Application Type	BLA Supplement
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Division / Office	DVRPA /OVRR
Committee Chair	Carmen Collazo-Custodio, PhD
Clinical Reviewer(s)	Darcie Everett, MD, MPH
Project Manager	Ramachandra Naik, PhD
Priority Review	No
Reviewer Name(s)	Rong Fu, PhD Mathematical Statistician
Review Completion Date / Stamped Date	
Supervisory Concurrence	Tsai-Lien Lin, PhD Team Leader, Bioassay & Viral Team, VEB/DB/OBE
	A. Dale Horne, Dr. P.H. Branch Chief, VEB/DB/OBE
Applicant	ID Biomedical Corporation of Quebec/ GlaxoSmithKline Biologicals
Established Name	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted
(Proposed) Trade Name	No Proprietary Name
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	3.75 μg Hemagglutinin H5N1 antigen with AS03 adjuvant
Dosage Form(s) and Route(s) of Administration	Emulsion for intramuscular injection
Dosing Regimen	0.25 mL (half the adult dose), administered as a 2 dose series approximately 21 days apart
Indication(s) and Intended Population(s)	Immunization against influenza disease caused by potential pandemic influenza A virus subtype H5N1 in healthy children aged 6 months to <18 years of age

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GLOSSARY

AE Adverse event

ATP	According-to-protocol
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CSR	Clinical study report
GMT	Geometric mean titer
GSK	GlaxoSmithKline
HA	Hemagglutinin
HI	Hemagglutination inhibition
MGI	Mean geometric increase
IR	Information request
MAE	Medically attended adverse event
pIMD	Potential immune-mediated disease
SAE	Serious adverse event
SCR	Seroconversion rate
SPR	Seroprotection rate
TVC	Total vaccinated cohort

1. Executive Summary

GlaxoSmithKline Biologicals (GSK) submitted BLA supplement STN 125419/39 to seek a pediatric indication for their Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (referred to as Q-Pan H5N1), in children 6 months to <18 years of age for prevention of disease caused by the influenza A virus H5N1 subtype. The application was supported by study Q-Pan 021, a randomized, placebo-controlled study to evaluate the immunogenicity and safety of Q-Pan H5N1. In addition, study Q-Pan 035 in children 6 months to <10 years was submitted to provide additional supportive safety data comparing adjuvanted to unadjuvanted Q-Pan H1N1 vaccine.

Immunogenicity

The primary objective of study Q-Pan-021 was met, with the lower bound of the 98.3% confidence interval (CI) of the seroprotection rate (SPR) for post-vaccination Hemagglutination Inhibition (HI) titer greater than 95% for each age stratum (6 to <36 months, 3 to <9 years, and 9 to <18 years), thus exceeding the pre-specified criterion of 70%.

Safety

Q-Pan H5N1 was associated with higher incidence of solicited local and some solicited general symptoms compared to placebo. Incidence of Grade 3 solicited symptoms was low. No notable differences were observed between the Q-Pan H5N1 and placebo in terms of the overall incidence of unsolicited adverse events (AEs), potential immune-mediated diseases (pIMDs), medically-attended adverse events (MAEs), or serious adverse events (SAEs). No death was reported in study Q-Pan-021. No additional safety concerns were identified in study Q-Pan-035. Two deaths were reported in the 2-dose adjuvanted Q-Pan H1N1 group, and one was reported in the 1-dose adjuvanted Q-Pan H1N1 group. The investigator did not assess any of them to be related to vaccination.

Overall, no major statistical issues were identified in the immunogenicity or safety analyses in this submission. The submitted data suggest that the primary immunogenicity objective was met. Evaluation of the imbalance of solicited symptoms associated with adjuvanted Q-Pan H5N1 vaccine as compared to placebo is referred to the medical and epidemiological reviewers.

2. Clinical and Regulatory Background

Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, also referred to as Q-Pan H5N1, was approved on November 22, 2013 for active immunization for prevention of disease caused by the influenza A virus H5N1 subtype in persons 18 years of age and older. GSK submitted this supplement to seek a pediatric indication in children 6 months to <18 years of age, based on data from study Q-Pan-021. In addition, the applicant also submitted data from study Q-Pan-035 to provide supportive safety information.

- Study Q-Pan-021 primarily evaluated immunogenicity as measured by vaccine-homologous virus HI titers, after two doses of half-volume Q-Pan H5N1 vaccine produced using the A/Indonesia/5/2005 influenza A (H5N1) virus and delivering 1.9 µg of hemagglutinin (HA) antigen and adjuvanted with $AS03_B$, in three age strata (6 to <36 months, 3 to <9 years, and 9 to <18 years).
- Study Q-Pan-035 assessed the capacity of adjuvanted and unadjuvanted vaccine containing A/California/7/2009 (H1N1)v-like HA antigen (referred to as Q-Pan H1N1) to demonstrate satisfactory safety in children 6 months to <10 years.

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

5.1 Review Strategy

This review focuses on the immunogenicity and safety objectives of study Q-Pan-021 and the safety objective of study Q-Pan-035. The submitted data, clinical study reports (CSRs), and subsequent amendments of the applicant's response to CBER's information requests (IRs) were reviewed.

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

This review is primarily based on Module 5 of STN 125419/39 (received on November 12, 2015), as well as several amendments: Amendments 1, 2, 3, 4, 14, and 19.

