Application Type	BLA Supplement Amendment
STN	125419/39/21
CBER Received Date	November 12, 2015
PDUFA Goal Date	September 11, 2016
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

ATP According-to-protocol

CI Confidence interval
CSR Clinical study report
GMT Geometric mean titer
HI Hemagglutination inhibition
SCR Seroconversion rate
SPR Seroprotection rate

1. Executive Summary

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. In the original clinical study report (CSR) of study Q-Pan-021, there was a change in the conduct of immunogenicity analyses from that specified in the protocol: the According-to-Protocol cohort for Immunogenicity (ATP-I cohort) at a specified time point in the analyses could include subjects for whom the Day 0 assay result was not available, whereas the protocol-defined ATP-I cohort required subjects to have assay results at both the specified time point and Day 0. CBER did not consider this change to be acceptable.

On August 10, 2016, GSK submitted Amendment 21 which included reanalyzed results for primary and secondary Hemagglutination Inhibition (HI) immunogenicity endpoints in compliance with the protocol-defined ATP-I cohort, as well as revised tables for subject disposition and demographic characteristics. This review focuses on this amendment and serves as an addendum to the original statistical review (dated August 11, 2016). I consider the applicant's reanalysis results to be acceptable.

2. SUMMARY OF STATISTICAL EVALUATION

The updated subject disposition table showed that the Day 42 ATP-I cohort included 562 and 211 subjects in the Q-Pan H5N1 and placebo groups, respectively. The demographic profile of the Day 42 ATP-I cohort was similar to that of the total vaccinated cohort. The original subject disposition table and demographic table in the CSR included additional 12 subjects (9 in Q-Pan H5N1 and 3 in placebo) who had either Day 0 or Day 42 HI titer missing but Day 21 HI titer available.

Table 1 presents the analysis results for the primary endpoint of Day 42 HI titer seroprotection rate (SPR) by treatment group and by age stratum, using the protocol-defined Day 42 ATP-I cohort. The primary objective was met, with the lower 98.3% confidence bounds for all three age strata in the Q-Pan H5N1 group exceeding the pre-specified criterion of 70%. The original primary analysis presented in the CSR included one additional Q-Pan H5N1 recipient who had the HI titer missing for Day 0 and had a Day 42 titer ≥1:40.

Table 1: 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	100.0	(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 <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
CI = confidence interval
Source: Table 3 of GSK's response in STN 125419/39/21

Table 2 summarizes SPRs, geometric mean titers (GMTs), and seroconversion rates (SCRs) for the Q-Pan H5N1 group at each time point by age stratum. For placebo recipients, SPRs and SCRs were ≤1.4% and GMTs were <10 for all age strata at all time points.

Table 2: A/Indonesia/05/2005 HI antibody parameters at Days 0, 21, 42, 182 and 385 in Q-Pan H5N1 group by age stratum (Adapted ATP cohort for immunogenicity[a])

Age stratum	Timing	N	Seroprotection rate			Geometric mean titer		Seroconversion rate		
			n	%	95% CI	Value	95% CI	n	%	95% CI
6 to <36 months	PRE	175	0	0	(0, 2.1)	5.2	(5.1, 5.4)	-		
	PI(D21)	172	100	58.1	(50.4, 65.6)	38.2	(33.3, 43.7)	98	57.0	(49.2, 64.5)
	PII(D42)	175	175	100	(97.3, 100)[b]	777.1	(705.6, 855.9)	175	100	(97.9, 100)
	PII(D182)	84	80	95.2	(88.3, 98.7)	90.6	(78.1, 105.0)	80	95.2	(88.3, 98.7)
	PII(D385)	63	54	85.7	(74.6, 93.3)	65.6	(55.9, 76.9)	53	84.1	(72.7, 92.1)
3 to <9 years	PRE	184	2	1.1	(0.1, 3.9)	5.6	(5.3, 5.9)	-		
	PI(D21)	183	109	59.6	(52.1, 66.7)	44.5	(39.0, 50.8)	107	58.5	(51.0, 65.7)
	PII(D42)	184	183	99.5	(96.3, 100)[b]	541.2	(482.5, 607.1)	183	99.5	(97.0, 100)
	PII(D182)	89	75	84.3	(75.0, 91.1)	57.4	(50.8, 64.9)	75	84.3	(75.0, 91.1)
	PII(D385)	84	46	54.8	(43.5, 65.7)	32.8	(28.0, 38.4)	45	53.6	(42.4, 64.5)
9 to <18 years	PRE	203	1	0.5	(0, 2.7)	5.7	(5.4, 6.1)	-		
	PI(D21)	203	108	53.2	(46.1, 60.2)	35.4	(31.7, 39.6)	105	51.7	(44.6, 58.8)
	PII(D42)	203	201	99.0	(95.8, 99.9)[b]	416.2	(371.5, 466.2)	201	99.0	(96.5, 99.9)
	PII(D182)	87	63	72.4	(61.8, 81.5)	50.2	(43.3, 58.2)	61	70.1	(59.4, 79.5)
	PII(D385)	95	27	28.4	(19.6, 38.6)	21.6	(18.6, 25.1)	23	24.2	(16.0, 34.1)

N=Number of subjects with results both pre and post results available
n/% = number/percentage of seroprotected or seroconverted subjects
PRE=Visit Day 0; PI(D21) = Visit Day 21; PII(D42) = Visit Day 42; PII(D182) = Visit Day 182; PII(D385) = Visit Day 385.
[a] The adapted ATP cohort for immunogenicity allows immunogenicity data for different time points to be presented in a single table. This adapted ATP-I cohort included Day 21 and Day 42 data obtained from the ATP-I Day 42 cohort; Day 182 data obtained from the ATP-I Day 182 cohort, and Day 385 data obtained from the ATP-I Day 385 cohort.
[b] 98.3% CI for Day 42 SPR
Source: Table 4 of GSK's response in STN 125419/39/21

3. CONCLUSIONS

The reanalysis results were generated using the protocol-defined ATP-I cohorts, and thus are acceptable.