Group in the adapted According to Protocol cohort for immunogenicity, Year 1, Q-Pan-021

Age and Timing	N	n	% subjects with HI titer ≥ 1:40	% with HI titer ≥ 1:40 95%CI	GMT	GMT 95%CI
6 to < 36 months Baseline	175	0	**0.0**	0.0, 2.1	**5.2**	5.1, 5.4
6 to < 36 months Day 21	172	100	**58.1**	50.4, 65.6	**38.2**	33.3, 43.7
6 to < 36 months Day 42	175	175	**100.0**	97.3, 100.0	**777.1**	705.6, 855.9
6 to < 36 months Day 182	84	80	**95.2**	88.3, 98.7	**90.6**	78.1, 105.0
6 to < 36 months Day 385	63	54	**85.7**	74.6, 93.3	**65.6**	55.9, 76.9
3 to < 9 years Baseline	184	2	**1.1**	0.1, 3.9	**5.6**	5.3, 5.9
3 to < 9 years Day 21	183	109	**59.6**	52.1, 66.7	**44.5**	39.0, 50.8

Age and Timing	N	n	% subjects with HI titer ≥ 1:40	% with HI titer ≥ 1:40 95%CI	GMT	GMT 95%CI
3 to < 9 years Day 42	184	183	**99.5**	96.3, 100.0	**541.2**	482.5, 607.1
3 to < 9 years Day 182	89	75	**84.3**	75.0, 91.1	**57.4**	50.8, 64.9
3 to < 9 years Day 385	84	46	**54.8**	43.5, 65.7	**32.8**	28.0, 38.4
9 to < 18 years Baseline	203	1	**0.5**	0.0, 2.7	**5.7**	5.4, 6.1
9 to < 18 years Day 21	203	108	**53.2**	46.1, 60.2	**35.4**	31.7, 39.6
9 to < 18 years Day 42	203	201	**99.0**	95.8, 99.9	**416.2**	371.5, 466.2
9 to < 18 years Day 182	87	63	**72.4**	61.8, 81.5	**50.2**	43.3, 58.2
9 to < 18 years Day 385	95	27	**28.4**	19.6, 38.6	**21.6**	18.6, 25.1

Source: Adapted from - sBLA 125419/039/021, Table 4, p.6
Baseline, Day 21, and Day 42 results were analyzed on protocol-defined ATP-I cohort at Day 42. Day 182 and 385 results were analyzed on their respective protocol-defined ATP-I cohort.
N number of subjects in each group with immunogenicity results available
n number of subjects with hemagglutination inhibition titer ≥ 1:40
HI hemagglutination inhibition
CI confidence interval
GMT geometric mean titer

Reviewer comment: Similar to the results seen in the adult trials, two doses are required in all age cohorts to reach the CBER guidance immune response criteria. HI titers decrease over time and decrease more dramatically in the older age cohorts. They decreased to below CBER guidance criteria by Day 182 in subjects 9 to < 18 years of age and by Day 385 in subjects 3 to < 9 years of age. SCRs were nearly identical to potential SPRs as expected in a population previously unexposed to the antigen.

GSK provided analyses of the secondary endpoints of neutralizing antibody against the vaccine-homologous strain A/Indonesia/05/2005 and the heterologous strain A/Vietnam/1194/2004. The [redacted] assays were performed in a randomly selected subset of subjects (40 subjects receiving Q-Pan and 10 subjects receiving placebo in each age group) at Days 0, 21, and 42, and Days 182 and 385.

Of the subjects with Day 42 [redacted] titers, 13 of 138 (9.4%) subjects were seropositive, defined as [redacted] antibody titer ≥ 28 1/DIL, for the vaccine-homologous strain at baseline. Most of these subjects had [redacted] titers that were barely positive (28). Of the subjects with Day 42 [redacted] titers, 49 of 137 (35.8%) subjects were seropositive for the heterologous strain at baseline. Of these subjects, one had an [redacted] titer of 113; the remainder had titers of 28 (35 subjects) or 57 (13 subjects). Baseline seropositive subjects were enrolled from all three countries.

The statistical reviewer performed an analysis of neutralizing antibody GMT using the protocol-defined ATP-I Day 42 cohort and subjects with [redacted] data at the other time points who were not eliminated from the ATP-I. These results differ slightly from those presented by GSK in the CSR. Based upon this analysis, vaccine homologous Day 42 GMTs in the Q-Pan Group were 856 for subjects 6 to <36 months of age, 658 for subjects 3 to <9 years of age, and 381 for subjects 9 to < 18 years of age. At Days 182

and 385, vaccine-homologous GMTs were approximately 75-85% of the peak value. Heterologous strain Day 42 GMTs in the Q-Pan Group were 68 for subjects 6 to <36 months of age, 72 for subjects 3 to <9 years of age, and 65 for subjects 9 to < 18 years of age. At Days 182 and 385, the heterologous strain GMTs were approximately 5-45% of the peak value.

Reviewer comment: Several changes in the [redacted] assays were implemented and submitted to the sBLA. The changes in assay method were reviewed by the CMC reviewer and the statistical assay reviewer and were not found to notably impact the assay performance. The bridging studies suggest that the assay used for this study may underestimate [redacted] titers at titers [redacted]. Please see Dr. Hana Golding's and Dr. Rong Fu's review of the neutralizing antibody assay submitted with this sBLA for a discussion of the assay and its validation.

Heterologous strain Day 42 GMTs in the Q-Pan Group were notably lower compared to Day 42 GMTs for the vaccine-homologous strain. At the 6 month and one year time points, the heterologous neutralizing antibody titers appear to decline less dramatically than the neutralizing antibody titers for the vaccine-homologous strain. Because of the way subgroups for [redacted] testing were defined in study Q-Pan-021 and the fact that samples were collected for three different randomly selected groups of subjects for testing at three different groups of time points (Days 0, 21, and 42; Day 182; and Day 385), Days 0, 21, and 42 [redacted] assay data were not available for any subjects tested at the Day 182 and subjects tested at the Day 385 time points. This limits interpretation of long term trend in neutralizing antibody levels.

6.1.11.3 Subpopulation Analyses

No subpopulation analysis, aside from age, was pre-specified in the protocol. In Amendment 19, in response to an IR requested July 1, 2016, GSK provided an analysis of subjects achieving an HI titer ≥ 1:40 and GMT by sex and geographic ancestry. This analysis appears in the Tables below for the Q-Pan Group.

Table 12 Number and proportion of subjects with Day 42 HI titers against the A/Indonesia/05/2005 virus strain ≥ 1:40 and Geometric mean titers for all study time points by sex in the Q-Pan Group in the adapted According to Protocol cohort for immunogenicity, Year 1, Q-Pan-021

Sex and Timing	N	n	% subjects with HI titer ≥ 1:40	% with HI titer ≥ 1:40 95%CI	GMT	GMT 95%CI
Male Baseline	301	1	**0.3**	0.0, 1.8	**5.5**	5.3, 5.6
Male Day 21	300	167	**55.7**	49.8, 61.4	**37.3**	33.9, 41.1
Male Day 42	299	297	**99.3**	97.6, 99.9	**529.2**	481.9, 581.1
Male Day 182	136	110	**80.9**	73.3, 87.1	**60.3**	53.2, 68.2
Male Day 385	133	68	**51.1**	42.3, 59.9	**32.4**	28.1, 37.4
Female Baseline	269	3	**1.1**	0.2, 3.2	**5.6**	5.4, 5.9
Female Day 21	267	156	**58.4**	52.3, 64.4	**41.5**	37.4, 46.2
Female Day 42	264	263	**99.6**	97.9, 100.0	**578.5**	526.7, 635.4
Female Day 182	124	108	**87.1**	79.9, 92.4	**67.5**	60.1, 75.8
Female Day 385	110	60	**54.5**	44.8, 64.1	**34.5**	29.6, 40.4

Source: Adapted from - sBLA 125419/039/19, Table 17, p.33

Baseline, Day 21, and Day 42 results were analyzed on protocol-defined ATP-I cohort at Day 42. Day 182 and 385 results were analyzed on their respective protocol-defined ATP-I cohort.
N number of subjects in each group with immunogenicity results available
n number of subjects with hemagglutination inhibition titer ≥ 1:40
HI hemagglutination inhibition
CI confidence interval
GMT geometric mean titer

Both males and females required two doses of Q-Pan to achieve the CBER guidance immune response criteria. A decline in immune response to below the guidance criteria is seen in both sexes by Day 385.

Reviewer comment: A slightly greater immune response is seen in females compared to males by proportion of subjects with HI titers ≥ 1:40 at Day 42 and GMT at Day 21-182. These differences are not statistically significant and are consistent with differences in immune response between sexes observed with many vaccines.

Table 13 Number and proportion of subjects with Day 42 HI titers against the A/Indonesia/05/2005 virus strain ≥ 1:40 and Geometric mean titers for all study time points by geographic ancestry in the Q-Pan Group in the adapted According to Protocol cohort for immunogenicity*, Year 1, Q-Pan-021

Geographic Ancestry and Timing	N	n	% subjects with HI titer ≥ 1:40	% with HI titer ≥ 1:40 95%CI	GMT	GMT 95%CI
African/African American Baseline	84	0	**0.0**	0.0, 4.3	**5.4**	5.1, 5.6
African/African American Day 21	81	53	**65.4**	54.0, 75.7	**44.1**	35.8, 54.4
African/African American Day 42	82	81	**98.8**	93.4, 100.0	**603.3**	490.8, 741.7
African/African American Day 182	35	26	**74.3**	56.7, 87.5	**61.8**	46.8, 81.6
African/African American Day 385	31	20	**64.5**	45.4, 80.8	**37.8**	27.5, 52.0
South East Asian Baseline	206*	0	**0.0**	0.0, 1.8	**5.5**	5.3, 5.8
South East Asian Day 21	207*	125	**60.4**	53.4, 67.1	**39.9**	35.4, 45.0
South East Asian Day 42	207*	207	**100.0**	98.2, 100.0	**556.1**	506.5, 610.4
South East Asian Day 182	114	99	**86.8**	79.2, 92.4	**60.5**	54.2, 67.6
South East Asian Day 385	89	55	**61.8**	50.9, 71.9	**38.3**	32.1, 45.6
White – Caucasian/ European Baseline	254	3	**1.2**	0.2, 3.4	**5.6**	5.4, 5.9
White – Caucasian/ European Day 21	254	135	**53.1**	46.8, 59.4	**38.1**	34.4, 42.3

Geographic Ancestry and Timing	N	n	% subjects with HI titer ≥ 1:40	% with HI titer ≥ 1:40 95%CI	GMT	GMT 95%CI
White – Caucasian/ European Day 42	249	247	**99.2**	97.1, 99.9	**545.3**	491.5, 605.0
White – Caucasian/ European Day 182	105	89	**84.8**	76.4, 91.0	**67.2**	58.1, 77.6
White – Caucasian/ European Day 385	108	48	**44.4**	34.9, 54.3	**30.6**	26.3, 35.5

Source: Adapted from - sBLA 125419/039/19, Table 18, p.34-36
Only geographic ancestries with > 10% of the According to Protocol Cohort for Immunogenicity at Day 42 are shown.
* One subject included in this table did not have baseline HI titers available, but had Day 21 and Day 42 immunogenicity laboratory results.
N number of subjects in each group with immunogenicity results available
n number of subjects with hemagglutination inhibition titer ≥ 1:40
HI hemagglutination inhibition
CI confidence interval
GMT geometric mean titer

As seen in other analyses of immunogenicity, in the three races most well-represented in the study, the immune response followed the same pattern, requiring two doses to reach CBER guidance criteria and declining after Day 42.

Reviewer comment: Peak GMT was highest in Africans/African Americans. Though there were small differences between geographic ancestry in proportion of subjects achieving HI titer ≥ 1:40 at each time point, no clear pattern emerges. None of the differences in immune response by geographic ancestry, including GMT, are statistically significant. Their clinical significance is unlikely to be important.

6.1.11.4 Dropouts and/or Discontinuations

Dropouts and discontinuations were handled in an acceptable manner and per protocol with respect to immunogenicity analyses. Please refer to Sections 6.1.10.1.3 Subject Disposition and 6.1.12.7 Dropouts and/or Discontinuations for details.

6.1.11.5 Exploratory and Post Hoc Analyses

In order to evaluate the effect of prior influenza immunization on immune response, CBER performed the analyses in the table below.

Table 14 FDA analysis of number and proportion of subjects with Day 42 HI titers against the A/Indonesia/05/2005 virus strain ≥ 1:40 and Geometric mean titers for all study time points by history of influenza vaccination in the previous 3 seasons in the Q-Pan Group in the adapted According to Protocol cohort for immunogenicity, Year 1, Q-Pan-021 (Adapted ATP cohort for immunogenicity)

Prior influenza vaccine In at least one season	Titer Timing	N	n	% subjects with HI titer ≥ 1:40	% subjects with HI titer ≥ 1:40 95% CI	GMT	GMT 95% CI
No Prior Influenza Vaccine	Baseline	312	1	0.3	0.0, 1.8	5.6	5.4, 5.8
	Day 21	309	188	60.8	55.2, 66.3	40.7	37.0, 44.8
	Day 42	312	312	100	98.8, 100.0	584.3	538.6, 633.9
	Day 182	152	129	84.9	78.2, 90.2	62.8	56.6, 69.8
	Day 385	139	73	52.5	43.9, 61.0	34	29.5, 39.2
Prior Influenza Vaccine	Baseline	250	2	0.8	0.1, 2.9	5.5	5.3, 5.7
	Day 21	249	129	51.8	45.4, 58.2	37.1	33.2, 41.4
	Day 42	250	247	98.8	96.5, 99.8	511.9	459.0, 571.0
	Day 182	108	89	82.4	73.9, 89.1	64.7	56.0, 74.8
	Day 385	103	54	52.4	42.4, 62.4	32.4	27.7, 37.9

Source: Reviewer-generated analysis from dataset SEROCOD
Baseline, Day 21, and Day 42 results were analyzed on protocol-defined ATP-I cohort at Day 42. Day 182 and 385 results were analyzed on their respective protocol-defined ATP-I cohort.
N number of subjects in each group with immunogenicity results available
n number of subjects with hemagglutination inhibition titer ≥ 1:40
HI hemagglutination inhibition
CI confidence interval
GMT geometric mean titer

Point estimates for peak GMTs at Day 42 are lower in subjects with a history of prior influenza immunization, though the results of this subgroup analysis are not statistically significant. GMTs at Days 182 and 385 are similar between subjects with and without a history of prior vaccination. A similar trend is seen when considering subjects with and without vaccination in the most recent year (2010-2011). When examined by age groups, the difference in Day 42 GMT based upon prior influenza vaccination appeared more pronounced in subjects 3 to 9 years of age and 9 to 18 years of age. Subjects 6 to 36 months of age that previously received influenza vaccine in any year had a slightly higher GMT at Day 42 compared to subjects who did not receive flu vaccine. When considering subjects with influenza vaccination in the most recent year, subjects 6 to 36 months of age demonstrated the same trend seen in older subjects.

Reviewer comment: While none of the GMTs of this post-hoc analysis are statistically significant, there may be a trend toward blunting of the immune response at Day 42 as demonstrated by GMT by HI with recent influenza vaccination.

6.1.12 Safety Analyses

6.1.12.1 Methods

Separate analyses of safety were carried out on the TVCs in Study Years 1 and 2. All subjects who received at least one dose of study vaccine or placebo, the TVC, were included in the safety analysis. The analysis of the solicited symptoms included only vaccinated subjects with documented safety data (subjects who had completed and returned the diary card).

Solicited adverse events were collected on the diary card for 7 days following each vaccination (Days 0 – 6). Unsolicited events were collected for 42 days total, 21 days following each vaccination (Days 0 – 41). MAAEs, SAEs, pIMDs, and concomitant medications were collected for one year following the second vaccination (Days 0 – 385).

The following intensity grading scales for solicited adverse events were pre-specified in the protocol:

Subjects 6 months to < 3 years

Pain at injection site
- 0 Absent
- 1 Minor reaction to touch
- 2 Cries/protests on touch
- 3 Cries when limb is moved/spontaneously painful

Redness and swelling at injection site
- 0 ≤20 mm
- 1 >20 to 50 mm
- 2 >50 to 100 mm
- 3 >100 mm

Fever (by any route or method)
- 0 <38.0°C (<100.4°F)
- 1 ≥38.0 – 38.4ºC (≥100.4 – 101.2°F)
- 2 ≥38.5 – 38.9ºC (≥101.3 – 102.1°F)
- 3 ≥39.0 – 40.0ºC (≥102.2 – 104.0°F)
- 4 >40.0°C (>104.0°F)

Irritability/Fussiness
- 0 Behavior as usual
- 1 Crying more than usual/no effect on normal activity
- 2 Crying more than usual/interferes with normal activity
- 3 Crying that cannot be comforted/prevents normal activity

Drowsiness
- 0 Behavior as usual
- 1 Drowsiness easily tolerated
- 2 Drowsiness that interfered with normal activity
- 3 Drowsiness that prevented normal activity

Loss of appetite
- 0 Appetite as usual
- 1 Eating less than usual/no effect on normal activity
- 2 Eating less than usual/interferes with normal activity
- 3 Not eating at all

Subjects 6 to < 18 years

Pain at injection site

0	Absent
1	Pain on touching the site, not otherwise
2	Pain on moving the limb which interfered with normal activities or required repeated use of pain relievers
3	Significant pain at rest; prevented normal activities as assessed by inability to attend/do work or school

Redness and swelling at injection site

0	≤20 mm
1	>20 to 50 mm
2	>50 to 100 mm
3	>100 mm

Fever (by any route or method)

0	<38.0°C (<100.4°F)
1	≥38.0 – 38.4ºC (≥100.4 – 101.2°F)
2	≥38.5 – 38.9ºC (≥101.3 – 102.1°F)
3	≥39.0 – 40.0ºC (≥102.2 – 104.0°F)
4	>40.0°C (>104.0°F)

Headache, fatigue, gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain), joint pain, muscle ache, shivering (chills), increased sweating

0	None
1	No effect on normal activities
2	Some interference with normal everyday activities or required repeated use of pain relievers (for headache, joint or muscle pain)
3	Prevented normal everyday activities as assessed by inability to attend/do work or school, or required intervention of a physician/healthcare provider

Reviewer comment: The above grading scale classifies redness and swelling of up to 20 mm as Grade 0 and is inappropriate for infants and children as young as 6 months of age. In an IR sent February 12, 2016, GSK was asked to present an analysis of these solicited local reactions using a more conservative grading scale which has been utilized in other studies of influenza vaccines:

Grade 0	*0 mm*
Grade 1	*> 0 to 20 mm*
Grade 2	*> 20 mm to 50 mm*
Grade 3	*> 50 mm*

In Amendment 39.3, GSK provided their rationale for utilizing the original grading scale, reasoning that they have used the protocol-specified grading scale in their FluLaval pediatric development program, which is licensed to age 3 and that a change in the grading of the redness and swelling would not alter the benefit/risk profile. It is the opinion of this Clinical Reviewer that redness and swelling of 20 mm, particularly in an infant, is notable enough to be reported and that presentation of solicited symptoms as "any" or "all" redness and swelling should reflect rates of redness and swelling measured > 0. Analyses of solicited local events below reflect the more conservative scale and have been used for all age groups in this study for consistency. The analyses below differ from those presented by GSK in the CSR. These analyses are presented in the PI and in PI negotiations GSK has agreed that they are accurate and relevant.