5.3 Table of Studies/Clinical Trials

Two clinical studies are summarized in Table 1.

Table 1: Overview of clinical studies

Study identification (study year)	Country	Design	Objectives	Population	Study groups (number of subjects in total vaccinated cohort)
Q-Pan-021	US, Canada,	Phase 2/3,	Immunogenicity,	Healthy children	Q-Pan H5N1 (N=607)

Year 1 (2011-2012)	Thailand	randomized, controlled, observer-blinded	reactogenicity/ safety	6 months to <18 years of age	Saline placebo (N=231)
Q-Pan-021 Year 2 (2012-2014)	US, Canada, Thailand	Open-label	Reactogenicity/ safety	Eligible Year 1 placebo recipients	Q-Pan H5N1 (N=155)
Q-Pan-035	Australia, Brazil, Columbia, Costa Rica, Mexico, Philippines, Singapore, Thailand	Phase 3, randomized, controlled, observer-blinded	Relative efficacy, immunogenicity, safety	Healthy children 6 months to <10 years of age	2-dose adjuvanted Q-Pan H1N1 (N=2048) 1-dose adjuvanted Q-Pan H1N1 + 1-dose saline placebo (N=2048) 2-dose unadjuvanted Q-Pan H1N1 (7.5 µg HA if <36 months old; 15 µg HA if ≥3 years old) (n=2049)

Source: Module 2, Tabular listing of clinical studies

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study Q-Pan-021

Title: 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.

6.1.1 Objectives

Primary objective

- To assess whether two doses of H5N1 antigen in association with AS03 adjuvant elicits an immune response, measured by post-immunization vaccine-homologous virus HI titers, that meets or exceeds CBER/CHMP (Committee for Medicinal Products for Human Use) young adult targets for proportion of subjects attaining post-immunization reciprocal HI titers ≥40 (i.e., SPR) against A/Indonesia/5/2005 virus (the CBER criterion requires the lower 95% confidence bound ≥70%; the CHMP criterion requires a point estimate >70%).

Secondary immunogenicity objectives regarding HI titer

- 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.

Secondary safety objective

- To describe the safety of Quebec-manufactured H5N1 antigen adjuvanted with AS03 in terms of solicited local and general reactogenicity events, clinical laboratory abnormalities, unsolicited AEs, MAEs, pIMDs, and SAEs compared with placebo in pediatric subjects 6 months to <18 years of age.

6.1.2 Design Overview

In Year 1, subjects were randomized to receive two doses (at a 21-day interval) of Q-Pan H5N1 vaccine or saline placebo in an 8:3 ratio. The randomization was conducted with a minimization procedure based on center, age (approximately 1:1:1 to 6 to <36 months, 3 to <9 years, and 9 to <18 years), and history of influenza vaccination (Yes/No). Placebo recipients who remained eligible and elected to receive the Q-Pan H5N1 vaccine after Day 385 were invited to participate in an open-label study in Year 2 for an additional 385 days follow-up. Immunogenicity blood samples were collected in Year 1 on Days 0, 21, 42, 182 (half of subjects), and 385 (the remaining half).

For safety data collection in both study years, diary cards were provided after each vaccination to record solicited local/general symptoms on the day of vaccination and during the next 6 days, and unsolicited AEs occurring through at least 21 days after vaccination. Reporting of MAEs, SAEs, pIMDs, and pregnancies continued through the end of study.

6.1.3 Population

The study population included generally healthy male or female children ≥6 months to <18 years of age at the time of the first vaccination. Placebo recipients who were to be ≥18 years at the time of being unblinded might still receive the Q-Pan H5N1 vaccine in Year 2 if all other criteria were satisfied.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study products, dosage, and administration are summarized in Table 2. Vaccines were administered by intramuscular injection.

Table 2: Dosage and administration

Year	Group	Day[a]	Test article	Antigen dose (μg)	Adjuvant	Volume[b] (mL)
1	Q-Pan H5N1	0, 21	Adjuvanted Q-Pan H5N1 Vaccine	1.9	$AS03_B$	0.25
	Placebo	0, 21	Saline placebo	-	-	0.25
2	Placebo	U0, U21	Adjuvanted Q-Pan H5N1 Vaccine	1.9	$AS03_B$	0.25

[a] Day U0 and Day U21 are study days in Year 2.
[b] Total volume of active vaccine dose (i.e., 0.125 mL antigen + 0.125 mL adjuvant, mixed).
Source: Tables 5 and 6 of study Q-Pan-021 CSR

6.1.6 Sites and Centers

This study was conducted in 11 centers in the US, 5 centers in Canada, and 1 center in Thailand. In Study Year 2, participating subjects were from all of these centers except one in Canada.

6.1.8 Endpoints and Criteria for Study Success

Primary endpoints:

- The proportion of subjects achieving a vaccine homologous H5N1 HI antibody titer ≥1:40 (i.e., SPR) at Day 42.
    - Criterion: the lower bound of the 98.3% CI for SPR at Day 42 ≥70%. This was evaluated independently in 3 age strata: 6 to <36 months, 3 to <9 years, and 9 to <18 years of age.

Secondary HI immunogenicity endpoints:
The secondary endpoints regarding vaccine homologous H5N1 HI antibody titers were assessed in terms of SPR and GMT on Days 0, 21, 42, 182, and 385, and seroconversion rate (SCR) and mean geometric increase (MGI) on Days 21, 42, 182, and 385. The SCR was defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination HI titer ≥1:40 or a pre-vaccination HI titer ≥1:10 and a ≥4-fold increase in post-vaccination HI titer.