The following criteria were used to grade the maximum intensity of unsolicited AEs, including SAEs:

Grade 1 (mild) = An AE which was easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Grade 2 (moderate) = An AE which was sufficiently discomforting to interfere with normal everyday activities.
Grade 3 (severe) = An AE which prevented normal, everyday activities [For example, in a child, a severe AE would have prevented attendance at school or day care and would have necessitated the administration of prescription (symptomatic or specific) corrective therapy.]

Causality of an AE was determined by the investigator based on blinded data, by answering the question "Is there a reasonable possibility that the AE may have been caused by the investigational product?" as a "yes" or "no" response.

Safety laboratory assessments were performed on Days 0, 42, 182, and 385. Given the events of autoimmune hepatitis in related vaccines, the protocol provided an algorithm, consistent with standard of care, describing the minimum requirements for assessment of alanine aminotransferase (ALT) abnormalities observed during the study. In the absence of ALT abnormalities, the investigator may have exercised his or her clinical judgment to initiate evaluation of suspected hepatobiliary disease, triggering the algorithm, but the investigator could not disregard, based on perceived clinical insignificance, ALT values that qualified for investigation per the algorithm. Any value that qualified for investigation per the algorithm had to be reported as an AE.

6.1.12.2 Overview of Adverse Events

During the 386-day study period, no subject died and no subject withdrew due to an AE or SAE. One SAE, type 1 diabetes, was also a pIMD and was assessed by the investigator as vaccine-related, occurring in a subject who received placebo.

The table below presents an overview and analysis of solicited and unsolicited AEs collected during the protocol specified periods.

Table 15: Summary of subjects experiencing solicited, unsolicited, and serious adverse events during the protocol-specified periods for monitoring for each type of event, Study Q-Pan-021, Year 1

	Q-Pan N = 607 n (%)	**Placebo N = 231 n (%)**
Subjects with diary card follow-up Days 0 - 6	**603**	**229**
Reporting any solicited AE	490 (81.3%)	138 (60.3%)
Reporting any local solicited AE	440 (73.0%)	90 (39.3%)
Reporting any general solicited AE	350 (58.0%)	99 (43.2%)
Reporting any unsolicited AE (Days 0-42)	243 (40%)	97 (42%)
Reporting any SAE (Days 0-385)	8 (1.3%)	4 (1.7%)
Reporting any pIMD (Days 0-385)	1 (0.2%)	1 (0.4%)

	Q-Pan N = 607 n (%)	**Placebo N = 231 n (%)**
Reporting any MAAEs (Days 0-385)	189 (31.1%)	77 (33.3%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 25, p.97 and Reviewer-generated analyses using dataset REACCOD
N number of subjects in the total vaccinated cohort
n number of subjects with the event

Reviewer comment: Though GSK presents their analysis of individual solicited adverse events out of the TVC with follow-up (symptom diaries returned), their analysis of any local solicited AE, any general solicited AE, and any solicited AE is presented based upon TVC. As this analysis is an extension of the analysis of solicited AEs, they are presented based upon TVC with follow-up in the table above. Numbers differ only slightly from those presented in the CSR.

Q-Pan H5N1 is reactogenic, with a majority of subjects reporting local solicited AEs and reporting general solicited AEs within one week of vaccination. However, rates of unsolicited adverse events, SAEs, and MAAEs were similar between study groups through Day 42 and Day 385. The rate of pIMDs in the Placebo Group was twice that of the Q-Pan Group; however, these rates reflect one event reported in each group.

Solicited Adverse Events

Overall compliance in returning symptom sheets (diary cards) was greater than 97% of those who received vaccine for each age strata for each vaccine dose in Year 1. In Year 2, compliance was ≥ 95% for each age strata for each vaccine dose.

Reviewer comment: Compliance with returning diary cards was high in both Years 1 and 2.

Local Solicited Adverse Events

Injection site AEs of pain, redness and swelling were solicited on subject diary cards for 7 days (Days 0 - 6) following each dose of study vaccine. The table below presents the number and percentage of subjects in each treatment group who experienced solicited local adverse events in Year 1 by age strata. These results are based on the more conservative grading scale for redness and swelling and differ from what GSK reports in their CSR.

Table 16 FDA Analysis of subjects with local adverse events solicited on the subject diary card following each dose and overall in the Total Vaccinated Cohort with follow-up by age stratum, Study Year 1, Study Q-Pan-021

	Q-Pan Dose 1 n (%)	**Q-Pan Dose 2 n (%)**	**Q-Pan Overall n (%)**	**Placebo Dose 1 n (%)**	**Placebo Dose 2 n (%)**	**Placebo Overall n (%)**
Age 6 - < 36 months with follow-up	**N = 195**	**N = 189**	**N = 196**	**N = 73**	**N = 72**	**N = 73**
- pain	77 (39.5%)	66 (34.9%)	93 (47.4%)	18 (24.7%)	14 (19.4%)	22 (30.1%)
- redness	43 (22.1%)	46 (24.3%)	66 (33.7%)	13 (17.8%)	11 (15.3%)	19 (26.0%)

	Q-Pan Dose 1 n (%)	Q-Pan Dose 2 n (%)	Q-Pan Overall n (%)	Placebo Dose 1 n (%)	Placebo Dose 2 n (%)	Placebo Overall n (%)
- swelling	37 (19.0%)	37 (19.6%)	56 (28.6%)	8 (11.0%)	7 (9.7%)	11 (15.1%)
Age 3 - < 9 years with follow-up	**N = 197**	**N = 194**	**N = 197**	**N = 76**	**N = 74**	**N = 76**
- pain	119 (60.4%)	103 (53.1%)	140 (71.1%)	23 (30.3%)	16 (21.6%)	29 (38.2%)
- redness	46 (23.4%)	36 (18.6%)	61 (31.0%)	9 (11.8%)	4 (5.4%)	10 (13.2%)
- swelling	39 (19.8%)	35 (18.0%)	55 (27.9%)	8 (10.5%)	6 (8.1%)	14 (18.4%)
Age 9 - < 18 years with follow-up	**N = 210**	**N = 209**	**N = 210**	**N = 80**	**N = 77**	**N = 80**
- pain	154 (73.3%)	133 (63.6%)	172 (81.9%)	13 (16.3%)	13 (16.9%)	18 (22.5%)
- redness	37 (17.6%)	35 (16.7%)	54 (25.7%)	4 (5%)	8 (10.4%)	10 (12.5%)
- swelling	43 (20.5%)	35 (16.7%)	60 (28.6%)	4 (5.0%)	4 (5.2%)	7 (8.8%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 66, p. 152-153 and Reviewer-generated analyses using dataset REACCOD
N number of subjects in the total vaccinated cohort with follow-up
n number of subjects with the event

Reviewer comment: All injection site reactions were reported at higher rates in all age groups in subjects receiving Q-Pan. The most common injection site reaction was pain in all age strata. Older subjects who received Q-Pan reported more injection site pain than younger subjects (82% of subjects 9 to < 18 years of age vs. 47% of subjects 6 to < 36 months of age). There was no consistent trend toward increased rates of reported local reactions following Dose 2 compared to Dose 1.

The table below summarizes the frequency of reports of Grade 2 and 3 solicited local adverse events.

Table 17 FDA Analysis of subjects with moderate to severe local adverse events solicited on the subject diary card following each dose and overall in the Total Vaccinated Cohort with follow-up by age stratum, Year 1, Study Q-Pan-021

	Q-Pan Dose 1 n (%)	Q-Pan Dose 2 n (%)	Q-Pan Overall n (%)	Placebo Dose 1 n (%)	Placebo Dose 2 n (%)	Placebo Overall n (%)
Age 6 - < 36 months with follow-up	**N = 195**	**N = 189**	**N = 196**	**N = 73**	**N = 72**	**N = 73**
- Grade 2/3 pain	22 (11.3%)	15 (7.9%)	30 (15.3%)	3 (4.1%)	1 (1.4%)	3 (4.1%)
- Grade 3 pain	3 (1.5%)	3 (1.6%)	5 (2.6%)	2 (2.7%)	0	2 (2.7%)
- Redness > 20 mm	7 (3.6%)	1 (0.5%)	8 (4.1%)	0	0	0

- Redness > 50 mm	0	1 (0.5%)	1 (0.5%)	0	0	0
- Swelling > 20 mm	4 (2.1%)	2 (1.1%)	6 (3.1%)	0	0	0
- Swelling > 50 mm	0	1 (0.5%)	1 (0.5%)	0	0	0
Age 3 - < 9 years with follow-up	**N = 197**	**N = 194**	**N = 197**	**N = 76**	**N = 74**	**N = 76**
- Grade 2/3 pain	32 (16.2%)	29 (14.9%)	48 (24.4%)	2 (2.6%)	0	2 (2.6%)
- Grade 3 pain	5 (2.5%)	8 (4.1%)	10 (5.1%)	0	0	0
- Redness > 20 mm	11 (5.6%)	3 (1.5%)	11 (5.6%)	0	0	0
- Redness > 50 mm	4 (2.0%)	2 (1.0%)	4 (2.0%)	0	0	0
- Swelling > 20 mm	11 (5.6%)	9 (4.6%)	14 (7.1%)	0	1 (1.4%)	1 (1.3%)
- Swelling > 50 mm	4 (2.0%)	2 (1.0%)	4 (2.0%)	0	1 (1.4%)	1 (1.3%)
Age 9 - < 18 years with follow-up	**N = 210**	**N = 209**	**N = 210**	**N = 80**	**N = 77**	**N = 80**
- Grade 2/3 pain	40 (19.0%)	32 (15.3%)	52 (24.8%)	4 (5.0%)	3 (3.9%)	4 (5.0%)
- Grade 3 pain	7 (3.3%)	3 (1.4%)	10 (4.8%)	2 (2.5%)	0	2 (2.5%)
- Redness > 20 mm	5 (2.4%)	3 (1.4%)	7 (3.3%)	0	0	0
- Redness > 50 mm	1 (0.5%)	0	1 (0.5%)	0	0	0
- Swelling > 20 mm	13 (6.2%)	11 (5.3%)	18 (8.6%)	0	0	0
- Swelling > 50 mm	4 (1.9%)	1 (0.5%)	4 (1.9%)	0	0	0

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 66, p. 152 and Reviewer-generated analyses using dataset REACCOD
N number of subjects in the total vaccinated cohort with follow-up
n number of subjects with the event

One subject, a 7-year-old in the Q-Pan Group, reported redness and swelling > 100 mm following Dose 1 and Dose 2. The maximum redness and swelling was approximately 130 mm and both resolved by Day 4 following each vaccination. The subject also reported Grade 3 pain, which resolved after two days following each vaccination. Following Dose 2 the subject also reported itching at the injection site for two days. No other unsolicited local symptoms or general solicited symptoms were reported by this subject.

Reviewer comment: Grade 2 and 3 injection site reactions were reported at greater rates in the Q-Pan Group compared to the Placebo Group. Grade 3 local reactions were not common (approximately 5% or less) in any age strata.

Duration: In Amendment 39.19, in response to an IR sent on July 1, 2016, GSK provided an analysis of solicited local adverse event duration. The mean durations were as follows: injection site pain (2.2 days Q-Pan, 1.7 days Placebo), redness (2.1 days Q-Pan, 1.6 days Placebo), and swelling (2.2 days Q-Pan, 1.7 days Placebo).

Reviewer comment: In general, reported systemic solicited symptoms resolved within several days.

Year 2 Solicited Local Adverse Events

An identical analysis of solicited adverse events was performed in study Year 2. The occurrence of local solicited reactions is reported below by age of the subject at the time he or she received their first dose of Q-Pan (Dose 3 in Year 2). These numbers differ from GSK's presentation of local events by the age of the subject at Dose 1 in Year 1.

Table 18 FDA Analysis of subjects with any and severe local adverse events solicited on the subject diary card following each dose and overall in the Total Vaccinated Cohort with follow-up by age stratum, Year 2, Study Q-Pan-021

	Q-Pan Dose 1 n (%)	Q-Pan Dose 2 n (%)	Q-Pan Overall n (%)
Age 6 - < 36 months with follow-up	**N = 7**	**N = 7**	**N = 7**
- pain	3 (42.9%)	2 (28.6%)	4 (57.1%)
- Grade 3 pain	1 (14.3%)	0	1 (14.3%)
- redness	3 (42.9%)	2 (28.6%)	4 (57.1%)
- redness > 50mm	0	0	0
- swelling	3 (42.9%)	1 (14.3%)	3 (42.9%)
- swelling > 50mm	0	0	0
Age 3 - < 9 years with follow-up	**N = 79**	**N = 78**	**N = 79**
- pain	47 (59.5%)	41 (52.6%)	54 (68.4%)
- Grade 3 pain	3 (3.8%)	0	3 (3.8%)
- redness	18 (22.8%)	22 (28.2%)	29 (36.7%)
- redness > 50mm	0	0	0
- swelling	19 (24.1%)	18 (23.1%)	27 (34.2%)
- swelling > 50mm	0	0	0
Age 9 - < 18 years with follow-up	**N = 63**	**N = 62**	**N = 63**
- pain	47 (74.6%)	36 (58.1%)	51 (81.0%)
- Grade 3 pain	3 (4.8%)	1 (1.6%)	4 (6.3%)
- redness	10 (15.9%)	11 (17.7%)	19 (30.2%)
- redness > 50mm	0	0	0
- swelling	8 (12.7%)	9 (14.5%)	14 (22.2%)
- swelling > 50mm	0	0	0
Age >18 years with follow-up	**N = 5**	**N = 5**	**N = 5**
- pain	2 (40.0%)	1 (20.0%)	2 (40.0%)
- Grade 3 pain	0	0	0
- redness	0	0	0
- redness > 50mm	0	0	0
- swelling	0	0	0
- swelling > 50mm	0	0	0

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 126, p. 400 – 401 and Reviewer-generated analyses using dataset REACCOD.

N number of subjects in the total vaccinated cohort with follow-up
n number of subjects with the event

Reviewer comment: It is difficult to draw definitive conclusions from the Year 2 data because there is no comparison group, the population willing to participate in a two-year study may differ in important ways from the Year 1 population, and few subjects fall into the two age group extremes. Despite these limitations, the Year 2 local solicited AE data is reassuring. Injection site pain was the only Grade 3 local solicited AE that was reported in Year 2. There was an increase in subjects 3 to < 9 years of age reporting injection site redness following Dose 2 compared to Dose 1, but this did not translate into an increase in severe redness.

Solicited General Adverse Events

The table below presents the number and percentage of subjects in each treatment group who experienced solicited general adverse events in Year 1 by age strata. A fever was defined as temperature ≥ 38.0˚C (≥100.4˚F) by any route or method

Table 19 Analysis of subjects with general adverse events solicited on the subject diary card following each dose and overall in the Total Vaccinated Cohort with follow-up by age stratum, Year 1, Study Q-Pan-021

	Q-Pan Dose 1 n (%)	Q-Pan Dose 2 n (%)	Q-Pan Overall n (%)	Placebo Dose 1 n (%)	Placebo Dose 2 n (%)	Placebo Overall n (%)
Age 6 month - < 3 years with follow-up	**N = 195**	**N = 189**	**N = 196**	**N = 73**	**N = 72**	**N = 73**
- drowsiness	51 (26.2%)	45 (23.8%)	74 (37.8%)	16 (21.9%)	14 (19.4%)	22 (30.1%)
- irritability/fussiness	71 (36.4%)	65 (34.4%)	99 (50.5%)	25 (34.2%)	17 (23.6%)	29 (39.7%)
- loss of appetite	42 (21.5%)	32 (16.9%)	57 (29.1%)	18 (24.7%)	14 (19.4%)	24 (32.9%)
- fever	24 (12.3%)	24 (12.7%)	44 (22.4%)	7 (9.6%)	5 (6.9%)	12 (16.4%)
Age 3 - < 6 years with follow-up	**N = 98**	**N = 98**	**N = 98**	**N = 49**	**N = 46**	**N = 49**
- drowsiness	15 (15.3%)	14 (14.3%)	27 (27.6%)	3 (6.1%)	5 (10.9%)	7 (14.3%)
- irritability/fussiness	17 (17.3%)	18 (18.4%)	29 (29.6%)	7 (14.3%)	6 (13.0%)	11 (22.4%)
- loss of appetite	12 (12.2%)	13 (13.3%)	22 (22.4%)	3 (6.1%)	3 (6.5%)	5 (10.2%)
- fever	7 (7.1%)	9 (9.2%)	15 (15.3%)	6 (12.2%)	4 (8.7%)	9 (18.4%)
Age 6 - < 9 years with follow-up	**N = 97**	**N = 96**	**N = 99**	**N = 27**	**N = 27**	**N = 27**
- fatigue	14 (14.4%)	12 (12.5%)	22 (22.2%)	0	1 (3.7%)	1 (3.7%)
- GI symptoms	11 (11.3%)	6 (6.3%)	17 (17.2%)	4 (14.8%)	2 (7.4%)	6 (22.2%)

	Q-Pan Dose 1 n (%)	Q-Pan Dose 2 n (%)	Q-Pan Overall n (%)	Placebo Dose 1 n (%)	Placebo Dose 2 n (%)	Placebo Overall n (%)
- headache	19 (19.6%)	19 (19.8%)	29 (29.3%)	1 (3.7%)	1 (3.7%)	2 (7.4%)
- increased sweating	5 (5.2%)	1 (1.0%)	6 (6.1%)	0	0	0
- joint pain	7 (7.2%)	9 (9.4%)	14 (14.1%)	0	2 (7.4%)	2 (7.4%)
- muscle aches	26 (26.8%)	24 (25.0%)	35 (35.4%)	3 (11.1%)	3 (11.1%)	5 (18.5%)
- shivering/chills	1 (1.0%)	4 (4.2%)	4 (4.0%)	0	0	0
- fever	8 (8.2%)	5 (5.2%)	13 (13.1%)	0	0	0
Age 9 - < 18 years with follow-up	**N = 209**	**N = 209**	**N = 210**	**N = 80**	**N = 77**	**N = 80**
- fatigue	52 (24.9%)	40 (19.1%)	67 (31.9%)	9 (11.3%)	13 (16.9%)	18 (22.5%)
- GI symptoms	16 (7.7%)	15 (7.2%)	26 (12.4%)	9 (11.3%)	5 (6.5%)	12 (15.0%)
- headache	56 (26.8%)	37 (17.7%)	71 (33.8%)	10 (12.5%)	11 (14.3%)	16 (20.0%)
- increased sweating	15 (7.2%)	5 (2.4%)	19 (9.0%)	2 (2.5%)	2 (2.6%)	4 (5.0%)
- joint pain	29 (13.9%)	17 (8.1%)	36 (17.1%)	3 (3.8%)	5 (6.5%)	7 (8.8%)
- muscle aches	68 (32.5%)	49 (23.4%)	88 (41.9%)	8 (10.0%)	8 (10.4%)	12 (15.0%)
- shivering/chills	11 (5.3%)	12 (5.7%)	21 (10.0%)	3 (3.8%)	5 (6.5%)	7 (8.8%)
- fever	3 (1.4%)	5 (2.4%)	6 (2.9%)	1 (1.3%)	2 (2.6%)	3 (3.8%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 68 and 70, p. 157-159 and 165-171
Fever is defined as ≥ 38.0˚C (100.4˚F) by any route.
N number of subjects in the total vaccinated cohort with follow-up
n number of subjects with the event

Subjects with at least one missing value for temperature and no fever documented on days 0-6 were considered as having reported fever in the table above. Documented fevers were noted in 21% of subjects 6 to < 36 months in the Q-Pan Group vs. 16% of the Placebo Group and in 13% of subjects 3 to < 6 years of age in the Q-Pan Group vs. 16% of the Placebo Group. Incidence of fever in other age groups did not change significantly with this analysis.