Secondary safety endpoints:
- The occurrence of specifically-solicited local and general signs and symptoms during a 7-day follow-up period after each vaccination, 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 vaccination, as well as overall (Day 0 up to Day 42 in Study Year 1 and Day U0 up to Day U42 in Study Year 2);
- The occurrence of SAEs, MAEs, and pIMDs through Day 385 after the first vaccination in Study Year 1 and through Day U385 after the first vaccination in Study Year 2;
- Occurrence and relationship to vaccination of adverse pregnancy outcomes through Day 385/Day U385 after the first vaccination in Study Year 1/Year 2.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Immunogenicity analysis
The exact CI for a proportion within a group was calculated using the Clopper-Pearson method. The GMT and 95% CIs were obtained based on log-transformed data within each group separately, and HI titers below the cut-off of the assay (<10) were replaced by half of the cut-off. The primary objective was assessed based on 98.3% CIs to adjust for multiplicity.

Safety analysis
Safety analyses were performed in a descriptive manner separately for Study Year 1 and Year 2. In handling the missing data, the analysis of solicited symptoms included only vaccinated subjects and doses with documented safety data (i.e., symptom screen/sheet completed). For analysis of unsolicited AEs, such as SAEs or AEs by primary Medical Dictionary for Regulatory Activities term, all vaccinated subjects were considered. Subjects who did not report the event were considered as subjects without the event.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Total vaccinated cohort (TVC)
For each study year, the TVC included all subjects who received at least one study vaccination during the relevant portion of the study. The TVC was used for primary analysis of safety data, per vaccine actually administered at the first dose.

According to protocol cohort for safety (ATP-S)
For each study year, the ATP-S cohort included all eligible subjects:

- who met all inclusion criteria and no exclusion criteria;
- who received at least 1 dose of study vaccine/placebo according to their treatment assignment;
- for whom the randomization code was unbroken during Study Year 1;
- who had not received any investigational or non-registered product (drug or vaccine) other than the study vaccine(s); and
- who had not received any non-study vaccine between the Day 0 visit and completion of the Day 42 visit.

ATP cohort for immunogenicity (ATP-I) – Days 42, 182, and 385 in Study Year 1
During the relevant analysis interval, the ATP-I cohort included all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures defined in the protocol, with no elimination criteria during the analysis interval) from the ATP-S cohort who

- received the vaccine/placebo doses during the specified interval per protocol treatment assignment;

and for whom:

- no immunoglobulins and/or any blood products were administered during the analysis interval;
- no chronic administration of immunosuppressants or administration of other immune-modifying drugs occurred during the analysis interval;
- assay results for antibodies against the vaccine-homologous H5N1 antigen for the blood sample taken at Day 0 and during the specified analysis interval were available.

The ATP-I cohort for Day 42 was used for the primary analysis of immunogenicity.

Change in the conduct of the study or planned analyses
The protocol defined ATP-I cohort for each time point (described above) requires subjects to have assay results at both the specified time point and Day 0. In conducting the analyses, these cohorts in fact included subjects with assay results available at the specified time point but could include subjects for whom the Day 0 assay result was not available. The rationale for this change was that for assessments of SPRs and GMTs by HI assay, Day 0 results were not required.

Reviewer's comments:
This change affected the disposition of the ATP-I cohort at Day 42, which was used to evaluate the primary objective. The CBER review team did not consider this change to be acceptable. An IR was sent requesting GSK to reanalyze the data in compliance with the protocol definition. See Section 6.1.10.1.3 and Section 6.1.11.1 below for detailed discussions and review comments on this issue.

6.1.10.1.1 Demographics

Table 3 summarizes the demographic characteristics for the TVC. These demographic characteristics were comparable between Q-Pan H5N1 and placebo groups overall, as well as within each age stratum.

Table 3: Summary of demographic characteristics (TVC)

Characteristics	Parameters or categories	Q-Pan H5N1 N=607		Placebo N=231		Total N=838	
		Value or n	%	Value or n	%	Value or n	%
Age (months)	Mean	85.7	-	82.8	-	84.9	-
	Standard Deviation	61.81	-	60.29	-	61.37	-
	Median	74.0	-	64.0	-	71.0	-
	Range	6-215	-	7-215	-	6-215	-
Sex	Female	285	47.0	116	50.2	401	47.9
	Male	322	53.0	115	49.8	437	52.1
Ethnicity	American Hispanic or Latino	68	11.2	25	10.8	93	11.1
	Not American Hispanic or Latino	539	88.8	206	89.2	745	88.9
Geographic Ancestry	White - Caucasian / European Heritage	271	44.6	106	45.9	377	45.0
	White - Arabic / North African Heritage	3	0.5	0	0	3	0.4
	Asian - South East Asian Heritage	211	34.8	83	35.9	294	35.1
	Asian - East Asian Heritage	1	0.2	0	0	1	0.1
	Asian - Central/South Asian Heritage	2	0.3	1	0.4	3	0.4
	African Heritage / African American	93	15.3	35	15.2	128	15.3
	American Indian or Alaskan Native	2	0.3	1	0.4	3	0.4
	Other	24	4.0	5	2.2	29	3.5

Source: Table 19 of study Q-Pan-021 CSR

6.1.10.1.3 Subject Disposition

The study enrolled 881 subjects in Year 1, of which 41 were screen failures without a treatment group number allocated and therefore not dosed. Two other subjects received treatment numbers but did not receive study vaccine (one in each treatment group). Therefore, a total of 838 subjects were included in the TVC. Subject disposition and completion/withdrawal from study for TVC are summarized in Table 4.