Reviewer comments: A higher proportion of subjects in the Q-Pan group reported most general solicited symptoms compared to the Placebo Group with the exception of gastrointestinal symptoms. The most commonly reported general solicited AE in subjects younger than six years old was irritability/fussiness. The most commonly reported general solicited AE in subjects six years of age and older was muscle aches.

Except for shivering in subjects 6 to < 9 years of age, which was reported in 4% of subjects following Dose 2, there was not a clinically significant increase in general reactions following Dose 2 compared to Dose 1.

Fever was common in both treatment groups in subjects younger than six years of age, though it was reported more frequently in the Q-Pan Group compared to the Placebo Group. In subjects 6 to < 9 years of age, there was a clinically significant difference in reports of fever between the Q-Pan Group (13%) and the Placebo Group (0%). Rates of Grade 2 and 3 fever were also higher in this age strata in the Q-Pan Group compared to Placebo. However, no fever was reported for this age group in Year 2. There is no clear clinically significant dose dependent increase in fever or other general solicited symptoms following Dose 2.

The table below presents the frequency of moderate and severe solicited general injection site reactions.

Table 20 Analysis of subjects with Grade 2 and 3 general adverse events solicited on the subject diary card following each dose and overall in the Total Vaccinated Cohort with follow-up by age stratum, Year 1, Study Q-Pan-021

	Q-Pan Dose 1 n (%)	Q-Pan Dose 2 n (%)	Q-Pan Overall n (%)	Placebo Dose 1 n (%)	Placebo Dose 2 n (%)	Placebo Overall n (%)
Age 6 - < 36 months with follow-up	**N=195**	**N=189**	**N=196**	**N=73**	**N=72**	**N=73**
- Grade 2/3 drowsiness	18 (9.2%)	18 (9.5%)	29 (14.8%)	4 (5.5%)	5 (6.9%)	8 (11.0%)
- Grade 3 drowsiness	4 (2.1%)	6 (3.2%)	8 (4.1%)	0	2 (2.8%)	2 (2.7%)
- Grade 2/3 irritability/ fussiness	21 (10.8%)	23 (12.2%)	32 (16.3%)	9 (12.3%)	6 (8.3%)	11 (15.1%)
- Grade 3 irritability/ fussiness	3 (1.5%)	7 (3.7%)	8 (4.1%)	2 (2.7%)	1 (1.4%)	2 (2.7%)
- Grade 2/3 loss of appetite	13 (6.7%)	11 (5.8%)	20 (10.2%)	6 (8.2%)	5 (6.9%)	11 (15.1%)
- Grade 3 loss of appetite	3 (1.5%)	3 (1.6%)	6 (3.1%)	1 (1.4%)	3 (4.2%)	4 (5.5%)
- Grade 2/3 fever	11 (5.6%)	12 (6.3%)	21 (10.7%)	4 (5.5%)	5 (6.9%)	9 (12.3%)
- Grade 3 fever	6 (3.1%)	4 (2.1%)	9 (4.6%)	2 (2.7%)	2 (2.8%)	4 (5.5%)
Age 3 - < 6 years with follow-up	**N=98**	**N=98**	**N=98**	**N=49**	**N=46**	**N=49**
- Grade 2/3 drowsiness	1 (1.0%)	3 (3.1%)	4 (4.1%)	0	1 (2.2%)	1 (2.0%)
- Grade 3 drowsiness	0	1 (1.0%)	1 (1.0%)	0	0	0
- Grade 2/3 irritability/ fussiness	3 (3.1%)	5 (5.1%)	7 (7.1%)	1 (2.0%)	1 (2.2%)	2 (4.1%)
- Grade 3 irritability/ fussiness	0	2 (2.0%)	2 (2.0%)	0	0	0

	Q-Pan Dose 1 n (%)	Q-Pan Dose 2 n (%)	Q-Pan Overall n (%)	Placebo Dose 1 n (%)	Placebo Dose 2 n (%)	Placebo Overall n (%)
- Grade 2/3 loss of appetite	2 (2.0%)	3 (3.1%)	5 (5.1%)	1 (2.0%)	1 (2.2%)	2 (4.1%)
- Grade 3 loss of appetite	1 (1.0%)	1 (1.0%)	2 (2.0%)	0	0	0
- Grade 2/3 fever	4 (4.1%)	5 (5.1%)	9 (9.2%)	2 (4.1%)	3 (6.5%)	4 (8.2%)
- Grade 3 fever	2 (2.0%)	3 (3.1%)	5 (5.1%)	1 (2.0%)	0	1 (2.0%)
Age 6 - < 9 years with follow-up	**N=97**	**N=96**	**N=99**	**N=27**	**N=27**	**N=27**
- Grade 2/3 fatigue	7 (7.2%)	5 (5.2%)	10 (10.1%)	0	0	0
- Grade 3 fatigue	0	0	0	0	0	0
- Grade 2/3 GI symptoms	4 (4.1%)	1 (1.0%)	5 (5.1%)	0	1 (3.7%)	1 (3.7%)
- Grade 3 GI symptoms	1 (1.0%)	0	1 (1.0%)	0	0	0
- Grade 2/3 headache	4 (4.1%)	8 (8.3%)	10 (10.1%)	0	0	0
- Grade 3 headache	0	2 (2.1%)	2 (2.0%)	0	0	0
- Grade 2/3 increased sweating	0	0	0	0	0	0
- Grade 3 increased sweating	0	0	0	0	0	0
- Grade 2/3 joint pain	1 (1.0%)	3 (3.1%)	4 (4.0%)	0	0	0
- Grade 3 joint pain	0	1 (1.0%)	1 (1.0%)	0	0	0
- Grade 2/3 muscle aches	5 (5.2%)	5 (5.2%)	8 (8.1%)	0	0	0
- Grade 3 muscle aches	1 (1.0%)	2 (2.1%)	3 (3.0%)	0	0	0
- Grade 2/3 shivering/chills	0	1 (1.0%)	1 (1.0%)	0	0	0
- Grade 3 shivering/chills	0	1 (1.0%)	1 (1.0%)	0	0	0
- Grade 2/3 fever	3 (3.1%)	3 (3.1%)	6 (6.1%)	0	0	0
- Grade 3 fever	3 (3.1%)	1 (1.0%)	4 (4.0%)	0	0	0
Age 9 - < 18 years with follow-up	**N=209**	**N=209**	**N=210**	**N=80**	**N=77**	**N=80**
- Grade 2/3 fatigue	13 (6.2%)	12 (5.7%)	21 (10.0%)	3 (3.8%)	2 (2.6%)	4 (5.0%)
- Grade 3 fatigue	1 (0.5%)	3 (1.4%)	4 (1.9%)	1 (1.3%)	1 (1.3%)	2 (2.5%)

	Q-Pan Dose 1 n (%)	Q-Pan Dose 2 n (%)	Q-Pan Overall n (%)	Placebo Dose 1 n (%)	Placebo Dose 2 n (%)	Placebo Overall n (%)
- Grade 2/3 GI symptoms	6 (2.9%)	7 (3.3%)	13 (6.2%)	2 (2.5%)	1 (1.3%)	3 (3.8%)
- Grade 3 GI symptoms	1 (0.5%)	2 (1.0%)	3 (1.4%)	1 (1.3%)	1 (1.3%)	2 (2.5%)
- Grade 2/3 headache	11 (5.3%)	13 (6.2%)	22 (10.5%)	3 (3.8%)	2 (2.6%)	5 (6.3%)
- Grade 3 headache	1 (0.5%)	5 (2.4%)	6 (2.9%)	1 (1.3%)	2 (2.6%)	3 (3.8%)
- Grade 2/3 increased sweating	5 (2.4%)	2 (1.0%)	7 (3.3%)	1 (1.3%)	0	1 (1.3%)
- Grade 3 increased sweating	1 (0.5%)	1 (0.5%)	2 (1.0%)	0	0	0
- Grade 2/3 joint pain	9 (4.3%)	3 (1.4%)	12 (5.7%)	1 (1.3%)	0	1 (1.3%)
- Grade 3 joint pain	1 (0.5%)	0	1 (0.5%)	0	0	0
- Grade 2/3 muscle aches	18 (8.6%)	14 (6.7%)	30 (14.3%)	3 (3.8%)	1 (1.3%)	3 (3.8%)
- Grade 3 muscle aches	2 (1.0%)	2 (1.0%)	4 (1.9%)	1 (1.3%)	0	1 (1.3%)
- Grade 2/3 shivering/chills	3 (1.4%)	4 (1.9%)	7 (3.3%)	2 (2.5%)	1 (1.3%)	3 (3.8%)
- Grade 3 shivering/chills	0	1 (0.5%)	1 (0.5%)	1 (1.3%)	0	1 (1.3%)
- Grade 2/3 fever	0	1 (0.5%)	1 (0.5%)	0	1 (1.3%)	1 (1.3%)
- Grade 3 fever	0	1 (0.5%)	1 (0.5%)	0	1 (1.3%)	1 (1.3%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 68 and 70, p. 157-159 and 165-171
Grade 2/3 fever is defined as ≥ 38.5˚C (101.3˚F).
Grade 3 fever is defined as ≥ 39˚C (102.2˚F).
N number of subjects in the total vaccinated cohort with follow-up
n number of subjects with the event

There were two subjects younger than six years of age, both in the Placebo Group, with Grade 4 fever. No other Grade 4 events occurred.

Reviewer comment: Subjects in the Q-Pan Group generally reported more Grade 2 and 3 solicited AEs compared to the Placebo Group. For subjects younger than 6 years of age, Grade 3 fever was reported at approximately 5%. Subjects in the Placebo Group also reported Grade 3 or greater fever at 2 – 6% depending on age strata. Grade 3 fever was also noted in subjects 6 – 9 years of age (4%). Clinically significant increases in Grade 3 fever were not observed following Dose 2 in any age strata. There were small increases in Grade 3 reports following Dose 2 for several solicited general reactions in the Q-Pan Group. With the exception of headache, these increases are small.

Duration: In Amendment 39.19, in response to an IR sent on July 1, 2016, GSK provided an analysis of solicited general adverse event duration. The mean durations were as follows: drowsiness (2.0 days Q-Pan, 1.9 days Placebo), irritability/fussiness (2.1 days Q-Pan, 2.0 days Placebo), loss of appetite (2.1 days Q-Pan, 2.1 days Placebo), and fever (1.9 days Q-Pan, 2.4 days Placebo) for subjects younger than 6 years-old and fatigue (2.0 days Q-Pan, 2.1 days Placebo), GI symptoms (1.9 days Q-Pan, 1.9 days Placebo), headache (2.0 days Q-Pan, 2.1 days Placebo), joint pain (2.0 days Q-Pan, 1.8 days Placebo), muscle aches (2.1 days Q-Pan, 2.0 days Placebo), increased sweating (1.5 days Q-Pan, 1.3 days Placebo), shivering (1.6 days Q-Pan, 1.4 days Placebo), and fever (1.5 days Q-Pan, 2.0 days Placebo) for subjects 6 years and older.

Reviewer comment: In general, reported systemic solicited symptoms resolved within several days.

Year 2 General Solicited Adverse Events

The occurrence of local solicited reactions is presented below by age of the subject at the time he or she received the first dose of Q-Pan (Dose 3 in Year 2). These numbers differ from GSK's presentation of solicited events by the age of the subject at Dose 1 in Year 1.

Table 21 FDA Analysis of subjects with general adverse events solicited on the subject diary card following each dose and overall in the Total Vaccinated Cohort with follow-up by age stratum, Year 2, Study Q-Pan-021

	Q-Pan Dose 1 n (%)	**Q-Pan Dose 2 n (%)**	**Q-Pan Overall n (%)**
Age 6 - < 36 months with follow-up	**N = 7**	**N = 7**	**N = 7**
- drowsiness	3 (42.9%)	3 (57.1%)	4 (57.1%)
- Grade 3 drowsiness	1 (14.3%)	0	1 (14.3%)
- irritability/fussiness	3 (42.9%)	3 (42.9%)	4 (57.1%)
- Grade 3 irritability/ fussiness	1 (14.3%)	0	1 (14.3%)
- loss of appetite	3 (42.9%)	2 (28.6%)	3 (42.9%)
- Grade 3 loss of appetite	0	0	0
- fever	0	0	0
- Grade 3 fever	0	0	0
Age 3 - < 6 years with follow-up	**N = 59**	**N = 59**	**N = 59**
- reporting drowsiness	15 (25.4%)	10 (16.9%)	18 (30.5%)
- reporting Grade 3 drowsiness	0	0	0
- reporting irritability/fussiness	16 (27.1%)	13 (22.0%)	22 (37.3%)
- reporting Grade 3 irritability/ fussiness	0	0	0
- reporting loss of appetite	10 (16.9%)	9 (15.3%)	14 (23.7%)
- reporting Grade 3 loss of appetite	0	0	0
- reporting fever	3 (5.1%)	2 (3.4%)	4 (6.8%)
- reporting Grade 3 fever	2 (3.4%)	0	2 (3.4%)
Age 6 - < 9 years with follow-up	**N = 20**	**N = 19**	**N = 20**
- reporting fatigue	0	1 (5.3%)	1 (5.0%)
- reporting Grade 3 fatigue	0	0	0
- reporting GI symptoms	0	0	0
- reporting Grade 3 GI symptoms	0	0	0

	Q-Pan Dose 1 n (%)	**Q-Pan Dose 2 n (%)**	**Q-Pan Overall n (%)**
- reporting headache	1	1	2 (10%)
- reporting Grade 3 headache	1 (5%)	1 (5%)	2 (10%)
- reporting increased sweating	0	0	0
- reporting Grade 3 increased sweating	0	0	0
- reporting joint pain	0	1 (5.3%)	1 (5.0%)
- reporting Grade 3 joint pain	0	0	0
- reporting muscle aches	3 (15%)	3 (15.8%)	4 (20%)
- reporting Grade 3 muscle aches	0	0	0
- reporting shivering/chills	0	0	0
- reporting Grade 3 shivering/chills	0	0	0
- reporting fever	0	0	0
- reporting Grade 3 fever	0	0	0
Age 9 - < 18 years with follow-up	**N = 63**	**N = 62**	**N = 63**
- reporting fatigue	10 (15.9%)	9 (14.5%)	17 (27.0%)
- reporting Grade 3 fatigue	0	1 (1.6%)	1 (1.6%)
- reporting GI symptoms	5 (7.9%)	4 (6.5%)	7 (11.1%)
- reporting Grade 3 GI symptoms	0	0	0
- reporting headache	16 (25.4%)	11 (17.7%)	23 (36.5%)
- reporting Grade 3 headache	0	1 (1.6%)	1 (1.6%)
- reporting increased sweating	4 (6.3%)	2 (3.2%)	5 (7.9%)
- reporting Grade 3 increased sweating	0	0	0
- reporting joint pain	11 (17.5%)	5 (8.1%)	13 (20.6%)
- reporting Grade 3 joint pain	0	0	0
- reporting muscle aches	24 (38.1%)	17 (27.4%)	30 (47.6%)
- reporting Grade 3 muscle aches	0	0	0
- reporting shivering/chills	3 (4.8%)	4 (6.5%)	7 (11.1%)
- reporting Grade 3 shivering/chills	0	2 (3.2%)	2 (3.2%)
- reporting fever	0	1 (1.6%)	1 (1.6%)
- reporting Grade 3 fever	0	0	0
Age >18 years with follow-up	**N = 5**	**N = 5**	**N = 5**
- reporting fatigue	0	0	0
- reporting Grade 3 fatigue	0	0	0
- reporting GI symptoms	0	0	0
- reporting Grade 3 GI symptoms	0	0	0
- reporting headache	0	0	0
- reporting Grade 3 headache	0	0	0
- reporting increased sweating	0	0	0
- reporting Grade 3 increased sweating	0	0	0
- reporting joint pain	0	0	0
- reporting Grade 3 joint pain	0	0	0
- reporting muscle aches	1 (20%)	1 (20%)	1 (20%)
- reporting Grade 3 muscle aches	0	0	0
- reporting shivering/chills	0	0	0

	Q-Pan Dose 1 n (%)	Q-Pan Dose 2 n (%)	Q-Pan Overall n (%)
- reporting Grade 3 shivering/chills	0	0	0
- reporting fever	0	0	0
- reporting Grade 3 fever	0	0	0

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 127 and 128, p.402-405 and 406-413 and Reviewer-generated analyses using dataset REACCOD
Grade 2/3 fever is defined as ≥ 38.5˚C (101.3˚F).
Grade 3 fever is defined as ≥ 39˚C (102.2˚F).
N number of subjects in the total vaccinated cohort with follow-up
n number of subjects with the event

At least two subjects were identified who were older than 6 years of age in Year 2, but were given the diary card(s) for subjects younger than 6 years of age. These subjects reported symptoms but are not included in the above table. They continue to appear in the number of subjects with follow-up in the appropriate age group; removing them does not significantly impact the results above.

Reviewer comment: While it is difficult to draw conclusions from the Year 2 data, in general the rates of general solicited AEs were similar to rates reported Year 1. Fever and Grade 3 fever was reported at a much lower rate in Year 2 compared to Year 1. There was no dose-dependent increase in general reactogenicity following Dose 2 in Year 2. These results are reassuring.

Based on reactogenicity observed in both years of Q-Pan-021, general reactions that can be expected to occur commonly and more frequently in association with Q-Pan administration include irritability, drowsiness, and loss of appetite in subjects younger than 6 years of age, fever in subjects younger than 9 years of age, and myalgia, joint pain, fatigue, headache, sweating and shivering in subjects 6 to < 18 years of age. Local injection site reactions of pain, redness, and swelling are also expected to occur commonly. The reactogenicity profile is acceptable given the disease pathogenicity.

Unsolicited Adverse Events

Subjects were monitored for all AEs for 42 days following the first vaccination (Days 0 to 41). Two hundred forty-three subjects in the Q-Pan Group (40%) and 97 subjects in the Placebo Group (42%) reported at least one AE beginning Days 0 to 41 or within 21 days following second vaccination. The table below shows this unsolicited adverse event rate by age strata.

Table 22 Unsolicited adverse events reported Day 0 – 41 or 21 days following the second vaccination in the Total Vaccinated Cohort by age strata, Year 1, Q-Pan-021

	Q-Pan		Placebo	
Age stratum	**N**	**n (%)**	**N**	**n (%)**
6 months - < 3 years	199	98 (49.2%)	75	39 (52.0%)
3 years - < 9 years	198	83 (41.9%)	76	31 (40.8%)
9 years - < 18 years	210	62 (29.5%)	80	27 (33.8%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 80, p. 222-233

N total subjects in the total vaccinated cohort
n number of subjects with an event

Reviewer comment: In each age stratum, the rate of unsolicited events is similar between the Q-Pan Group and the Placebo Group.

Language proposed in the PI describes the rate of unsolicited adverse events with onset within 21 days following either dose. This is consistent with language in the PI describing the adult study. Using these criteria, 39.4% of subjects in the Q-Pan Group and 40% of subjects in the Placebo Group reported an unsolicited adverse event. Eleven events in four subjects in each study group are excluded by these criteria. All of these events were non-serious, mild to moderate common childhood illnesses with an onset date 21-24 days following the first vaccination in subjects who received two vaccinations. All events were assessed by the investigator as unrelated. Both methods of assessment were pre-specified in the protocol. The presentation used in this review are those that the reviewer believes to be most accurate within the limitations of the datasets provided – onset within 42 days following the first vaccination or 21 days following the second vaccination.

The most common unsolicited adverse events occurring within the 42 day study period in the Q-Pan Group were cough (5.9% of Q-Pan, 7.4% Placebo), nasopharyngitis (4.8% Q-Pan, 7.8% Placebo), rhinorrhea (4.4% of Q-Pan, 5.6% of Placebo), pyrexia (4.0% Q-Pan, 4.8% Placebo), upper respiratory tract infection (URI and viral URI) (3.8% Q-Pan, 3.5% Placebo), pharyngitis (including oropharyngeal pain and pharyngeal erythema) (3.5% Q-Pan, 3.5% Placebo), ear infections (ear infection, otitis media, and acute otitis media) (3.0% Q-Pan, 2.6% Placebo), vomiting (2.8% Q-Pan, 3.9% Placebo), and diarrhea (2.1% Q-Pan, 5.2% Placebo).

Events reported in the Q-Pan Group at a rate of ≥ 0.5% of subjects and at a rate at least twice that of the Placebo Group were the following:

- all administration site events combined (eczema, anesthesia, bruising, pruritus, reaction, and nodule) (1.6% Q-Pan, 0.4% Placebo)
- gastroenteritis (gastroenteritis and gastroenteritis viral) (1.2% vs. 0.4%)
- eye infections (conjunctivitis, conjunctivitis infective, and eye infection) (1.0% vs. 0.4%)
- varicella (0.7% vs. 0%)
- fatigue (0.5% vs. 0%).

When the analysis is limited to unsolicited AEs occurring within seven days following either dose of the vaccine (Days 0 – 6), events occurring in the Q-Pan Group at a rate of ≥ 0.5% of subjects and at least twice that of the Placebo Group were the following:

- eye infections (conjunctivitis, conjunctivitis infective, and eye infection) (0.5% vs. 0%)
- gastroenteritis (gastroenteritis and gastroenteritis viral) (0.7% vs. 0)
- contusion (0.7% vs. 0)
- headache (0.8% vs. 0.4%)

Reviewer comment: The most common events, overall and by age group, were common pediatric symptoms. Injection site reactions and some common childhood infections occurred at a greater rate in the Q-Pan Group compared to the Placebo Group. Injection site reactions would be expected to occur at a greater rate in the Q-Pan Group. It is possible that gastrointestinal symptoms, which are known to occur in association with Q-

Pan H5N1, could be interpreted as gastroenteritis and subsequently appear above as occurring more frequently in the Q-Pan Group. Several events were reported at higher rates in the Placebo Group compared to the Q-Pan Group; because of the uneven randomization, a very small number of events could lead to an imbalance in this direction (two in Placebo versus one or none in Q-Pan). Most likely, the discrepancy in some infection rates being reported more frequently in the Q-Pan Group occurred by chance, particularly given the uneven randomization (8:3) and the commonality of these events. In the event of an H5N1 pandemic, a small increase in risk of non-serious infections may be an acceptable risk in most cases.

Twenty-two subjects (3.6%) in the Q-Pan Group and 10 subjects (4.3%) in the Placebo Group reported at least one Grade 3 unsolicited adverse event in the 42 days following the first vaccination. The most common Grade 3 unsolicited AEs in the Q-Pan group were fever (1.2% Q-Pan, 0.4% Placebo) and diarrhea (0.5% Q-Pan, 0% Placebo). The age group 9 to < 18 years had a higher rate of Grade 3 events in the Q-Pan Group compared to the Placebo Group (4.8% Q-Pan, 2.5% Placebo). This discrepancy between groups was not observed in this age stratum when considering SAEs.

Thirty-seven subjects (6.1%) in the Q-Pan Group and 7 subjects (3.0%) in the Placebo Group reported an unsolicited event in the 42 days following the first vaccination that was assessed by the investigator as related to vaccination. The most common related unsolicited AEs in the Q-Pan Group were all injection site symptoms combined (1.5% Q-Pan, 0.4% Placebo), vomiting (0.7% Q-Pan, 0.4% Placebo), injection site bruising (0.5% Q-Pan, 0.4% Placebo), and cough (0.5% Q-Pan, 0.4% Placebo). Subjects in the Q-Pan Group in the two youngest age strata, reported a higher rate of events assessed as related compared to subjects in the Placebo Group (6 months - < 3 years: 7.5% Q-Pan, 2.7%; 3 years - < 9 years: 7.6% Q-Pan, 2.6% Placebo).

Four grade 3 events were assessed as related, occurring in two subjects in the Q-Pan Group. Myalgia and chills were reported in a 5 year-old boy occurring on the day after vaccination with Dose 2 and resolving one day later. Nausea and abdominal pain were reported in a 16 year-old girl occurring nine days after Dose 1 and resolving eight days later. She was revaccinated and no other unsolicited events were reported.

Reviewer's comment: Grade 3 unsolicited AE rates were similar in the Q-Pan and Placebo groups. Grade 3 fever and diarrhea were reported more frequently during the 42 day study period in the Q-Pan Group than the Placebo Group. More subjects in the Q-Pan Group compared to the Placebo Group reported events that the investigator assessed as related. Injection site reactions were the only related AEs that clearly occurred at a greater rate in the Q-Pan Group compared to the Placebo Group.

The following unsolicited AEs occurred within the 42 day study period and are considered notable by the clinical reviewer:

- One 7 year-old subject reported an upper respiratory tract infection of mild intensity and asthma exacerbation of moderate intensity three days following the first dose of Q-Pan. Seven days following vaccination, pneumonitis of mild intensity was reported. All events were assessed by the investigator as related to vaccination. The subject had a current history of asthma and a past history of pneumonitis. She was treated with antibiotics and asthma medication and the events resolved.

Reviewer comment: While this event was somewhat similar to a fatal event that occurred in study Q-Pan H1N1-035 (Section 8.4.1), this event was of lesser severity and resolved. There is a temporal relationship with vaccine in this event, as with the fatal event. It is difficult to determine whether the vaccine may have contributed to this individual event. In subjects in this age group, upper respiratory tract infections were reported at a higher frequency in the 42-day study period in the Q-Pan Group (5.6%) than the Placebo Group (2.6%).

- One event of paresthesia was reported in a 15 year-old subject in the Q-Pan Group 14 days after the first vaccination. The event lasted one day and was assessed as unrelated by the investigator. The subject also reported dizziness and right hand twitching at approximately the same time and eye and lip twitching approximately one week following dose 2.
- One event of hypoesthesia, described as numbness of right arm, was reported in a 12 year-old subject in the Q-Pan Group on the day of second vaccination. The event resolved 8 days later and was assessed by the investigator as related. This subject also reported hypoesthesia of the right leg 183 days following the second vaccination, resolving 7 days later.

  Reviewer comment: There are spontaneous reports of paresthesia after vaccination with Arepanrix (Q-Pan H1N1). One article from Canada, which reviewed reports from its passive surveillance system, identified paresthesia as the third-most-common adverse event, after allergic-like symptoms and local reactions, for vaccines administered between October 26 and December 31, 2009.[19] The authors noted that the Québec VAERS system had received just 32 reports of paresthesia among >10 million doses of seasonal influenza vaccine administered between 2003 and 2009 and that the rate of reporting to the same system was thus 25-fold higher in association with the 2009 AS03-adjuvanted vaccine. Of note, paresthesia after Pandemrix (D-Pan H1N1) has also been noted in reports from Sweden and France (3-6).[20, 21, 22, 23] Based on the review of the literature, the OBE reviewer, Dr. Maria Said, recommended inclusion of paresthesia in the PI in the post-marketing safety section.

- There were two events indicative of allergy (urticaria and hypersensitivity) within one week of vaccination. Both were attributed to the use of an analgesic gel and were reported as general or non-administration site.

- A 13 year-old subject had moderate dizziness and “shakiness” beginning 1 and 2 days after the second dose, respectively, and lasting 7 and 5 days. The events were assessed by the investigator as related.

- No narcolepsy was reported in the study. Somnolence was reported, which was actually described by the investigator as “drowsiness,” a known reaction and solicited adverse event.

Year 2 Unsolicited Adverse Events

In Year 2, 41 subjects (26.5%) in the Q-Pan Group reported at least one unsolicited adverse event in the 42-day study period. The table below summarizes the unsolicited adverse events by age at the first vaccination with Q-Pan (Dose 3 Year 2).

Table 23 Unsolicited adverse events reported Day 0 – 41 or 21 days following either vaccination with Q-Pan (Dose 3) in the Total Vaccinated Cohort by age group, Year 2, Q-Pan-021

	Q-Pan	
Age at Dose 3 Year 2	**N**	**n**
6 to < 36 months	7	2 (28.6%)
3 to < 9 years	79	32 (40.5%)
9 to < 18 years	64	22 (34.4%)
≥ 18 years	5	1 (20.0%)

Source: Adapted from sBLA 125419/039; Clinical Study Report 114464 and Reviewer-generated analysis using the dataset WUNSOL.
N total subjects in the total vaccinated cohort
n number of subjects with an event

Reviewer comment: Rates of unsolicited AEs were similar to or lower than rates reported during the same time period in Year 1.

Three subjects (1.9%) reported Grade 3 unsolicited AEs: 1) a 3 year-old with Grade 3 abdominal discomfort ("vomiting"), chills, and pain on the day of Dose 1 and a moderate cough two days later, 2) a 2 year-old with Grade 3 nasopharyngitis and diarrhea on the day of Dose 1, and 3) a 7 year-old with Grade 3 vomiting and diarrhea 17 days following Dose 1 and Grade 3 cough, sore throat, and bilateral otitis media, 8 – 12 days following Dose 4. The third subject also reported bronchial hyperreactivity and lymphadenopathy of moderate intensity 12 days following Dose 4. No Grade 3 events were assessed as related

Reviewer comment: For each of these subjects, at least one Grade 3 event is also a solicited AE. While, it is possible that these Grade 3 events represent intercurrent infection, they could also be related to vaccine administration.

Three subjects (1.9%) reported AEs that the investigator assessed as related during the same time period: 1) a four year-old with rash on the day of Dose 1, 2) a three year-old with elevated temperature one day following Dose 1, and 3) a nine year-old with shoulder, left arm, and neck muscular pain one day following Dose 2.

The most commonly reported unsolicited AEs in the 42-day study period were nasopharyngitis (6.5%), cough (5.8%), vomiting (2.6%), and pyrexia (2.6%). The most commonly reported unsolicited AEs in the 7 days following either dose of vaccine were rash (rash and generalized rash) (2.6%), cough (1.9%), and nasopharyngitis (1.9%).

Reviewer comment: Four subjects reported rash beginning Days 0 – 2 following Dose 1 of Q-Pan in Year 2. One of these, a rash on the buttocks was considered related by the investigator. In Year 1, reported occurrence of rash was not unbalanced between study groups in the 7 days following vaccination and in the 42-day study period, with five subjects in each group reporting some type of rash in the first four days following vaccination.

Medically Attended Adverse Events

Subjects were monitored for MAAEs from Day 0 to 385. During this time, 189 subjects (31.1%) In the Q-Pan Group and 77 subjects (33.3%) in the Placebo Group reported at

least one MAAE. The table below shows the MAAEs reported during the study period by age stratum.

Table 24 Medically attended adverse events reported Day 0 – 385 in the Total Vaccinated Cohort by age strata, Year 1, Q-Pan-021

	Q-Pan		Placebo	
Age stratum	**N**	**n**	**N**	**n**
6 months - < 3 years	199	66 (33.2%)	75	27 (36.0%)
3 years - < 9 years	198	64 (32.3%)	76	28 (36.8%)
9 years - < 18 years	210	59 (28.1%)	80	22 (27.5%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 94, p. 272-286
N total subjects in the total vaccinated cohort
n number of subjects with an event

Reviewer comment: Medically attended adverse events were reported at similar rates overall and by age stratum between the two study groups.

The most frequently reported MAAEs in the Q-Pan Group were ear infections (ear infection, otitis media, and acute otitis media) (5.9% Q-Pan, 6.9% Placebo), upper respiratory tract infection (including viral upper respiratory tract infection) (5.4% Q-Pan, 3.9% Placebo), pharyngitis (pharyngitis, viral pharyngitis, pharyngeal erythema, and oropharyngeal pain) (5.3% Q-Pan, 2.6% Placebo), cough (3.5% Q-Pan, 3.0% Placebo), and pyrexia (2.5% Q-Pan, 2.2% Placebo).

MAAEs reported in the 385-day study period in the Q-Pan Group at a rate of ≥ 0.5% of subjects and at a rate at least twice that of the Placebo Group were pharyngitis (including pharyngitis, viral pharyngitis, pharyngeal erythema, and oropharyngeal pain) (5.3% Q-Pan, 2.6% Placebo), abdominal pain (includes upper and lower abdominal pain) (1.8% Q-Pan, 0% Placebo), any fracture (1.3% Q-Pan, 0% Placebo), asthma and bronchial hyperreactivity (1.2% Q-Pan, 0.4% Placebo), croup (1.0% Q-Pan, 0.4% Placebo), nasal congestion (0.8% Q-Pan, 0% Placebo), laceration (0.8% Q-Pan, 0.4% Placebo), arthralgia (0.8% Q-Pan, 0.4% Placebo), seasonal allergy and allergic rhinitis (0.7% Q-Pan, 0% Placebo), infectious mononucleosis (0.7% Q-Pan, 0% Placebo), headache (including tension headache) (0.7% Q-Pan, 0% Placebo), dysuria (0.7% Q-Pan, 0% Placebo), and excoriation (0.5% Q-Pan, 0% Placebo). If streptococcal pharyngitis is considered with other preferred terms for pharyngitis, there is less of an imbalance (6.8% Q-Pan, 5.2% Placebo). If wheezing is considered with asthma and bronchial hyperreactivity, there is less of an imbalance (1.6% Q-Pan, 0.9% Placebo).

Reviewer comment: Many of these imbalances are likely to have occurred by chance (for example, laceration, excoriation). The infections above are common and do not appear to occur at rates outside of what might be expected in this population.

Twenty-four subjects (4.0%) in the Q-Pan Group and 11 subjects (4.8%) in the Placebo Group reported at least one Grade 3 MAAE within approximately one year following vaccination. These rates are almost the same as the Grade 3 unsolicited AEs within 42 days following vaccination.

Six subjects (1.0%) in the Q-Pan Group and one subject (0.4%) in the Placebo Group reported at least one MAAE that was assessed as related to vaccination. Only two events were not discussed with unsolicited events above. The only related MAAE reported in the Placebo Group was Type 1 Diabetes, reported as a Grade 3 MAAE, an SAE, and a pIMD (Section 6.1.12.4). One subject in the Q-Pan Group reported alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased 168 days following Dose 2 resolving at study conclusion (see Section 6.1.12.6).

Three cases of convulsion were reported during Study Year 1, all occurring in the Q-Pan Group:

- A 30 month-old boy developed a febrile convulsion 11 days after Dose 1. He was hospitalized for three days. The event was reported as an SAE and assessed as not related to vaccine. He received Dose 2. He did not report any fever or other general solicited adverse events within 7 days following Dose 1 or Dose 2 or unsolicited adverse events in the 42-day observation period.
- A 4 year-old, reported a convulsion 212 days post Dose 2 with duration of one day and intensity grade 3. The event was reported as a medically attended visit and considered not related to the study vaccine. This subject also reported seven days of intermittent vomiting beginning on the day of the second vaccination.
- A 27 month-old reported a possible seizure one day prior to the onset of an upper respiratory tract infection. The seizure, which was reported as a medically attended visit, occurred 134 days post Dose 2, had an intensity of grade 2, resolved one day later, and was considered not related to the vaccine.

No cases of convulsion were reported in study Year 2.

Reviewer comment: Seizure was reported in adult study, Q-Pan-002, exclusively in the Q-Pan Group, occurring 35-346 days after the second dose in subjects with no history of seizure. Consequently, any occurrence of any convulsion was examined closely in this review. The information available for the SAE of febrile seizure contained conflicting information regarding whether the subject had a fever at the time of the event. The CIOMS report also notes that he had no signs of infection prior to the event. There is a temporal relationship between the vaccine and this event. As there was no sign of infection and no clear report of fever, this reviewer determines that there is no alternative plausible cause for the event. This event is within a window of increased risk of febrile convulsion following influenza vaccine as stated by GSK. Information is limited on the other two events of seizure as they were not SAEs. Both occurred in young children, did not lead to a hospital admission, and resolved in one day. One was associated with a concurrent viral infection and was described as "possible seizure". None was treated with an antipyretic. Given the available information, the etiology of these events is unknown. It is possible that both of these events could have been febrile convulsions occurring more than four months following vaccine administration and thus, unlikely to be related to vaccination.