Table 4: Number of subjects vaccinated, completed, and withdrawn in Study Year 1 and 2 with reason for withdrawal (TVC)

	Year 1			Year 2
	Q-Pan H5N1	Placebo	Total	Placebo[a]
	N	N	N (%)	N
Total vaccinated cohort	607	231	838 (100%)	155
Day 42 ATP-I cohort	571	214	785 (93.7%)	-
Subjects completed	565	217	782	152
Subjects withdrawn	42	14	56	3
Reasons for withdrawal				
Serious/Non-serious Adverse Event	0	0	0	0
Protocol violation	0	0	0	0
Consent withdrawal (not due to an AE)	7	4	11	1
Migrated/moved from study area	7	2	9	0
Lost to follow-up (with incomplete vaccination course)	7	2	9	0
Lost to follow-up (with complete vaccination course)	17	6	23	2
Sponsor study termination	0	0	0	0
Other reasons	2	0	2	0

[a] Placebo recipients in Study Year 1 receiving Q-Pan H5N1 in Study Year 2.

Source: Tables 13, 15-17 of study Q-Pan-021 CSR

Reviewer's comments:
It appears that two subjects in the Q-Pan H5N1 group who withdrew from the study in Year 1 were not included in this table. Review of the data revealed that reasons for withdrawal were missing for these two subjects.

Regarding the number of subjects in the Day 42 ATP-I cohort, as mentioned in Section 6.1.10.1, there was a change from the protocol in the cohort definition in the CSR. This cohort would include 773 subjects (562 in Q-Pan H5N1 and 211 in placebo) according to the protocol-specified definition. The applicant's primary analysis of the SPR included 774 subjects (563 in Q-Pan H5N1 and 211 in placebo), as shown in Table 5 below. The disposition Table 4 and a demographic table for this cohort in the CSR included 785 subjects (571 in Q-Pan H5N1 and 214 in placebo). An IR was sent requesting clarification on the apparent discrepancy in these numbers between tables and reanalyses of data for this cohort using the protocol definition. GSK responded in STN 125419/39/14 that the discrepancy was due to Table 4 including 12 subjects who had missing HI titers for either Day 0 or Day 42, but who had available HI titers for Day 21. GSK's rationale was to use all available data appropriately for the needed analyses. GSK also suggested not regenerating the disposition and demographic tables using the protocol-defined ATP-I cohort at Day 42.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Table 5 presents the SPRs by treatment group and age stratum for the ATP-I cohort at Day 42. The primary objective was met, with the lower 98.3% confidence bounds for all three age strata in the Q-Pan H5N1 group >95%, exceeding the pre-specified criterion of 70%.

Table 5: Evaluation of primary objective: SPR for HI antibodies against the H5N1 A/Indonesia virus strain (A/Indonesia/05/2005) at Day 42 by age stratum (ATP-I cohort at Day 42)

Study Group	Age stratum	N	n	%	98.3% CI
Q-Pan H5N1	6 to<36months	175	175	100	(97.3, 100)
	3 to <9 years	185	184	99.5	(96.4, 100)
	9 to <18 years	203	201	99.0	(95.8, 99.9)
Placebo	6 to<36months	64	0	0.0	(0.0, 7.2)
	3 to <9 years	71	0	0.0	(0.0, 6.5)
	9 to <18 years	76	1	1.3	(0.0, 8.6)

n/% = number/percentage of subjects with HI titer ≥1:40
Source: Table 21 of study Q-Pan-021 CSR

Reviewer's comments:
As mentioned in Section 6.1.10.1.3, the change in definition of Day 42 APT-I cohort resulted in the inclusion in the primary analysis of one Q-Pan H5N1 recipient aged 3 to <9 years who had missing Day 0 HI titer. In responding to CBER's IR (STN 125419/39/14), GSK did not conduct the reanalyses as requested and provided the main rationales for not doing so, as described in Section 6.1.10.1.3 and Section 6.1.10.1. The review team did not consider GSK's response to be acceptable; thus, CBER informed

GSK that reanalyzed results of the protocol-specified Day 42 ATP-I would be presented in our reviews and the package insert. The subject with missing Day 0 HI titer had a titer ≥1:40 at Day 42. Therefore, for the Q-Pan H5N1 3 to <9 years age stratum, the reviewer recalculated the SPR and 98.3% CI as 99.5% (96.3%, 100%) (n=183, N=184), using the protocol defined ATP-I cohort at Day 42.

6.1.11.2 Analyses of Secondary Endpoints

Table 6 presents the SPRs and GMTs for the Q-Pan H5N1 group by age stratum. For placebo recipients, SPRs were <1.5% and GMTs were <10 for all age strata at Days 0, 21, 42, 182, and 385. The results show that, starting from Day 42, the youngest age stratum showed higher immunogenicity levels than the other two age strata.