Year 2 Medically Attended Adverse Events

In Study Year 2, 36 subjects (23.2%) reported MAAEs from Day 0 to 385. The most common MAAEs were upper respiratory tract infection (including viral upper respiratory tract infection) (3.2%), ear infection (ear infection, otitis media, acute otitis media) (3.2%), pyrexia (2.6%), and cough (2.6%).

The following events were noted in Year 1 as occurring at a greater frequency in the Q-Pan Group than in the Placebo Group with the rate of occurrence in Year 2 in parentheses (Please note, subjects are older in Year 2): oropharyngeal pain (1.9%), abdominal pain (0.6%), any fracture (1.3%), asthma, bronchial hyperreactivity, and wheezing (0.6%), croup (0%), nasal congestion (0%), laceration (0%), arthralgia (0%), seasonal allergy and allergic rhinitis (0.6%), infectious mononucleosis (0%), headache (0.6%), dysuria (0%), and excoriation (0.6%).

Reviewer comment: It is not possible to directly compare data from Year 1 and Year 2 as Year 2 subjects do not have a comparison group, are older, and may be different from the Year 1 Q-Pan subjects in other ways (e.g. willingness and ability to participate in a trial for > two years). There were no safety concerns noted through Year 2 MAAEs analysis, which were not noted in Year 1. The rate of fracture of any bone was the same in Year 2 as it was in Year 1. This reviewer is unaware of a biologically plausible mechanism connecting fracture and Q-Pan H5N1 vaccine.

Concomitant Medications

The Applicant provided an analysis of concomitant medications. In Year 1, 346 subjects in the Q-Pan Group (57.0%) and 114 subjects in the Placebo Group (49.4%) used a concomitant medication during the 21 days following either vaccination. The table below shows the rates of concomitant medication use during the 21 days following vaccination by study group and age stratum.

Table 25 Concomitant medication use and antipyretic use in the 21 days following either vaccination by age stratum in the Total Vaccinated Cohort, Year 1, Q-Pan-021

	Any Concomitant Medication				**Antipyretic Medication**			
	Q-Pan		**Placebo**		**Q-Pan**		**Placebo**	
Age Strata	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
6 to < 36 months	199	124 (62.3%)	75	40 (53.3%)	199	95 (47.7%)	75	29 (38.7%)
3 to < 9 years	198	120 (60.6%)	76	35 (46.1%)	198	77 (38.9%)	76	24 (31.6%)
9 to < 18 years	210	102 (48.6%)	80	39 (48.8%)	210	75 (35.7%)	80	17 (21.3%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 98, p. 291
N total subjects in the total vaccinated cohort
n number of subjects with the event or characteristic

Reviewer comment: More subjects used concomitant medications in the Q-Pan Group than in the Placebo Group in the primary 42-day study period in the two youngest age strata. Subjects in all age strata used antipyretics more in the Q-Pan Group than in the Placebo group. This increased use of antipyretics accounts for the difference in concomitant medication use between the two groups in the youngest age strata, but does not appear to account for the difference in the two groups for subjects age 3 to < 9 years. In this age strata there appears to be a difference in medications started following vaccination. Medications in this age group appear to be distributed between different classes; no clear imbalance between groups in a particular class (for example, antibiotics, medications for respiratory tract infections) was identified. GSK reports there was a small increase in the use of concomitant medications and antipyretics following the second dose (51% and 37%, respectively) compared to the first dose (46% and

32%, respectively) in the youngest cohort and that this difference was not due to prophylactic use of medications. Clinically significant increases in fever were not observed following Dose 2 in this age group. A medication is flagged as an antipyretic regardless of the indication for which it was used. Consequently, this difference is not necessarily indicative of a greater incidence of fever and may reflect the higher rate of pain reported by Q-Pan subjects.

6.1.12.3 Deaths

No deaths were reported in Study Year 1 or Study Year 2.

6.1.12.4 Nonfatal Serious Adverse Events

Year 1

From Day 0 to 42, two subjects (0.3%) in the Q-Pan Group and no subjects in the Placebo Group reported an SAE. From Day 0 to 385, 10 SAEs were reported by 8 of 607 subjects (1.3%) in the Q-Pan Group and 4 SAEs by 4 of 231 subjects (1.7%) in the Placebo Group. One SAE of type 1 diabetes mellitus, which occurred in a subject in the Placebo Group, was assessed by the investigator as related to study vaccine and was also classified as a pIMD. One SAE of pyelonephritis occurred in a 35 month-old female subject during the screening period prior to the first vaccination. This event is not included in the table below.

Table 26 Serious adverse events reported by subjects from Day 0 to Day 385, Total Vaccinated Cohort, Year 1, Study Q-Pan-021

Study Group	Age at Event/ Gender	SAE	Day of onset post-vaccine	Last dose prior to SAE	Duration (days)	Outcome
Q-Pan	13 m/o F	Bronchial hyperreactivity	106	2	7	Resolved
		Upper respiratory tract infection	106	2	10	Resolved
	33 m/o F	Pneumonia	152	2	5	Resolved
	29 m/o M	Febrile convulsion	11	1	3	Resolved
	4 y/o M	Inguinal hernia	347	2	5	Resolved
	4 y/o M	Influenza	100	2	2	Resolved
	16 y/o M	Bone contusion (rib)	6	2	12	Resolved
		Infectious Mononucleosis	88	2	63	Resolved
	17 y/o F	Abortion, spontaneous	261	2	1	Resolved
	18 y/o M	Infectious Mononucleosis	118	2	45	Resolved
		Dehydration	122	2	3	Resolved
Placebo	34 m/o M	Lymphadenitis (granulomatous)	105	2	18	Resolved
	3 y/o M	Asthma	310	2	4	Resolved

Study Group	Age at Event/ Gender	SAE	Day of onset post-vaccine	Last dose prior to SAE	Duration (days)	Outcome
	10 y/o M	Type 1 Diabetes mellitus	200	2	-	Not recovered
	15 y/o M	Suicidal ideation	176	2	4	Resolved

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 31, p. 105
SAE serious adverse event

See Section 6.1.12.2, Medically Attended Adverse Events, for a description of the SAE of febrile convulsion. See Section 9.1.1, Human Reproduction and Pregnancy Data, for a description of the spontaneous abortion.

Year 2
Two of 155 subjects (1.3%) in Year 2 reported an SAE. Neither event was assessed as related to the vaccine.

Table 27 Serious adverse events reported by subjects from Day 0 to Day 385, Total Vaccinated Cohort, Year 2, Study Q-Pan-021

Age at Event/ Gender	SAE	Day of onset post-vaccine	Last dose prior to SAE	Duration (days)	Outcome
7 y/o M	Wound (foot, puncture)	232	4	24	Resolved
4 y/o F	Scarlet Fever	169	4	13	Resolved

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114464, Table 149, p. 426
SAE serious adverse event

Reviewer comment: Most SAEs occurred several months following the last dose of study vaccine. In the opinion of the reviewer, with the exception of the febrile convulsion (see Section 6.1.12.2), all SAEs have a clear alternative etiology other than vaccination.

6.1.12.5 Adverse Events of Special Interest (AESI)

From Day 0 to Day 385, one subject (0.2%) in the Q-Pan Group and one subject (0.4%) in the Placebo Group reported a pIMD:

- A 3 year-old girl with a past medical history of conjunctivitis, upper respiratory tract infection, ganglion cyst, gastroesophageal reflux, otitis media, sinusitis, and congenital lacrimal duct closure and a current medical history of constipation, bronchiolitis, and urine odor enrolled in the study. She reported taking MiraLAX at enrollment. She received two doses of Q-Pan, reporting fever to 39.3°C following the first vaccination and 38.9°C following the second vaccination. Six months after the second vaccination, she developed alopecia and weight loss. A TSH at that time was reported to be normal. She presented four months later with persistent alopecia and diarrhea and a complete blood count (CBC) was within normal limits. During the one-year follow-up, she reported 27 other unsolicited symptoms, many of them infections, including urinary tract infection, sinusitis, pharyngitis, fever, conjunctivitis, upper respiratory tract infection,

bronchiolitis, pneumonia, herpangina, otitis media, bronchitis, cough, and scarlet fever. Referral was made to a dermatologist, who recommended vitamins and iron, and a gastroenterologist. No further information was provided. The subject was followed until study conclusion and the alopecia was unresolved at that time. The investigator assessed the event as not related to study vaccine and did not provide an alternative etiology.

- A 10 year-old boy in the Placebo Group, developed type 1 diabetes mellitus six months after the second vaccination. This event was also an SAE and was assessed by the investigator to be causally related to study vaccine.

GSK submitted Amendments 39.1 and 39.8 to address IRs sent on January 20, 2016 and May 19, 2016, respectively, regarding the report of alopecia.

No pIMDs were reported in Study Year 2.

Reviewer comment: Alopecia in this subject is temporally related to Q-Pan and represents a pIMD. The subject reported multiple infections prior to study enrollment and numerous AEs during the study, including many different types of infections, diarrhea, and weight loss. This presentation seems to suggest the subject may have a chronic medical condition leading to immune dysfunction, malabsorption, and failure to thrive. Despite the possibility of such a condition at baseline, it is still possible the vaccine could have contributed to the precipitation of an immune-mediated alopecia. In their IR responses, GSK was unable to provide any further information or overarching diagnosis for this subject. Please see Section 8.4.8 for a description of the events of alopecia in study Q-Pan-035.

6.1.12.6 Clinical Test Results

Laboratory evaluations for safety were completed for all subjects on Days 0 and 42, for half of subjects on Day 182 and for the other half of subjects on Day 385. Evaluations consisted of complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, bilirubin (total and direct), and creatinine. No blood samples were collected during Study Year 2.

The protocol directed investigators to reevaluate elevated ALT > the upper limit of normal (ULN) and > 2 times baseline or > 3 times the ULN and to investigate the etiology of persistent or symptomatic elevated ALT > 3 times the ULN. Any ALT abnormality triggering investigation via the algorithm was to be reported as an AE. ALT abnormalities in the Q-Pan Group that qualified for further evaluation are summarized in the Table below.

Table 28 FDA Analysis of subjects receiving Q-Pan with elevated ALT levels requiring further evaluation per protocol-specified algorithm, Year 1, Study Q-Pan-021

Age	Baseline ALT/AST (U/L)	Study Day	Value (U/L)	Reported as AE?	Duration/ Outcome	Related per Investigator	Associated symptoms/ diagnoses?
5 y	ALT 20	Day 182	ALT 57	N	unknown	unknown	No
15 y	ALT 32 AST 23	Day 182	ALT 69 AST 59	Y	ALT unresolved AST 21 days	N	Yes – diarrhea/abdominal pain for 9 days starting 17 days before, gastroenteritis/sore throat for 4 days starting 21 days after laboratory evaluation
5 y	ALT 14	Day 42 Day 182	ALT 64 ALT 15	N	140 days	unknown	Yes – scarlet fever for 7 days starting10 days before laboratory evaluation

Age	Baseline ALT/AST (U/L)	Study Day	Value (U/L)	Reported as AE?	Duration/ Outcome	Related per Investigator	Associated symptoms/ diagnoses?
13 y	ALT 28 AST 25	Day 182	ALT 65 AST 53	Y	resolving	Y	Yes – type 2 diabetes/ metabolic syndrome one month after laboratory evaluation
3 y	ALT 31 AST 31	Day 42 Day 182	ALT 70 AST 43 ALT 50 AST 38	N	unknown	unknown	No
5 y	ALT 17 AST 33 T/D Bili 0.2/0.1	Day 182	ALT 55 AST 65 T/D Bili 0.2/0.2	N	unknown	unknown	No
6 y	ALT 23 AST 32	Day 182	ALT 73 AST 167	N	unknown	unknown	No
6 y	ALT 23 AST 30	Day 182	ALT 73 AST 149	N	unknown	unknown	No
18 m	ALT 63* AST 47	Day 42 Day 182	ALT 132 AST 122 ALT 15 AST 31	Y	145 days/ resolved	N	Yes – nasopharyngitis for 5 days starting 2 days before laboratory evaluation

Source: sBLA 125419/039 Reviewer-generated analysis using dataset WRNGLB.
* baseline value > upper limit of normal
ALT alanine aminotransferase
AST aspartate aminotransferase
T/D Bili total/direct bilirubin

No subjects had values of ALT > 3 times the ULN reported. All subjects in the table above had ALT > ULN and > 2 times baseline. The protocol specified that these subjects were retested in 2 weeks and if ALT < 3 times the ULN, no further follow-up was specified. An additional 16 year-old subject who received Q-Pan had elevated liver enzymes at baseline (ALT 93, AST 48), which increased at Day 42 (ALT 125, AST 62) and returned to baseline at Day 385. This event did not require further evaluation per the algorithm, but was assessed by the investigator as related to vaccination. For laboratory abnormalities investigators were instructed to use their clinical judgement in determining the clinical significance and need for reporting. All subjects in the table above completed the study; none were lost to follow-up.

Reviewer comment: No subjects qualified for investigation of the etiology of liver abnormalities identified through safety laboratory analysis based on algorithm specified in the protocol. All abnormalities of liver enzymes (ALT and AST) were Grade 1 or Grade 2 (as per FDA Guidance Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials[24]). Seven subjects had abnormalities that were reported as not resolved to baseline or no further laboratory information is available. Though it is reassuring that all of these subjects were followed through Day 385, with a telephone contact that would be expected to have identified any clinical MAAEs through that time. While mild to moderate elevations in liver enzymes were observed in some subjects following vaccination, these abnormalities do not alter the overall risk benefit assessment of the vaccine.

In addition to the above noted abnormalities three subjects reported bilirubin elevations unresolved at study completion. Two teenage subjects with normal baseline liver function in the Q-Pan group reported mild elevations in total bilirubin without liver enzyme abnormalities at Day 42 and moderate elevations (<2 times the ULN) at Day 385. Both reported no other associated AEs. One three-year old with normal baseline liver function in the Q-Pan group reported moderate elevations (<2 times the ULN) in total bilirubin without liver enzyme abnormalities at Day 42 and was unable to have a

laboratory assessment after that. No pertinent AEs were reported and a telephone contact was completed at Day 385.

Several subjects were reported to have direct bilirubin elevated and greater than total bilirubin. In amendment 39.22, in response to an IR dated August 4, 2016, GSK verified that these apparently discrepant laboratory results were the actual values obtained and transmitted from the laboratory. A total of 15 subjects were identified with direct bilirubin greater than total, 11 in the Q-Pan group and 4 in the Placebo Group. Since April 2013, the laboratory has implemented reevaluation of any values with this error. If the inconsistency persists, the results are reported as "unable to obtain satisfactory results; possible interfering substances". Consequently, GSK indicates that interference is likely the cause of the inconsistent values.

Reviewer comment: No subjects with the inconsistency and elevated direct bilirubin reported abdominal symptoms or jaundice. These inconsistencies do not significantly impact safety data quality.

Other laboratory abnormalities following administration of Q-Pan H5N1 were not clinically significant, as determined by the Clinical Reviewer, with the following exceptions that are noted because of the degree of abnormality (Grade 3):

- A 34 month-old with hemoglobin (Hgb) of 12.9 mg/dL at baseline reported an elevated Hgb to 19.0 mg/dL at day 42, decreasing to normal at Day 182. Red blood cell count was also elevated to $6.6x10^{12}$/L at Day 42. The hemoglobin elevation was reported by the investigator as having a 21-day duration and was assessed as not related. No other AEs were reported.
- An 11 month-old with a baseline hemoglobin of 8.9 mg/dL had a decrease in hemoglobin to 7.4 mg/dL at Day 385. No other pertinent AEs were noted.
- A 14 month-old with a baseline white blood cell count (WBC) within normal limits at $16.7x10^9$/L, had an elevated WBC to $23.4x10^9$/L at Day 182 with elevated neutrophils of $18.88x10^9$/L. No AEs are reported for the subject who completed the study.
- A 14 year-old with a low baseline WBC of 3.8×10^9/L and normal baseline neutrophil count of 2.06×10^9/L had a decrease in WBC to 2.6×10^9/L and neutrophil count to 0.8×10^9/L on Day 42. At Day 182, WBC had risen to 4.0×10^9/L, which was still low, and neutrophils were within normal limits. The subject reported no AEs throughout the study.
- A 21 month-old with a low baseline neutrophil count of 1.29×10^9/L and a normal baseline WBC of had a decrease in neutrophil count to 0.78×10^9/L and WBC to 4.9×10^9/L at Day 42. At Day 385, WBC and neutrophil counts as risen to normal levels. No AEs were reported throughout the study.

Reviewer comment: All of the above noted laboratory abnormalities are unlikely to affect the overall risk benefit profile of the vaccine.

6.1.12.7 Dropouts and/or Discontinuations

No subjects discontinued the study due to an AE in either study year.

6.1.13 Study Summary and Conclusions

Study Q-Pan H5N1-021 was a Phase 2/3, multi-center, observer-blind, placebo-controlled study to evaluate the safety and immunogenicity of an antigen-sparing H5N1

influenza vaccine adjuvanted with AS03B in healthy subjects 6 months through 17 years of age. Subjects were stratified into three age groups and received vaccine at half the adult dose as a two-dose series 21 days apart. Immunogenicity was evaluated at Day 21 (after one dose), 42 (primary endpoint), and 6 months and one year following the final vaccination. Safety was evaluated at various time points over the approximately one-year study period and included local and general solicited reactions, unsolicited AEs, MAAEs, SAEs, pIMDs, concomitant medications, and laboratory investigations.

The study met its primary objective, meeting immunogenicity criteria, based on HI titers, agreed upon by CBER and GSK (lower bound of the CI for proportion of subjects with HI titers ≥ 1:40 > 70%) for each age strata. Point estimates for proportion were 100% in subjects 6 to 36 months, 99.5% for subjects 3 to 9 years, and 99% for subjects 9 to 18 years of age. Two doses of vaccine were needed to meet the immunogenicity criteria. Immunogenicity declined in subjects 6 months to one year following vaccination, with a more rapid decline in older subjects.

The vaccine demonstrated significant reactogenicity, but overall rates of adverse events reported through the long-term follow-up period were similar between vaccine and placebo groups. Injection site reactions were common, with pain being the most frequently reported local solicited adverse reaction in all age strata. Systemic reactions were also common, with irritability and myalgias being the most frequently reported general solicited adverse reactions in subjects younger than six years of age and six years of age and older, respectively. There were no significant differences between study groups in rates of unsolicited adverse events reported in the 42 days following the first vaccination and in MAAEs, SAEs, and pIMDs reported in the year following study vaccination. The safety results of the uncontrolled crossover study generally corroborated the results in Year 1. One SAE with a temporal association with Q-Pan, febrile seizure 11 days following the first vaccination, had no identified alternative plausible cause. Alopecia was the only pIMD identified after receiving Q-Pan. Mild to moderate elevations in liver enzymes and other safety laboratory assessments were observed in some subjects following vaccination in Year 1. However, these abnormalities do not alter the overall risk benefit assessment of the vaccine. Overall, the safety demonstrated an acceptable profile.

7. Integrated Overview of Efficacy

No integrated overview of immunogenicity was performed. Immunogenicity data relevant to this sBLA were collected in one study, which is reviewed in Section 6.1

8. Integrated Overview of Safety

One pivotal clinical trial, Q-Pan-021, was conducted to support the expansion of use of Q-Pan H5N1 into the pediatric population. As a result, GSK did not provide an Integrated Summary of Safety (ISS). However, in support of the use of Q-Pan H5N1 in a pediatric population, the Applicant included the results of study Q-Pan-035, in which approximately 4000 children 6 months - < 10 years of age received one or two doses with a related, non-US licensed vaccine, Q-Pan H1N1, containing AS03 adjuvant. (See Section 2.6 for the regulatory history regarding the submission of these data.) The pertinent safety results, in particular SAEs, pIMDs, and other unsolicited adverse events, of that trial are reviewed in this Section. A summary of pertinent results from Q-Pan-021 will also be presented here. Please see Section 6.1.12 for detailed safety results of Q-Pan-021.

Study FLU Q-PAN H1N1-035 (referred to as Q-Pan-035) was entitled "A phase III, observer-blind, randomized, controlled, multi-center, multi-country trial to evaluate the safety and relative efficacy of pandemic monovalent A/California/7/2009 (H1N1)v-like vaccines manufactured in Québec, Canada in children aged 6 months to less than 10 years of age." The study was a randomized, placebo-controlled, observer-blind, multicenter trial, conducted in 8 countries outside of the US (Australia, Brazil, Colombia, Costa Rica, Mexico, Philippines, Singapore, and Thailand). In this trial, 6145 subjects 6 months through 9 years of age received Influenza A (H1N1) Virus Monovalent Vaccine, with or without ASO3 adjuvant. Subjects were randomized 1:1:1 to receive one of three formulations: a two-dose series with the adjuvanted vaccine (n = 2048, Group A), one dose of adjuvanted vaccine followed by saline placebo (n = 2048, Group B), or two doses of unadjuvanted vaccine (n = 2049, Group C, 7.5 µg for children 6 months through 2 years of age and 15 µg for children 3 through 9 years of age). All groups received the injections 21 days apart. The treatment groups were divided into two groups based on age: 6 months - < 36 months and 3 years - < 10 years. Randomization included a minimization procedure by center, prior seasonal influenza vaccination history, and age (approximately 1:1 with no more than 75% of subjects in either age stratum).

Reviewer comment: CBER considered the safety results of an additional 4000 pediatric subjects who received a related vaccine to potentially add important information to the assessment of the safety of Q-Pan H5N1 and in particular the AS03 adjuvant. As Q-Pan H1N1 and Q-Pan H5N1 are different vaccines with distinct antigens, they may have very distinct reactogenicity profiles. Given this fact, the focus of the review below is on unsolicited events, SAEs, and pIMDs.

8.1 Safety Assessment Methods

In study Q-Pan 035, diary cards were used to collect safety information up to Day 42. Local (pain, redness, swelling) and general (drowsiness, irritability/fussiness, fever, loss of appetite for subjects < 6 years of age, fatigue, fever, gastrointestinal symptoms, headache, joint pains, myalgia, shivering, sweating for children > 6 years of age) solicited adverse events were queried on the diary card for seven days following each vaccination (Day 0 – 6). All unsolicited AEs were collected for 21 days following each vaccination (through study Day 42). MAAEs, SAEs, and pIMDs were collected for one year following the second vaccination. No safety laboratory information was collected. Descriptive statistics were used to analyze safety data.

Reviewer comment: Procedures and time points for collection of safety data were almost identical in studies Q-Pan-035 and Q-Pan-021.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The TVC for study Q-Pan-035 was 6145 subjects (Group A – 2048, Group B – 2048, Group C – 2049), with 4096 receiving at least one dose of adjuvanted H1N1 vaccine. The TVC for Q-Pan-021 was 838 (607 Q-Pan, 231 Placebo).

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

In Q-Pan-035, subjects in each treatment group were placed into two different age cohorts (6 to < 36 months and 3 to < 10 years). In the overall TVC of Q-Pan-035, the

mean age was 4 years (SD 2.64, median 4) and was nearly identical in each treatment group. In comparison, in Q-Pan-021, the mean age was 7 years (SD 5.11, median 6 years) and subjects in the Q-Pan Group were an average of 3 months older than the Placebo Group. In study Q-Pan-035, subjects were 50% male; 40% were Asian, 11% White – Caucasian/European, 1% African/African American, and 48% other racial groups. An analysis of ethnicity in Q-Pan-035 was not presented by GSK. In Q-Pan-021, subjects were 52% male, driven by a higher proportion of males in the Q-Pan Group. The study population was 36% were Asian, 45% White – Caucasian/European, 15% African/African American, 0.4% American Indian/Alaskan Native, 0.4% White – Arabic/ North African, and 3.5% other racial groups. Hispanics made up 11% of the Q-Pan-021 TVC.

Reviewer comment: Subjects in Q-Pan-035 were younger compared to Q-Pan-021 by study design. The two age cohorts in Q-Pan-035 were similar to the youngest two age strata in Q-Pan-021. Based upon 2015, US census data, the study population of Q-Pan-035 was not similar to the racial composition of the US. Asians and other races were over-represented; Whites and African Americans were underrepresented.[2]

8.2.3 Categorization of Adverse Events

In Q-Pan-035, all verbatim terms for unsolicited AEs 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. In Amendment 39.23, in response to an IR sent August 17, 2016, GSK clarified that MedDRA version 15 was used for study Q-Pan-035; version 16.1 was used for study Q-Pan-021.

Reviewer comment: MedDRA tends to "split" closely related events leading to greater specificity around an event but less sensitivity. For the purposes of this review, in the analyses of unbalanced events, "split" events were "lumped." The lumped terms are noted. This was handled similarly in Q-Pan-021 (Section 6.1.12.2).

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

No pooled analysis was conducted because the vaccines evaluated are different, only two studies were reviewed, and the Q-Pan-035 study size is so large that it would dominate any analysis. Instead, results from the two studies are presented for comparison.

8.4 Safety Results

8.4.1 Deaths

There were three deaths in study Q-Pan-035, all assessed by investigators as not related to study vaccine:

- A 6 month-old developed pneumonia and "asthma exacerbation" seven days after receiving the first dose of Q-Pan H1N1 with AS03 vaccine (Group B) and died 13 days later.
- A 10 year-old drowned 299 days after receiving the second dose of Q-Pan H1N1 with AS03 vaccine (Group A).

- A 20 month-old developed parasitic gastroenteritis, intestinal obstruction, and aspiration pneumonia 95 days after receiving the second dose of Q-Pan H1N1 with AS03 vaccine (Group A) and died 7 days later.

In Amendment 39.16, in response to an IR sent on July 1, 2016, GSK clarified the time line of the first event. The 6 month-old subject in Group B had a history of hospitalization for pneumonia, which was unknown at study enrollment. On Day 7 following vaccination, the subject was developed a productive cough, which was initially treated with salbutamol. On Day 11, the cough persisted and watery nasal discharge was noted. On Day 17, he was irritable and cyanotic and was seen in the emergency room. He was diagnosed with pneumonia, confirmed by chest x-ray, admitted, and treated with IV antibiotics, steroids, bronchodilators, and oxygen. A fever to 39.4˚C was noted that day; none was described previously. No blood or sputum cultures or testing for viral pathogens were performed. The pneumonia quickly progressed to septic shock, respiratory failure, and death on Day 19.

There were no deaths in study Q-Pan-021 (Section 6.1.12.3).

Reviewer comment: The reviewer has reviewed the CIOMS narratives and the case report forms of each of these cases. The 10 year-old and 20 month-old both have plausible alternative causes for their death other than study vaccination. In the opinion of the reviewer, the case of the 6 month-old is more concerning for possible relationship to the study vaccine. Though the subject had a history of pneumonia, he had no apparent evidence of a disease process ongoing at the time of first vaccination. One week following vaccination with Q-Pan H1N1 with AS03, he developed a cough that progressed, and he acutely deteriorated 10 days later. It is not possible to determine definitively if the vaccine contributed to the subject's deterioration or death. In the event of a pandemic, it would be likely that children with prior medical problems and underlying conditions would receive vaccine. These children may even be targeted for early vaccination given their perceived increased risk of severe disease and complications.

To attempt to address the above concerns, analyses were conducted on SAEs and unsolicited events occurring not only within study defined time periods of 42 and 385 days following first vaccination, but also in the 7 and 14 days following each vaccination. This reviewer did not identify any SAE that was similar in nature, time course AND outcome in Q-Pan-021. However, one subject in Q-Pan-021 reported mild asthma and pneumonitis during the two-week post-vaccination time frame, which resolved. Please see section 6.1.12 for the results of these analyses in Q-Pan-021 and below for the results in Q-Pan-035.

8.4.2 Nonfatal Serious Adverse Events

In Study Q-Pan-035, serious adverse events were monitored for the 385-day study period. At least one SAE, including the fatal events described above, was reported by 8 (0.4%), 8 (0.4%), and 9 (0.4%) subjects in Groups A, B, and C in the 42 days following first study vaccination, respectively. At least one SAE, including the fatal events described above, was reported by 76 (3.7%), 66 (3.2%), and 68 (3.3%) subjects in Groups A, B, and C by the Day 385 visit, respectively. See the table below for SAE rates by age, study group and post vaccination time period.

Table 29 Serious adverse events reported Days 0 – 42 and Days 0 – 385 in the Total Vaccinated Cohort by age strata, Q-Pan-035

Time Period	Age group	Group A N	Group A n (%)	Group B N	Group B n (%)	Group C N	Group C n (%)
Day 0 – 42	6 to < 36 months	610	5 (0.8%)	612	5 (0.8%)	613	5 (0.8%)
Day 0 – 42	3 to 10 years	1438	3 (0.2%)	1436	3 (0.2%)	1436	4 (0.3%)
Day 0 – 385	6 months - < 3 years	610	35 (5.7%)	612	29 (4.7%)	613	33 (5.4%)
Day 0 – 385	3 years - < 10 years	1438	41 (2.9%)	1436	37 (2.6%)	1436	35 (2.4%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114000, Table 1044, p. 2211-2235
N Total number in subgroup
n number of subjects with SAE

In Q-Pan-021, two subjects (0.3%) in the Q-Pan Group and no subjects in the Placebo Group reported an SAE from Day 0 to 42. From Day 0 to 385, 10 SAEs were reported by 8 of 607 subjects (1.3%) in the Q-Pan Group and 4 SAEs by 4 of 231 subjects (1.7%) in the Placebo Group.

Reviewer comment: In Q-Pan-035, the rate of SAEs reported within the 42-day primary study period is nearly identical in each study group by age strata. While it appears that there may be a small imbalance in SAEs reported in 3 to < 10 year old subjects within the 385-day study period with a dose-response relationship (Group A > Group B > Group C), this pattern is not observed in subjects 6 months to 3 years. SAEs in Q-Pan-021 were uncommon and similar between treatment groups. An analysis by age group is difficult due to the small numbers.

One SAE was assessed by the investigator as related. A 6 month-old female from Brazil in Group B was seen in the emergency room with a mild gastroenteritis beginning 12 hours following the placebo vaccination (Dose 2) and resolving 7 days later. She did not report any symptoms following the first vaccination.

Reviewer comment: This SAE is not related to Q-Pan or placebo vaccination in the opinion of this reviewer.

The most common SAEs in the adjuvanted groups were gastroenteritis due to any cause (including viral gastritis, n = 23), pneumonia (including viral, n = 21), and asthma (asthma, asthmatic crisis, bronchial hyperreactivity, and bronchospasm, n = 17). An imbalance was noted between the adjuvanted and unadjuvanted vaccine groups in the rate of reported SAEs of asthma or reactive airway disease. SAEs of asthma and/or asthmatic crisis were reported by 13 subjects in the adjuvanted groups (0.3%) and 3 subjects in the unadjuvanted group (0.1%). SAEs of asthma, asthmatic crisis, bronchial hyperreactivity, and bronchospasm were reported in 17 subjects in the adjuvanted groups (0.4%) and 4 subjects in the unadjuvanted group (0.2%). These events occurred from 5 days to 334 days following vaccination with most events occurring more than 100 days following vaccination.

In Q-Pan-021, one SAE of bronchial hyperactivity was reported in the Q-Pan Group and one of asthma was reported in the Placebo Group, both > 100 days from last vaccination. An apparent imbalance in asthma and bronchial hyperreactivity MAAEs was lessened when wheezing was included (1.6% Q-Pan, 0.9% Placebo).

Reviewer comment: The imbalance in SAEs with airway hyperreactivity is not due to an imbalance in diagnoses of asthma at enrollment between study groups. The delayed onset of most SAEs of asthma (> 100 days post vaccination), effectively rules out an allergic reaction to study vaccine. One theory is that an imbalance in new asthma diagnoses could represent increased susceptibility to respiratory tract infections. However, in Study -035 URIs were reported as MAAEs at similar rates between study groups. The imbalance in asthma SAEs is most likely due to chance.

Because of the subject who experienced a fatal SAE of pneumonia and asthma exacerbation, in which symptoms were first noted on Day 7 after vaccination, SAEs reported within one week and two weeks of active vaccination were reviewed. Rates of SAEs within one week following either vaccination were 0.2% in Group A, 0% in Group B, and 0.1% in Group C. Four subjects in Group A reported five SAEs: dengue fever on Day 2 (n=1), pyelonephritis on Day 4 (n=1), hepatitis and nasopharyngitis on Day 5 (n=1, see below for details), and bronchial hyperreactivity on Day 5 (n=1) following either vaccination. No subjects in Group B reported SAEs within one week following the dose of Q-Pan H1N1. Two subjects in Group C reported SAEs: dengue fever on Day 2 and concussion on Day 2, both of which were considered SAEs by the investigator because subjects were observed in the emergency room for six hours. Rates of SAEs within two weeks following immunization with active vaccine were 0.3% in Group A, 0.05% in Group B, and 0.3% in Group C. Additional SAEs that occurred in the second week following either vaccination were: appendicitis on Days 8, 8, and 9 following either vaccination (n=3) in Group A; pneumonia and asthma on Day 7 (n = 1, noted above) in Group B; and gastroenteritis on Day 7 (n=1), upper respiratory tract infection on Day 8 (n=1), urinary tract infection on Day 9 and 11 (n=2), and tonsillitis on Day 9 (n=1) in Group C.

Reviewer comment: With the exception of the three SAEs of appendicitis, there was no clear pattern of an increased risk of SAEs shortly following Q-Pan H1N1 with AS03 in study Q-Pan-035. While more subjects in Group A reported SAEs within one week of receiving Q-Pan H1N1 with AS03, this was not seen following test article dosing in Group B, with the notable exception of the fatal event. However, rates above for Group B are lower at least in part because only one active vaccine was administered. For some events, similar infectious events were reported in the unadjuvanted arm in the second week following vaccination (for example, pyelonephritis in Group A, urinary tract infection in Group C). The total number of these events is small and limit the conclusions that can be drawn.

During the one-year follow-up period, nine subjects reported appendicitis: five in Group A (0.2%), two in Group B (0.1%), and two in Group C (0.1%). Three of the subjects that reported appendicitis in Group A had event onset dates of Day 8 following Dose 1, Day 8 following Dose 2, and Day 9 following Dose 2. There were six additional cases of appendicitis, reported in two subjects in each treatment group occurring Days 115 – 332 following the second dose. No narratives reported an identified pathogen causing the

appendicitis. One subject with appendicitis at Day 8 was also diagnosed with pulmonary tuberculosis at admission. No events of appendicitis were reported in Q-Pan-021.

Reviewer comment: It is unclear why there is a cluster of reports of acute appendicitis 8-9 days following vaccination with Q-Pan H1N1 with AS03 in Group A, compared to B and C. It is theoretically possible the immune stimulating adjuvant could be contributing to gastrointestinal lymphocytic inflammation leading to appendicitis. No cases were noted in Group B in this time frame. Because of the close temporal relationship to vaccination, these events have been recommended for inclusion in the PI.

One subject in Group B reported an SAE of papillary thyroid cancer. The subject received two vaccinations, Q-Pan H1N1 with AS03 and placebo, and initially reported no adverse events to the study site. Two months following the second dose, almost three months following the subject's first and only dose of Q-Pan, she was evaluated for a neck mass. Subsequently, a biopsy was performed showing papillary thyroid cancer. Per the narrative, she was treated with total thyroidectomy and radioactive iodine. Following treatment she was noted to have metastasis to the mediastinum and possibly cervical lymph nodes. The SAE was ongoing at the end of the study.

Reviewer comment: Thyroid cancer is rare in children and there was no alternative plausible cause identified for this subject. Children younger than 20 years account for 1.8% of 13.9 per 100,000 cases diagnosed each year. A biologic mechanism by which Q-Pan H1N1 vaccination could contribute to thyroid cancer in a short time period is unknown and it is possible that this could happen by chance. In study Q-Pan-002, one of the pivotal trials for licensure in adults, three subjects who had received Q-Pan H5N1 with AS03 and no placebo recipients, reported thyroid cancer. Two of the subjects in the adult study reported the event of thyroid cancer starting soon after vaccination, on Days 21 and 29. No events of thyroid cancer were reported in control groups in these studies. It is unlikely that the vaccine could have caused the initial insult that led to cellular transformation into a malignancy. As the basis of determining the start date of the event of neck mass in the 4 year-old subject in Q-Pan-035 is unknown and the start date appears to be retrospectively applied, it is not clear if or how the vaccine contributed to the event.

Two subjects reported hepatitis not identified as being due to a viral etiology, one SAE and one MAAE. An 8 month-old male in Group A, who developed an SAE of hepatitis, presented with fever five days following the first vaccination. He was noted to have elevated transaminases (up to 9 x the ULN) and unconjugated hyperbilirubinemia (2.3 mg/dL, ULN = 0.5 mg/dL) and was admitted. Initially, he had no other symptoms but one day later was diagnosed with nasopharyngitis. A work-up was negative for infectious, autoimmune (based on nonreactive antinuclear, anti-mitochondrial, anti-Smith, anti-LKM, and anti-smooth muscle antibodies), or obstructive causes of the hepatitis. Clinically he improved and the event was considered resolved. At study conclusion his transaminases remained slightly elevated (< 1 times the ULN). A 5 year-old male in Group B was diagnosed with an MAAE of hepatitis of moderate intensity 235 days following Dose 2, approximately 8 ½ months following vaccination with Q-Pan H1N1 with AS03. The event resolved 18 days later. The subject was lost to follow-up, and the investigator was not able to implement the algorithm for assessing abnormal LFTs. At the last study contact, on Day 373, the subject was reported to be in good health. Subjects in Q-Pan-021 had laboratory evaluations for elevated liver enzymes. While,

several subjects in the Q-Pan Group had elevations requiring protocol-specified reevaluation, no subjects were clinically diagnosed with overt hepatitis.