Table 6: Q-Pan H5N1 group: A/Indonesia/05/2005 HI antibody parameters (SPR and GMT) at Days 0, 21, 42, 182, and 385 by age stratum (ATP-I cohorts - Year 1)

			SPR			GMT	
Age stratum	Timing	N	n	%	95% CI	Value	95% CI
6 to <36 months	PRE	182	1	0.5	(0.0, 3.0)	5.3	(5.1, 5.5)
	PI(D21)	179	105	58.7	(51.1, 66.0)	38.7	(33.9, 44.2)
	PII(D42)	175	175	100	(97.3, 100.0)[a]	777.1	(705.6, 855.9)
	PII(D182)	84	80	95.2	(88.3, 98.7)	90.6	(78.1, 105.0)
	PII(D385)	63	54	85.7	(74.6, 93.3)	65.6	(55.9, 76.9)
3to <9 years	PRE	184	2	1.1	(0.1, 3.9)	5.6	(5.3, 5.9)
	PI(D21)	184	110	59.8	(52.3, 66.9)	44.6	(39.2, 50.9)
	PII(D42)	185	184	99.5	(96.4, 100.0)[a]	543.8	(484.9, 609.8)
	PII(D182)	89	75	84.3	(75.0, 91.1)	57.4	(50.8, 64.9)
	PII(D385)	85	47	55.3	(44.1, 66.1)	32.8	(28.1, 38.4)
9 to <18 years	PRE	204	1	0.5	(0.0, 2.7)	5.7	(5.4, 6.1)
	PI(D21)	204	108	52.9	(45.8, 59.9)	35.3	(31.7, 39.5)
	PII(D42)	203	201	99.0	(95.8, 99.9)[a]	416.2	(371.5, 466.2)
	PII(D182)	87	63	72.4	(61.8, 81.5)	50.2	(43.3, 58.2)
	PII(D385)	95	27	28.4	(19.6, 38.6)	21.6	(18.6, 25.1)

[a] 98.3% CI for SPR at Day 42
Source: Table 22 of study Q-Pan-021 CSR

Reviewer's comments:
Using the protocol-defined ATP-I cohort for each study time point would only yield slight changes in the results for SPR and GMT compared to the applicant's results in the CSR.

6.1.11.3 Subpopulation Analyses

Overall, among Q-Pan H5N1 recipients, SPRs at Day 42 were very high across subgroups of sex and race, which have at least moderate sample sizes (i.e., African heritage/African American, Asian – South East Asian heritage, and White – Caucasian/European heritage), with 95% lower confidence bounds all greater than 93%. No remarkable differences were observed between the sex or race groups.

6.1.12 Safety Analyses

6.1.12.1 Methods

Please refer to Section 6.1.9 for statistical methods used in the safety analyses. Below is a summary of the safety analysis results.

Solicited local/general symptoms

Solicited local and general symptoms by intensity are tabulated by age stratum in Table 7 and Table 8 for Year 1. Overall, the Q-Pan H5N1 group reported apparently higher incidences of solicited local symptoms and several general symptoms than the placebo group. No increase in the frequency of any solicited symptom was noted after the second dose of Q-Pan H5N1 vaccine. No Grade 3 solicited symptoms were reported in >6% of Q-Pan H5N1 recipients. The incidence of solicited symptoms after Q-Pan H5N1 vaccine in the open-label Study Year 2 was similar to that reported for Q-Pan H5N1 recipients in Study Year 1.

Table 7: Incidence of solicited local symptoms reported during the 7-day post-vaccination periods by treatment and age stratum (TVC)

	Q-Pan H5N1 %			**Placebo %**		
Symptoms	**Any**	**Grade 2[a] or 3[b]**	**Grade 3**	**Any**	**Grade 2[a] or 3[b]**	**Grade 3**
6 to <36 months	N=196			N=73		
Pain	47.4	15.3	2.6	30.1	4.1	2.7
Redness	5.6	0.5	0	0	0	0
Swelling	4.6	0.5	0	0	0	0
3 to <9 years	N=197			N=76		
Pain	71.1	24.4	5.1	38.2	2.6	0
Redness	5.6	2.0	0.5	0	0	0
Swelling	7.1	2.0	0.5	1.3	1.3	0
9 to <18 years	N=210			N=80		
Pain	81.9	24.8	4.8	22.5	5.0	2.5
Redness	3.3	0.5	0	0	0	0
Swelling	8.6	1.9	0	0	0	0

N = number of subjects with at least one documented dose and with safety data available.
% = number/percentage of subjects reporting the symptom at least once
[a] Grade 2: Swelling/redness defined as >50 to 100 mm.
[b] Grade 3: Swelling/redness defined as >100 mm.
Source: Table 66 of study Q-Pan-021 CSR

Table 8: Incidence of solicited general symptoms reported during the 7-day post-vaccination periods by treatment and age stratum (TVC)

	Q-Pan H5N1 %			Placebo %		
Symptoms	**Any**	**Grade 2 or 3 or ≥38.5ºC**	**Grade 3 or ≥39.0ºC**	**Any**	**Grade 2 or 3 or ≥38.5ºC**	**Grade 3 or ≥39.0ºC**
6 to <36 months	N=196			N=73		
Irritability/fussiness	50.5	16.3	4.1	39.7	15.1	2.7
Drowsiness	37.8	14.8	4.1	30.1	11.0	2.7
Loss of appetite	29.1	10.2	3.1	32.9	15.1	5.5
Fever[a]	22.4	10.7	4.6	16.4	12.3	5.5
3 to <6 years	N=98			N=49		
Irritability/fussiness	29.6	7.1	2.0	22.4	4.1	0
Drowsiness	27.6	4.1	1.0	14.3	2.0	0
Loss of appetite	22.4	5.1	2.0	10.2	4.1	0
Fever[a]	15.3	9.2	5.1	18.4	8.2	2.0
6 to <9 years	N=99			N=27		
Muscle aches	35.4	8.1	3.0	18.5	0	0
Headache	29.3	10.1	2.0	7.4	0	0
Fatigue	22.2	10.1	0	3.7	0	0
Joint pain	14.1	4.0	1.0	7.4	0	0
Gastrointestinal	17.2	5.1	1.0	22.2	3.7	0
Shivering	4.0	1.0	1.0	0	0	0
Sweating	6.1	0	0	0	0	0
Fever[a]	13.1	6.1	4.0	0	0	0
9 to <18 years	N=210			N=80		
Muscle aches	41.9	14.3	1.9	15.0	3.8	1.3
Headache	33.8	10.5	2.9	20.0	6.3	3.8
Fatigue	31.9	10.0	1.9	22.5	5.0	2.5
Joint pain	17.1	5.7	0.5	8.8	1.3	0
Gastrointestinal	12.4	6.2	1.4	15.0	3.8	2.5
Shivering	10.0	3.3	0.5	8.8	3.8	1.3
Sweating	9.0	3.3	1.0	5.0	1.3	0
Fever[a]	2.9	0.5	0.5	3.8	1.3	1.3

N = number of subjects with at least one documented dose and with safety data available.
% = number/percentage of subjects reporting the symptom at least once
[a] Fever was displayed by temperature (any: ≥38.0ºC).
Source: Tables 68 and 70 of study Q-Pan-021 CSR

Reviewer's comments:

1. *The grading scale for redness and swelling used by the applicant (Grade 1: >20 to 50 mm) might be liberal for a pediatric population per the medical reviewer's perspective. An IR was sent requesting rationales for the applicant's grading scales and recalculations using a more conservative scale, "Grade 1: >0 to 20 mm." GSK responded and proposed not to modify the grading scale applied in studies Q-Pan-021 and Q-Pan-035. Please refer to the medical officer's review for details regarding solicited AEs. Overall, under the more conservative grading scales, Q-Pan H5N1 recipients still reported more redness and swelling symptoms than placebo recipients.*

2. *The medical officer observed that three US study sites appeared to have lower percentages of total subjects reporting any, local, and general solicited adverse events in Year 1 when compared to other study sites. An IR was sent to GSK asking for explanation. GSK's response (STN 125419/39/2) stated that the reporting frequency by site in the Q-Pan H5N1 group for each of the 3 outcomes varied over a*

wide range, and the 95% CIs for the 3 sites identified by CBER overlapped with a few other sites. Moreover, the number of subjects in the placebo group was small, leading to wide CIs for the site-specific data; nevertheless, several sites in the placebo group also showed reporting frequencies similar to the 3 sites identified by CBER. Overall, GSK considered that CBER's observation was most likely due to random variation across sites.

Unsolicited adverse events

In Study Year 1, 243 (40.0%) Q-Pan H5N1 recipients and 97 (42.0%) placebo recipients reported at least one unsolicited AE up to 42 days after the first vaccination. The percentages of subjects reporting a Grade 3 unsolicited AE were 3.6% and 4.3% in Q-Pan H5N1 and placebo groups, respectively. In Year 2, 41 (26.5%) and 3 (1.9%) subjects reported at least one unsolicited AE and Grade 3 unsolicited AE up to 42 days after the first vaccination, respectively.

Reviewer's comments:

The analyses of unsolicited AEs "up to 42 days after the first vaccination" included events that occurred within 21 days post each dose, as well as events that occurred during the period between Day 22 and prior to dose 2, if dose 2 was administered later than Day 21. If only counting the unsolicited AEs reported within 21 days post each dose, then the incidence rates became 39.4% for Q-Pan H5N1 and remained the same for placebo in Year 1.

Medically-attended adverse events

MAEs were reported in 189 (31.1%) Q-Pan H5N1 recipients and 77 (33.3%) placebo recipients throughout Study Year 1. During Year 2, MAEs were reported in 36 (23.2%) subjects.

Potential immune-mediated diseases

In Study Year 1, one pIMD (alopecia, assessed as not related to study vaccine by the investigator) was reported for one Q-Pan H5N1 recipient (0.2%), and one pIMD (type 1 diabetes mellitus, assessed as related to study vaccine by the investigator) was reported for one placebo recipient (0.4%). In Year 2, no subjects reported pIMDs.

6.1.12.3 Deaths

No deaths were reported in either year of the study.

6.1.12.4 Nonfatal Serious Adverse Events

During Study Year 1, SAEs were reported for 8 (1.3%) subjects in the Q-Pan H5N1 group and 4 (1.7%) subjects in the placebo group. One placebo recipient reported an SAE (type 1 diabetes mellitus) that was assessed by the investigator to be related to vaccination. During Study Year 2, 2 SAEs (wound and scarlet fever), not considered related to vaccination, were reported in 2 (1.3%) subjects.