Reviewer comment: The cause of hepatitis in both subjects in Q-Pan-035 is undetermined. In the 8 month-old, the hepatitis appears to have been associated with an acute febrile illness. A work-up did not identify an etiology. The following tests were either not completed or not provided to GSK: Anti-actin antibodies, parvovirus IgM and IgG, Hepatitis E IgM and IgG, serum copper, alpha-1 anti-trypsin, and immunoglobulin levels. *Based on the information provided, it does not appear that acetaminophen toxicity or genetic causes were investigated. In the 5 year-old, the event was reported as moderate, not resulting in admission, and resolved within three weeks. A work-up to determine etiology was not available. Autoimmune hepatitis has been reported in association with D-Pan H1N1, D-Pan H5N1, and Q-Pan H5N1 in study Q-Pan-002 in adults. Laboratory investigations appear to rule out an autoimmune etiology in the 8 month-old. The cause in the 5 year-old is unknown, though the reported 18-day duration, makes autoimmune hepatitis unlikely.*

Seizure

Because new-onset convulsion was reported in the pivotal adult trials exclusively in subjects receiving Q-Pan H5N1 with AS03 and it is conceivable that cataplexy could be reported as seizure, reports of convulsion were examined closely in studies Q-Pan-021 (section 6.1.12.4) and Q-Pan-035. In Q-Pan-035, 15 subjects reported febrile convulsion and 6 subjects reported convulsion during the one-year study period. After analyzing the information available in CIOMS forms, CRFs, and in Amendment 39.10, a response to an IR sent June 16, 2016, this clinical reviewer has determined that two subjects were likely misclassified: one subject with reported convulsion in Group A actually had a febrile convulsion and one subject in Group B with two reported febrile convulsions actually had a seizure disorder. This subject started an antiepileptic following the second febrile convulsion. This seizure disorder may not have been of new onset as the subject reported a febrile convulsion prior to study enrollment. Taking into account the misclassifications, 15 subjects reported febrile convulsion (Group A n=5, Group B n=5, Group C n=5) and 6 subjects reported convulsion (Group A n=2, Group B n=3, Group C n=1). Onset of febrile convulsion ranged from 34 to 330 days following the last vaccination; reported duration ranged from 1 to 18 days. Onset of convulsion ranged from 7 to 339 days following a vaccination; duration ranged from 1 to 6 days. The febrile convulsion of 18-day duration was reported in a 4 year-old female with a history of febrile convulsion, 330 days after second adjuvanted study vaccine. In Amendment 39.12, in response to an IR sent June 16, 2016, GSK notes that it is unclear why this subject reported prolonged duration of febrile convulsion and no temperatures were recorded during this time. They report she was in good health at study conclusion 1.5 months later.

An SAE of febrile convulsion was reported in one subject in the Q-Pan Group in Study Q-Pan-021 11 days following study vaccine. Two additional subjects in the Q-Pan Group reported MAAEs of convulsion.

Reviewer comment: Convulsion was identified in the original BLA review as occurring exclusively in subjects receiving adjuvanted vaccine. Three events of convulsion were reported in the Q-Pan Group in study Q-Pan-021, though it is possible all events may represent a febrile convulsion. In Q-Pan H1N1-035, febrile convulsion was reported at an identical rate between subjects in the adjuvanted and unadjuvanted groups. There

are four subjects reporting febrile convulsion that do not have another coincident infection reported. Each of these subjects was treated with antipyretics or other medications suggesting a coincident infection. Information to assess four of the six subjects with convulsion is limited as the events were reported as MAAEs, not SAEs. However, with the available information, all of the subjects with convulsion had either pre-existing epilepsy (n=2) or possible alternate plausible causes (n=4, neurocysticercosis, family history of seizure disorder in two cousins, electrolyte imbalance, coincident diarrheal illness).

8.4.3 Study Dropouts/Discontinuations

For study Q-Pan H1N1-035, GSK reports that one subject discontinued the study due to a non-fatal adverse event of upper respiratory tract infection occurring at the time the second vaccination was due. GSK reports that the study completion rate by study Group was 96.2% in Group A, 95.8% in Group B, and 96.0% in Group C.

Reviewer comment: During review, at least three subjects were noted who did not receive the second vaccination and reported an SAE around the time the second vaccination was due. The number provided above may underestimate the number of subjects who discontinued study vaccine but remained in the study for safety follow-up.

8.4.4 Common Adverse Events

Unsolicited Adverse Events and Medically Attended Events in -035
Subjects were monitored for all unsolicited AEs for 42 days following the first vaccination (Days 0 to 42). Unsolicited AEs within 42 days and MAAEs within one year were reported at similar rates in each study group (See the tables below). Unsolicited AEs assessed by the investigator as related to vaccination were reported at similar rates in each group, but Grade 3 unsolicited events were reported more frequently in Group C (1.2%) compared to the adjuvanted groups (0.5% in Group A, 0.9% in Group B).

Table 30 Unsolicited adverse events reported Day 0 – 41 or 21 days following the second vaccination in the Total Vaccinated Cohort by age strata, Q-Pan-035

Age stratum	-035 Group A N	-035 Group A n (%)	-035 Group B N	-035 Group B n (%)	-035 Group C N	-035 Group C n (%)	-021 Q-Pan N	-021 Q-Pan n (%)	-021 Placebo N	-021 Placebo n (%)
6 - < 36 months	610	350 (57.4%)	612	350 (57.2%)	613	355 (57.9%)	199	98 (49.2%)	75	39 (52.0%)
3 - < 9 or 10 years	1438	563 (39.2%)	1436	554 (38.6%)	1436	540 (37.6%)	198	83 (41.9%)	76	31 (40.8%)
9 - < 18 years	-	-	-	-	-	-	210	62 (29.5%)	80	27 (33.8%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114000, Table 1044, p. 2211-2235
N total subjects in the total vaccinated cohort
n number of subjects with the event

Table 31 Medically attended adverse events reported Day 0 – 385 in the Total Vaccinated Cohort by age strata, Q-Pan-035

Age stratum	-035 Group A N	-035 Group A n (%)	-035 Group B N	-035 Group B n (%)	-035 Group C N	-035 Group C n (%)	-021 Q-Pan N	-021 Q-Pan n (%)	-021 Placebo N	-021 Placebo n (%)
6 - < 36 months	610	429 (70.3%)	612	429 (70.1%)	613	427 (69.7%)	199	66 (33.2%)	75	27 (36.0%)
3 - < 9 or 10 years	1438	760 (52.9%)	1436	744 (51.8%)	1436	763 (53.1%)	198	64 (32.3%)	76	28 (36.8%)
9 - < 18 years	-	-	-	-	-	-	210	59 (28.1%)	80	22 (27.5%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114000, Table 1059, p. 2332-2266
N total subjects in the total vaccinated cohort
n number of subjects with the event or characteristic

In both studies rates of unsolicited AEs reported within 42 days following the second study vaccination and rates of MAAEs reported within one year following the second study vaccination were similar between treatment groups of the same study.

The following notable event was not necessarily common, but is described here for lack of a better location.

- Two allergic reactions were reported within one week of either vaccination. One 7 month-old subject in Group A reported a mild allergic reaction one day following the second dose of Q-Pan H1N1 with AS03. The reaction consisted of a generalized urticarial rash. The subject was treated with loratadine. The event resolved three days later and was assessed as related by the investigator. One subject in Group C reported a mild allergic reaction five days following the second dose of unadjuvanted vaccine assessed as not related by the investigator.

Reviewer comment: The urticarial rash one day following the second vaccination is temporally related to the first dose after priming and could have been caused by antigen or adjuvant. Symptoms were reported as mild and resolved with over the counter medication. There were no temporally associated severe allergic reactions reported.

8.4.5 Clinical Test Results

No safety laboratory tests were conducted for Study Q-Pan-035. Please see section 6.1.12.6 for a description of laboratory results in study Q-Pan-021.

8.4.6 Systemic Adverse Events

The table below presents an analysis of fever by dose and age group from study Q-Pan-035.

Table 32 Analysis of subjects in Group A with fever solicited on the subject diary card following each dose and overall in the Total Vaccinated Cohort with follow-up by age stratum, Study Q-Pan-035

Age stratum	Dose 1 N	Dose 1 n	Dose 2 N	Dose 2 n	Overall N	Overall n
6 months to 3 years	597	77 (12.9%)	582	148 (25.4%)	597	198 (33.2%)
3 to < 6 years	707	59 (8.3%)	689	99 (14.4%)	709	145 (20.5%)
6 to < 10 years	700	34 (4.9%)	690	61 (8.8%)	701	89 (12.7%)

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114000, Table 1030 and 1031, p. 2153-2161 and p. 2162-2172
N Total number of subjects evaluated
n Number of subjects with event

Reviewer comment: In their CSR, GSK presents their data using the TVC as N. The table above uses the TVC with follow-up. Proportions change slightly (by tenths of a percent) based on this difference. Overall trends remain the same.

It is not appropriate to integrate the systemic reactogenicity in the pediatric population from study Q-Pan-035 with study Q-Pan-021 because the vaccines evaluated in each study utilized different antigens. Post marketing reports noted an increase in reactogenicity, particularly fever, following the second dose of D-Pan or Q-Pan H1N1 with AS03 adjuvant. As expected, in Q-Pan H1N1-035, fever was noted at a greater rate following Dose 2 compared to Dose 1 (See the table above). No dose-dependent increase in reactogenicity following Dose 2 was observed in Q-Pan H5N1-021. Please see section 6.1.12.2 for details of systemic reactogenicity in Q-Pan-021.

8.4.7 Local Reactogenicity

Not applicable.

Reviewer comment: It is not appropriate to integrate the local reactogenicity in the pediatric population from study Q-Pan-035 with study Q-Pan-021 because the vaccines use different antigens and consequently, are likely to have different reactogenicity profiles. Please see section 6.1.12.2 for local reactogenicity in Q-Pan-021.

8.4.8 Adverse Events of Special Interest

The protocol contained a pre-specified list of pIMDs and investigators could use their judgement to categorize an AE that did not appear of the list as a pIMD. During and after the study, eight AEs were labeled as pIMDs by investigators. Of these, two events of glomerulonephritis were identified as pIMDs following database lock and unblinding. One of these events, erythema multiforme, was changed to nonspecific viral exanthem following database lock.

Reviewer comment: During the review, this clinical reviewer identified three medically–attended events within the datasets that were not reported as pIMDs by the investigator, but are likely to be immune-mediated: glomerulonephritis in one subject and hypothyroid in two subjects. Little information regarding the presentation, evaluation, and diagnosis of the events was collected because all were MAAEs, not SAEs, which would require submission of a CIOMS form with a narrative from the study site. CBER requested additional information, which GSK reported was unavailable. Both diagnoses are often of an immune-mediated etiology: post-infectious glomerulonephritis and autoimmune thyroiditis. It is recognized that iodine deficiency plays a significant role in the etiology of hypothyroidism in many of the countries in which this study was conducted. However, both subjects with hypothyroidism were treated with levothyroxine and one of them continued the medication chronically. In the absence of any information to indicate these events are not immune-mediated, they are considered as pIMDs by this clinical reviewer.

Seven subjects in the adjuvanted groups (0.2%) and four subjects in the unadjuvanted group (0.2%) reported pIMDs during the study. Two events of alopecia areata were assessed by the Investigators as possibly related to study vaccine. The table below shows all of the pIMDs identified by investigators and this clinical reviewer. Narratives of each event appear below the table.

Table 33 Potential immune-mediated diseases reported from Day 0 to 385

Study Group	Age at Day 0/ Gender	pIMD	Last active dose prior to SAE	Day of onset post-H1N1 vaccine	Duration (days)	Outcome
A	8 y/o F	Alopecia areata†	2	67	263	Resolved
B	22 m/o M	Idiopathic thrombocytopenic purpura	1	290	-	Unresolved
B	4 y/o F	Glomerulonephritis§	1	31	6	Resolved
B	5 y/o F	Glomerulonephritis	1	112	7	Resolved
B	7 y/o F	Alopecia areata†	1	103	190	Resolved
B	7 y/o F	Hypothyroidism§	1	74	-	Unresolved
B	9 y/o M	Hypothyroidism§	1	30	18	Resolved
C	10 y/o M	Guillain-Barre	2	166	187	Resolved
C	3 y/o M	Erythema multiforme*	2	347	-	Resolving
C	6 y/o F	Glomerulonephritis‡	2	67	36	Resolved
C	7 y/o F	Glomerulonephritis‡	1	4	11	Resolved

Source: Adapted from - sBLA 125419/039; Clinical Study Report 114000, Table 24, p.4336
Day of onset for Group B subjects is reported from their last dose of Q-Pan H1N1 (Dose1)
* Following database lock and unblinding, diagnosis changed to nonspecific viral exanthem
† Assessed by the investigator as related to vaccine
‡ Changed to pIMD following database lock and unblinding
§ Not reported as a pIMD by Investigator, but considered a pIMD by the Clinical Reviewer

Brief narratives of pIMDs are reported below:

- An 8-year old female, enrolled in the Philippines, with no preexisting conditions, was randomized to Group A and received two doses of Q-Pan H1N1. She reported alopecia areata 67 days after receiving the second dose of study vaccine. Laboratory tests for thyroid function, antinuclear antibody, and a complete blood cell count were normal. There was no family history of alopecia areata. She was treated with triamcinolone and the event resolved 263 days later. The investigator assessed the event as possibly related to study vaccine or possibly related to stress induced by transfer to a new school. The subject's sister also participated in this study and was diagnosed with a pIMD of alopecia areata.
- A 22-month old male, enrolled in Thailand, was randomized to Group B. He reported an SAE of idiopathic thrombocytopenic purpura (ITP) 290 days after receiving the first dose of study vaccine. Eight days prior to the event, the subject reported a fever to 38.0°C with urinary tract infection symptoms. He was treated with paracetamol and cough medication. Five days prior to the event, the subject was vaccinated with a Japanese encephalitis vaccine. The subject was hospitalized after experiencing epistaxis and ecchymosis of both legs and the abdomen. A bone marrow aspirate revealed increased megakaryocytes and he was diagnosed with ITP. He was treated with prednisolone, omeprazole, red blood cells, and platelet concentrate. His bleeding improved, but he continued to experience recurrent symptoms of ITP and the event was not resolved almost four months after his final study visit. The investigator assessed the event as not related to study vaccine.

- A 7-year old female, enrolled in the Philippines, was randomized to Group B. She reported alopecia areata 103 days after receiving the first dose of study vaccine. Clinical laboratory tests approximately seven months later for thyroid function, antinuclear antibody, and a complete blood cell count were normal. The subject's sister also participated in this study and was diagnosed with a pIMD of alopecia areata approximately one month earlier. She was treated with triamcinolone and the event resolved 176 days after onset. The investigator considered the event to be possibly related to study vaccine and possibly related to stress induced by transfer to a new school.
- A 5-year old female, enrolled in Colombia, who was randomized to Group B reported an SAE of postinfectious glomerulonephritis 112 days after receiving the first dose of study vaccine. She reported tonsillitis 1 week prior to the event. The subject also experienced mild acute renal failure. Treatment was initiated with furosemide, penicillin, and restricted fluids. Renal failure was considered resolved 2 days later. The glomerulonephritis was considered resolved in 7 days. The event was considered by the investigator to be unrelated to study vaccine.
- A 3-year old male with no reported past medical history, enrolled in Brazil. He reported an event of erythema multiforme 347 days after receiving the second dose of unadjuvanted Q-Pan H1N1 vaccine (Group C). The subject also reported an intercurrent illness of upper respiratory tract infection beginning five days earlier. He was treated with hydroxyzine. The investigator never reported the event as a pIMD. GSK reports that after unblinding, the investigator changed the diagnosis to a non-serious AE of nonspecific viral exanthem. At the conclusion of the follow-up period, the event was considered to be resolving.

  Reviewer comment: According to the CRFs, the change of the assessment of this event as being "a rash associated with a viral process" and "not a pIMD" appears to have occurred within days of reporting the event and prior to any unblinding. Additionally, the subject reports an intercurrent viral illness. No information is available on duration of the event. In the opinion of this Clinical Reviewer, the revised assessment is probably accurate and this event represents a viral exanthem. However, as the event does not appear to have been formally changed prior to database lock, the event will appear in the PI as a pIMD. If this event is not considered a pIMD, pIMD event rates change only slightly (0.15% in the adjuvanted group).

- A 6-year old female, enrolled in the Philippines experienced acute glomerulonephritis 2 days after a parotitis and 67 days after receiving the second dose of unadjuvanted Q-Pan H1N1 vaccine (Group C). Laboratory tests 6 days after onset revealed elevated antistreptolysin. She was treated with furosemide and the event was resolved approximately 11 months after onset. The event was assessed by the investigator to be unrelated to study vaccine.
- A 7-year old female in the Philippines with a personal and family history (sibling) of scabies lesions since one month before the event onset, reported acute glomerulonephritis 4 days after receiving unadjuvanted Q-Pan H1N1 vaccine (Group C). Laboratory tests 4 days after onset revealed elevated antistreptolysin. She was treated with permethrin, nifedipine, and furosemide and the event resolved 11 days later. The event was assessed by the investigator to be unrelated to study vaccine.

- A 10-year old male, enrolled in Mexico, with a history of infection of an unknown type approximately two months before event onset, developed Guillain-Barré syndrome 166 days after receiving the second dose of unadjuvanted Q-Pan H1N1 vaccine (Group C). Electromyography two weeks after onset of symptoms was consistent with the diagnosis. Treatment consisted of rehabilitation therapy. Six months after onset, the subject was considered to have recovered. The event was assessed by the investigator as not related to study vaccine and possibly due to the infection in August 2010 or to incidental illness.