6.1.12.5 Adverse Events of Special Interest (AESI)

NA

6.1.12.6 Clinical Test Results

Please refer to the medical officer's review.

6.1.12.7 Dropouts and/or Discontinuations

No subjects prematurely discontinued from the study due to an AE or SAE in either year. Similar proportions of subjects withdrew from the study in each treatment group.

6.2 Study Q-Pan-035

Title: 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.

6.2.1 Objectives

Secondary safety objective

- To describe the safety of AS03 adjuvanted (Group A) and unadjuvanted (Group C) Québec-manufactured pandemic A/California vaccines in terms of solicited local and general AEs, unsolicited AEs, SAEs, MAEs, and pIMDs, for all subjects and in each age stratum.

6.2.2 Design Overview

Subjects were randomized in a ratio of 1:1:1 to receive adjuvanted (1- or 2-dose) or unadjuvanted (2-dose) Q-Pan H1N1 vaccine at a 21-day interval. The randomization used a minimization procedure based on center, age stratum (6 to <36 months and 3 to <10 years; approximately 1:1 with no more than 75% of subjects in either age stratum), and prior seasonal influenza vaccination status (Yes/No). The treatment groups by age stratum were:

- Group A: two doses of adjuvanted Q-Pan H1N1 vaccine
  - A1: Subjects 6 to <36 months of age
  - A2: Subjects 3 to <10 years of age
- Group B: one dose of adjuvanted Q-Pan H1N1 vaccine + one dose of saline placebo
  - B1: Subjects 6 to <36 months of age
  - B2: Subjects 3 to <10 years of age
- Group C: two doses of unadjuvanted Q-Pan H1N1 vaccine
  - C1: Subjects 6 to <36 months of age: 7.5 μg antigen
  - C2: Subjects 3 to <10 years of age: 15 μg antigen

For safety data collection, diary cards were provided for subjects to record both solicited (for 7 days after each vaccination) and unsolicited events (for 21 days after each vaccination). Reporting of MAEs, pIMDs, or SAEs continued through the end of the study (Day 385).

6.2.3 Population

Subjects enrolled in this study were male or female children 6 months to <10 years of age at the time of the first vaccination and who were in stable health status.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Table 9 presents a summary of the dose administration for each group.

Table 9: Dosage and administration

Day	Group	Age stratum[a]	Dose (µg)	Vaccine	Adjuvant	Volume[b] (mL)
0, 21	A	A1 and A2	1.9	Q-Pan H1N1	$AS03_B$	0.25
0	B	B1 and B2	1.9	Q-Pan H1N1	$AS03_B$	0.25
21	B	B1 and B2	-	Saline placebo	-	0.5
0, 21	C	C1	7.5	Q-Pan H1N1	-	0.25
0, 21	C	C2	15	Q-Pan H1N1	-	0.5

[a] A1, B1, and C1: 6 to <36 months; A2, B2, and C2: 3 to <10 years.
[b] For active vaccine, volume referred to unmixed (antigen only) or mixed (antigen and adjuvant) doses depending on group.
Source: Table 7 of study Q-Pan-035 CSR

6.2.6 Sites and Centers

This study was conducted at 17 centers in 8 countries: Australia, Brazil, Colombia, Costa Rica, Mexico, Philippines, Singapore, and Thailand.

6.2.8 Endpoints and Criteria for Study Success

Secondary safety endpoints

- The occurrence of solicited local and general signs and symptoms during a 7-day follow-up period after each administration of adjuvanted or unadjuvanted vaccine or of saline placebo;
- The occurrence of all unsolicited AEs 21 days following each dose of adjuvanted or unadjuvanted vaccine or of saline placebo;
- The occurrence of MAEs, pIMDs, and SAEs throughout the study.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Please refer to Section 6.1.9.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

TVC included all subjects who received at least one study vaccination. The primary analysis of safety was performed on the TVC, according to the actual treatment received.

6.2.10.1.1 Demographics

For the overall population of the TVC, the mean age was 4.3 years; 49.8% were female; the racial distribution was 11.3% white, 1.4% black, 39.5% Asian, and 47.8% other. These demographic profiles were comparable across three treatment groups.

6.2.10.1.3 Subject Disposition

The study enrolled 6266 subjects, among whom 121 (1.9%) were not allocated to study vaccine and therefore did not receive study treatment. Overall, 6145 subjects received study treatment and constituted the TVC (2048, 2048, and 2049 subjects in Groups A, B,

and C, respectively). Table 10 shows numbers of subjects vaccinated and withdrawn with reason for withdrawal by age stratum.

Two subjects <3 years of age (at their first dose) inadvertently received 15 µg HA rather than 7.5 µg HA and were included in the analysis for the vaccine dose (15 µg) they actually received. Two subjects >3 years of age (at their first dose) inadvertently received 7.5 µg HA rather than 15 µg HA and were included in the analysis for the vaccine dose (7.5 µg) they actually received.