The following cases were identified by the Clinical Reviewer as pIMDs:

- A 4-year old female subject, enrolled in the Philippines, with no preexisting medical condition was randomized to Group B and received Q-PAN H1N1 vaccine followed by placebo. In between the two injections, she reported a non-specific viral exanthema, which resolved in two days, and an infected knee wound on June 8. The wound was treated with antibiotics and resolved in 17 days. Thirty one days after Q-Pan H1N1 vaccine administration, the child was diagnosed with acute glomerulonephritis. She was treated with furosemide and antibiotics and the event resolved within a week. The investigator indicated that the glomerulonephritis was not related to the vaccine and that the subject did not report a pIMD.
- A 7-year female subject, enrolled in Brazil, with a current history of asthma and a past history of epilepsy, which was untreated at study enrollment, was randomized to Group B. She was diagnosed with hypothyroidism 74 days following the first dose of study vaccine. Levothyroxine treatment was initiated six months following vaccination. The event and treatment were ongoing at the end of the study. The investigator indicated the event was not related to vaccine and that the subject did not report a pIMD. This subject also reported a convulsion during the study.
- A 9-year old male subject, enrolled in Colombia, with no pre-existing medical condition was randomized to Group B and received adjuvanted Q-PAN H1N1 vaccine followed by placebo. Thirty days after Q-Pan H1N1 vaccine administration, on the day of placebo dose administration, he was diagnosed with hypothyroidism. He was prescribed levothyroxine. The event duration was reported as 18 days and the levothyroxine was discontinued approximately 2 months later. The investigator assessed the event as not related to vaccine and indicated the subject did not report a pIMD.

Reviewer comment: In Amendment 39.12, in response to an IR sent June 16, 2016, GSK stated that the cause of the two cases of hypothyroidism was unknown to them. A common cause of hypothyroidism is autoimmune thyroiditis. Both subjects are treated with levothyroxine, one of them chronically. Iodine treatment, indicating iodine deficiency, is not reported for either. Given the limited information available, these events will be considered pIMDs.

Of the eleven pIMDs, this Clinical Reviewer assesses that four have no alternative plausible cause adequately explaining the event – both events of alopecia areata and both events of hypothyroidism. All of these events were reported in subjects receiving the adjuvanted vaccine.

One additional subject in Group B reported an MAE of selective IgA immunodeficiency of mild intensity occurring one day following first vaccination with Q-Pan H1N1 adjuvanted with AS03. The event was considered resolving at study conclusion. The subject reported a medical history of furunculosis that was active at the time of study enrollment, for which he received multiple doses of penicillin prior to initial vaccination. This event was not assessed as a pIMD or SAE by the investigator, but is noted here as it is an immune deficiency.

Reviewer comment: In Amendment 39.12, in response to an IR sent June 16, 2016, GSK reported that no further information was available concerning this diagnosis, including laboratory results. Selective IgA immunodeficiency is a heterologous disorder with many potential causes, including genetic etiologies. It is not clear whether the start date indicates the day of laboratory diagnosis or the day that symptoms began. If the laboratory diagnosis was made one day following Q-Pan vaccination, it is unlikely that the vaccine could have contributed to the de novo development of an immune deficiency in such a short time period. This subject received two vaccinations. Per protocol, immunodeficient conditions are a contraindication to further vaccination. In the IR response, GSK noted that it was not known when the laboratory results were available to the site and that because selective IgA deficiency does not preclude vaccination with inactivated vaccines, there was no impact on subject safety.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

See section 8.4.6 for a discussion of dose dependency of fever following Q-Pan H1N1.

8.6 Safety Conclusions

Based upon discussions with CBER, GSK submitted and CBER reviewed the safety results of the study Q-Pan-035 in support of this sBLA. The study was a Phase 3, multi-center, observer-blind, active controlled trial evaluating a related vaccine, Q-Pan H1N1 with and without AS03 adjuvant in children 6 months through 9 years of age.

Approximately 4000 children received one or two doses of the adjuvanted vaccine and approximately 2000 subjects received the unadjuvanted vaccine. While the rate of fever following the second dose of vaccine in the adjuvanted group was increased, solicited adverse reactions are not discussed further here because they are not relevant to Q-Pan H5N1, for which this dose-dependent increase was not observed in Q-Pan-021. As in Q-Pan-021, rates of unsolicited AEs within 42 days following the first vaccination, and SAEs and MAAEs within one year following the second vaccination were similar between the adjuvanted and unadjuvanted groups. In study Q-Pan-035, eleven pIMDs were reported during the study through one year following the second dose, of which four have no alternative plausible cause identified by this reviewer. The rate of pIMD was 0.2% in both the adjuvanted and the unadjuvanted groups. In study Q-Pan-021, two pIMDs were reported, one in the Q-Pan Group (alopecia, 0.2%), and one in the Placebo group (type 1 diabetes, 0.4%). When considering both pediatric studies Q-Pan H5N1-021 and Q-Pan H1N1-035, the rates of reported pIMDs do not appear to be different between the adjuvanted vaccine groups and the control groups.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Q-Pan H5N1 has not been evaluated in pregnant women. Please see the clinical review of the original BLA to describe the pregnancies occurring in the adult studies. Two additional subjects reported pregnancy in study Q-Pan-021.

- A 17 year-old female subject became pregnant with a last menstrual period approximately 7 months following the last vaccination. At nine weeks of gestation, the subject experienced a spontaneous abortion. The investigator assessed the event was unrelated.
- A female subject became pregnant with a last menstrual period approximately six months after following the last vaccination. This pregnancy ended after 36 weeks of gestation with the delivery of a female infant with low birth weight (2.3 kg).

Reviewer comment: In both events, conception occurred many months subsequent to vaccination. There is no evidence of direct causal effect on the spontaneous abortion or the low birth weight infant.

9.1.2 Use During Lactation

Q-Pan H5N1 has not been evaluated in lactating women. The PI was updated to reflect changes prescribed by the Pregnancy Labeling and Lactation Rule.

9.1.3 Pediatric Use and PREA Considerations

Pediatric Post-marketing Requirements
In consultation with FDA's Pediatric Review Committee (PeRC), CBER deferred submission of studies for all pediatric subgroups for the original BLA because the product was ready for approval for use in adults and the pediatric studies had not been completed. The following deferred pediatric studies were listed in the November 22, 2013, approval letter as the required postmarketing pediatric studies under the Pediatric Research Equity Act (PREA) [Section 505B(a) of the Food Drug and Cosmetic Act (FDCA)]:

PMR #1: Deferred pediatric study Q-Pan H5N1-AS03-021 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy persons 6 months to < 18 years of age.

Final Protocol Submission: March 2, 2012
Study Completion Date: September 30, 2014
Final Report Submission: April 30, 2015

PMR # 2: Deferred pediatric study Q-Pan-023 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy children 6 months to < 36 months of age.

Final Protocol Submission: February 28, 2017

Study Completion Date: December 31, 2018
Final Report Submission: June 30, 2019

PMR # 3: Deferred pediatric study Q-Pan-024 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy persons 6 months to < 18 years of age. Study Q-Pan-024 will be conducted only if study Q-Pan-023 identifies a pediatric dose that is different than that evaluated in study Q-Pan H5N1=AS03-021.

Final Protocol Submission: June 30, 2018
Study Completion Date: April 30, 2020
Final Report Submission: October 31, 2020

PMR # 4: Deferred pediatric study Q-Pan-025 under PREA to evaluate the safety and immunogenicity of Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted when administered to healthy infants < 6 months of age.

Final Protocol Submission: October 31, 2021
Study Completion Date: July 31, 2022
Final Report Submission: December 31, 2022

This pediatric plan, specifically PMRs #2 and 3, was developed taking into account an observed dose-dependent increase in fever and other common adverse reactions in children 6 months to < 36 months of age administered related, non-U.S. licensed pandemic strain H1N1 influenza vaccines adjuvanted with AS03 (Arepanrix and Pandemrix). On September 8, 2014, CBER and GSK held a meeting to address GSK's overall pediatric study plan that was part of the postmarketing pediatric requirements for the Q-Pan H5N1 BLA. During this meeting, CBER indicated that 1) based on preliminary review of the immunogenicity and safety data from study Q-Pan-021 submitted to IND 13413, conducting additional dose-ranging studies in children 6 months to < 18 years of age was not necessary as the existing immunogenicity and safety data may be adequate to support submission of a supplemental application for licensure of Q-Pan H5N1 for use in persons 6 months to < 18 years of age, and 2) a "shelf-ready'' protocol for study Q-Pan-025 to evaluate Q-Pan H5N1 vaccine in infants less than 6 months of age in the event of an H5N1 pandemic would be desirable.

On July 27, 2016, DVRPA presented the pediatric assessment children 6 months through 17 years of age and their recommendations for other PMRs to the Pediatric Review Committee (PeRC). The committee agreed that 1) the product has been fully assessed in children 6 month to 17 years of age, 2) based upon adequate safety data from the study, GSK be released from PMRs #2 and 3, and 3) to revise PMR#4 to remove dates, making the timelines for this requirement contingent upon the occurrence of an imminent pandemic threat.

GSK submitted to the this sBLA a protocol for study FLU-Q-Pan H5N1-AS03-025 (Q-Pan-025), entitled "An open-label study of the safety and immunogenicity of a two-dose series of GSK Biologicals' AS03-adjuvanted A/Indonesia/05/2005 (H5N1) vaccine in children less than 6 months of age," for implementation in the event of an imminent pandemic threat of Influenza H5N1. The co-primary objectives of study Q-Pan-025 are to evaluate whether vaccination with Q-Pan H5N1 adjuvanted with AS03 results in an HI

antibody titer ≥ 1:40 that meets FDA CBER guidance criteria for pandemic influenza vaccines and to describe the reactogenicity and safety of the vaccine. The study will be conducted at multiple study centers in North America. Approximately 60 healthy infants from 6 weeks to six months of age will be enrolled. Subjects will be enrolled into a single cohort that will receive Q-Pan H5N1 vaccine administered intramuscularly as a two-dose series 21 days apart. Amendments 39.7, 39.9, 39.10, 39.11, 39.15, and 39.21 regarding timelines for the deferred pediatric study, were submitted to the sBLA.

Reviewer comment: Protocol Q-Pan-025 and associated amendments were reviewed as part of this sBLA and comments were sent to GSK on September 2, 2016. The revised protocol will be submitted to IND13413.

9.1.4 Immunocompromised Patients

Insufficient data evaluating use in immunocompromised populations.

9.1.5 Geriatric Use

Not applicable to this supplement as only the pediatric population is evaluated. Please see the original Clinical Review for data on use in the geriatric population.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

Influenza A H5N1 has caused significant outbreaks in poultry. If human to human transmission is achieved, a catastrophic worldwide pandemic could ensue, given the virus' demonstrated case fatality rate of 60%.

To prevent or minimize the effects of such a pandemic, GSK and the U.S. government partnered to develop an antigen-sparing H5N1 vaccine adjuvanted with AS03. Q-Pan H5N1 was licensed in 2013 for use in adults to prevent disease caused by the virus strain contained in the vaccine. To address PREA, four post-marketing studies were required following licensure to evaluate the vaccine in the pediatric population.

Study Q-Pan-021, submitted as the pivotal trial for this sBLA, fulfills PREA PMR#1. The study evaluated 838 subjects 6 months to 18 years of age randomized 8:3 to receive either two pediatric doses of Q-Pan H5N1 (607 subjects) or placebo (231 subjects) administered intramuscularly at a 21-day interval. In each of three age groups, the study met its immunogenicity success criterion of a lower bound of the confidence interval around the proportion of subjects with HI titer ≥ 1:40 at Day 42 > 70%. Both local and systemic reactions were commonly reported following vaccination. Injection site pain was the most frequent symptom, reported by 47-82% subjects. Injection site erythema, injection site swelling, irritability, drowsiness, loss of appetite, myalgias, arthralgias, fatigue, headache, sweating, shivering, and fever were also commonly reported and reported at greater rates than in the placebo group. Although the vaccine was reactogenic, rates of unsolicited adverse events within 42 days of initial vaccination and medically attended adverse events and serious adverse events within a year following vaccination were similar between study groups. Two potential immune mediated events were reported – alopecia in the Q-Pan group and type 1 diabetes in the placebo group.

Uncontrolled crossover data from Year 2 did not reveal any additional safety concerns. Overall, the vaccine demonstrated an acceptable safety profile and a favorable risk benefit profile in the pediatric population.

Study Q-Pan-H1N1-035 was also submitted to support assessment of Q-Pan H5N1. CBER considered the safety data, in particular the unsolicited adverse events, serious adverse events, and potentially immune-mediated adverse events, as relevant to the review of Q-Pan H5N1 because the study evaluated GSK's non-US licensed H1N1 AS03-adjuvanted vaccine, manufactured using the same process, in the pediatric population. A total of 6096 subjects 6 months to 10 years of age were randomized 1:1:1 to one dose of adjuvanted vaccine, two doses of adjuvanted vaccine, or two doses of unadjuvanted vaccine at a 21 day interval. Fever demonstrated a dose-dependent increase following dose two, in contrast to what was observed in Q-Pan-021. One death, due to pneumonia and sepsis, occurred within the 42-day primary study period in a subject who received adjuvanted vaccine. Rates of unsolicited adverse events in the primary study period, and medically attended adverse events, serious adverse events, and potentially immune mediated diseases within one year following second vaccination were similar between study groups. Safety outcomes for Q-Pan-035 were generally supportive. Pertinent safety information, including specific SAEs with a temporal association or no alternative plausible cause and all pIMDs, will be added to the package insert.

Based upon these results, and in consultation with PeRC, we consider that study Q-Pan-021 fulfills the pediatric assessment of the product in children 6 months through 17 years of age and we have decided to release GSK from two of the remaining three PREA PMRs in which they were to evaluate lower antigen and adjuvant dosing regimens if the safety profile of the dosing regimen evaluated in -021 proved unacceptable. In order to address the final PMR, GSK has submitted a protocol for a study that will evaluate Q-Pan H5N1 in infants from birth to 6 months of age in the event of a declared H5N1 pandemic threat. This reviewer recommends expanding the indication for use of Q-Pan H5N1 to persons 6 months through 17 years of age increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 34 Risk Benefit Analysis of Q-Pan H5N1 in the pediatric population, 6 months through 17 years of age

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 ~50% mortality in adults and children. • 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	• There are two pandemic H5N1 vaccines licensed in the U.S; neither is currently licensed in children. • As an antigen-sparing vaccine, Q-Pan H5N1 requires less antigen (1.9 µg x 2 vaccinations for children) due to the addition of AS03 adjuvant. • Antigen dose sparing allows for more rapid production of large amounts of vaccine.	• Q-Pan H5N1 addresses an unmet medical need for children.
Clinical Benefit	• One pivotal clinical trial in persons 6 months to 18 years of age was conducted and submitted in the sBLA. • Immunogenicity was demonstrated based on seroprotection rates, 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 confirmed during an actual H5N1 pandemic event.	• Immunogenicity data support extending the use of this vaccine to children. • Confirming benefit in infants up to six months will require evaluating the safety and immunogenicity of the vaccine during a time of widespread circulation of an H5N1 influenza virus.
Risk	• The most substantial risks of vaccination with Q-Pan H5N1 in children are associated with local and systemic reactions. Pain, erythema, and swelling are common injection site reactions in children 6 months of age and older. Common systemic reactions with this vaccine include irritability, drowsiness, loss of appetite, and fever in children younger than 6 years of age and myalgias, arthralgias, fatigue, headache, sweating, shivering, and fever in those older than 6 years of age. • Majority of subjects experience mild local and systemic reactions with resolution in several days. • Severe pain occurred in up to 5% of subjects 3 to 18 years of age. Fever ≥ 39˚C occurred in up to 5% of subjects 6 months to 9 years of age. • One pIMD occurred among approximately 750 children receiving Q-Pan H5N1. pIMDs did not occur more frequently in association with Q-Pan H5N1 than placebo. • A 2- to 16-fold increased risk of narcolepsy has been observed in persons < 20 years of age in association with a related AS03 adjuvanted influenza vaccine (Pandemrix). • Narcolepsy was not reported in this study, nor in another study of a related vaccine with AS03 adjuvant in children.	• 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. Reported immune mediated events are biologically plausible and have been temporally associated with AS03 adjuvanted influenza vaccines. • Current safety data of Q-Pan H5N1 in children is insufficient to estimate rates of rare adverse events.
Risk Management	• Q-Pan H5N1 is 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 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 this sBLA, the vaccine produces a robust immune response in children 6 months through 17 years of age. The immune response leads to a statistically significant rise in HI antibody titer, a surrogate endpoint for influenza vaccine effectiveness based upon seasonal influenza data.

As seen in adults, Q-Pan H5N1 is commonly associated with transient local injection-site and general, systemic adverse reactions with pain at the injection site, irritability, and muscle aches being the most common adverse reactions. The safety data in the pediatric population of this and closely related vaccines suggest that there are similar rates of immune-mediated adverse events in study vaccine and control populations. The pediatric 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 persons at increased risk of exposure to H5N1 or during a pandemic results in an overall favorable risk/benefit profile for Q-Pan H5N1.

11.3 Discussion of Regulatory Options

Please see section 9.1.3 for a discussion of the recommendations for the remaining deferred pediatric studies required by PREA.

11.4 Recommendations on Regulatory Actions

The data are sufficient to recommend approval of Q-Pan H5N1 for use in the pediatric population 6 months through 17 years of age. Study Q-Pan-021 fulfills pediatric PMR #1. In addition, the reviewer recommends release from PMR #2 and 3 as further dose finding studies are not necessary based on review of the submitted study.

11.5 Labeling Review and Recommendations

Major changes recommended and negotiated for the Q-Pan H5N1 PI included:

- Addition of safety and immunogenicity data from study Q-Pan-021 to support expanding usage of the vaccine to the pediatric population of individuals 6 months through 17 years old.
- Description of solicited reactions by subject age and using a more conservative grading scale for measurable local injection site reactions, appropriate for a young pediatric population
- Adding relevant safety data from the uncontrolled crossover portion of study Q-Pan-021 (Year 2)
- Inclusion of an SAE with a temporal association and no alternative plausible cause, as is consistent with the adult section of the PI
- Adding relevant safety data from study Q-Pan H1N1-035, a related AS03 adjuvanted influenza product manufactured using the same processes as Q-Pan H5N1
- Revisions to the Pregnancy and Lactation sections as required by the Pregnancy and Lactation Labeling Rule (PLLR)
- Adjustment of immunogenicity results to reflect data from the pre-specified, according to protocol population

11.6 Recommendations on Postmarketing Actions

GSK will be required to do the following:

- Submit a draft protocol to IND 13413, incorporating CBER's feedback generated through this review, Q-Pan-025 for evaluation of immunogenicity and safety in infants birth to 6 months of age to be activated the event of an imminent pandemic threat. Submission of a final protocol will be required within two weeks of an imminent pandemic threat.
- As specified in the November 22, 2013 Approval Letter of the original BLA (125419/0) and Amendment 39.25, submitted in response to an IR sent August 31, 2016, GSK commits to report all serious or non-serious cases of narcolepsy (with or without cataplexy), autoimmune hepatitis, anaphylaxis, Bell's palsy, convulsion, demyelinating disorders, encephalitis, Guillain-Barré syndrome, neuritis, vasculitis, and vaccination failure, following vaccination with Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, as 15-day expedited reports to the Vaccine Adverse Event Reporting System (VAERS).