Table 10: Number of subjects vaccinated and withdrawn with reason for withdrawal by age stratum (TVC)

	Group A1	Group A2	Group B1	Group B2	Group C1	Group C2	Total
Total vaccinated cohort	610	1438	612	1436	613	1436	6145
Number of subjects withdrawn	34	63	39	56	35	67	294
Reasons for withdrawn							
Serious adverse event	1	1	1	0	0	0	3
Non-serious adverse event	0	0	0	1	0	0	1
Protocol violation	0	0	0	1	2	1	4
Consent withdraw (not due to an AE)	16	30	13	28	12	33	132
Migrated/move from study area	1	6	6	8	7	3	31
Lost to follow-up (with incomplete vaccination course)	4	3	4	2	2	5	20
Lost to follow-up (with complete vaccine course)	9	19	11	15	8	19	81
Other	3	4	4	1	4	6	22

Source: Table 30 of study Q-Pan-035 CSR

6.2.11 Efficacy Analyses

NA for this application

6.2.12 Safety Analyses

6.2.12.1 Methods

Please refer to Section 6.1.9 for the methods of safety analyses.

In summary, subjects in Group A (2-dose adjuvanted vaccine) generally reported higher incidences of solicited local and general symptoms than in Groups B and C. No notable safety concerns were identified for subjects in Group A in terms of the overall incidence of unsolicited AEs, MAEs, or pIMDs.

- Up to Day 42, similar proportions of subjects in Groups A, B, and C reported at least one unsolicited AE (44.6%, 44.1%, and 43.7%, respectively). Grade 3 unsolicited AEs were reported by 0.5%, 0.9%, and 1.2% of subjects in Groups A, B, and C, respectively. The proportion of subjects reporting at least one unsolicited AE was higher among subjects aged 6 to <36 months (57.2%-57.9%) than in subjects aged 3 to <10 years (37.6%-39.2%) in each of Groups A, B, and C.
- Through Day 385, at least one MAE was reported in 58.1%, 57.3%, and 58.1% of subjects in Groups A, B, and C, respectively. The proportion of subjects reporting at least one MAE was higher among subjects aged 6 to <36 months (69.7%-70.3%) than among subjects aged 3 to <10 years (51.8%-53.1%) in each of Groups A, B, and C.

- Through Day 385, 8 pIMDs were reported in 8 subjects (1 [0.05%], 3 [1%], and 4 [0.2%] in Groups A, B, and C, respectively). Please refer to the medical officer's review for details of the pIMDs.

Reviewer's comments:
As in study Q-Pan-021, "up to Day 42" unsolicited AEs included events that occurred during the period between Day 22 and prior to dose 2. If only events occurring within 21 days post each vaccination are considered, the proportion of subjects reporting unsolicited AEs will remain similar (43.6%, 42.8%, and 42.4% in Groups A, B, and C, respectively).

6.2.12.3 Deaths

Three deaths were reported during the study: 2 subjects in Group A and 1 in Group B. None of the deaths were considered related to vaccination by the investigator.

6.2.12.4 Nonfatal Serious Adverse Events

Through Day 385, SAEs were reported in 3.7%, 3.2%, and 3.3% of subjects in Groups A, B, and C, respectively. One SAE, gastroenteritis, reported in Group B1 was considered by the investigator to be related to study vaccine.

Reviewer's comments:
The reviewer calculated the proportions of subjects reporting non-fatal SAEs in Groups A, B, and C as 3.6%, 3.2, and 3.3%, respectively. Subjects aged 6 to <36 months were more likely to experience an SAE than subjects aged 3 to <10 years, across all three treatment groups.

6.2.12.5 Adverse Events of Special Interest (AESI)

NA

6.2.12.6 Clinical Test Results

NA

6.2.12.7 Dropouts and/or Discontinuations

One subject in Group B discontinued from the study due to a non-serious AE (upper respiratory tract infection). This event was considered unrelated to study vaccine by the investigator. The drop-out rates were similar and low across treatment groups.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Immunogenicity

The primary objective of study Q-Pan-021 was met, with the lower bound of the 98.3% CI of the post-vaccination HI titer SPR at Day 42 greater than 95% for each age stratum, thus exceeding the pre-specified criterion of 70%.

Safety (study Q-Pan-021)

- Q-Pan H5N1 vaccine was associated with higher incidence rates of solicited local and several solicited general symptoms compared to placebo. Incidence rates of Grade 3 solicited symptoms were low.
- Similar proportions of Q-Pan H5N1 recipients reported any or Grade 3 unsolicited AEs up to Day 42 compared to placebo recipients.
- In Year 1, 1 (0.2%) Q-Pan H5N1 recipient and 1 (0.4%) placebo recipient reported pIMDs. No pIMD was reported in Year 2. In Year 1, SAEs were reported in 1.3% and 1.7% of Q-Pan H5N1 and placebo recipients, respectively. In Year 2, SAEs were reported in 1.3% of subjects receiving Q-Pan H5N1. No SAE or pIMD reported in the Q-Pan H5N1 group was considered by the investigator as related to vaccination.
- No deaths were reported in either year of the study.

Safety (study Q-Pan-035)

No additional safety concerns were identified in study Q-Pan-035, comparing adjuvanted Q-Pan H1N1 vaccine to unadjuvanted vaccine. Two deaths were reported in the 2-dose adjuvanted Q-Pan H1N1 group, and one was reported in the 1-dose adjuvanted Q-Pan H1N1 group. None of them were assessed as related to vaccination by the investigator.

10.2 Conclusions and Recommendations

Overall, no major statistical issues were identified in the immunogenicity or safety analyses in this submission. Evaluation regarding the imbalance in solicited symptoms associated with adjuvanted Q-Pan H5N1 vaccine as compared to placebo is referred to the medical and epidemiological reviewers.