



CBER- GSK CONFERENCE CALL SUMMARY

Date and Time:	August 10, 2012, 9:45 AM – 10:30 AM
Location:	CBER Conf. WOC2-3326; Conference call
STN #:	125419/0
Sponsor:	ID Biomedical Corporation of Quebec (dba GlaxoSmithKline Biologicals)
Product:	Influenza A (H5N1) Virus Monovalent Vaccine

CBER/FDA ATTENDEES

Carmen Collazo-Custodio
Theresa Finn
Marion Gruber
Andrea James
Tsai-Lien Lin
Douglas Pratt
Kirk Prutzman
Wellington Sun
Elizabeth Sutkowski
Jeremy Wally

GSK ATTENDEES

Katalin Abraham
Donna Boyce
Dominique Descamps
Barbara Howe
Bruce Innis
Ping Li
Michael Schwartz
David Vaughn

1.0 PURPOSE

The objectives of this conference call were:

- To provide an update on the outcome of the July 20, 2012, Mid-Cycle review meeting.
- To have a general discussion about the upcoming VRBPAC in November.

2.0 BACKGROUND

The topic of the licensure pathway for the Q-Pan H5N1 vaccine [also referred to as Influenza A (H5N1) Virus Monovalent Vaccine in this document] has been discussed both with the sponsor and in several meetings held during the IND phase of this investigational product and also in the context of a discussion on *Licensure Pathways for Pandemic Influenza Vaccines* that took place on February 29, 2012, during the Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting.

Relevant to this discussion, during a prior Type C meeting held on October 11, 2011, between CBER and GSK, CBER stated the following:

“We evaluated the information presented in your briefing package (submitted on September 9, 2011) regarding your proposed approach for inclusion of the Canadian H1N1 vaccine effectiveness studies in the BLA submission. On page 9 of the briefing materials, you propose that the following data package “*would be adequate to demonstrate clinical benefit and to support full approval of Q-Pan H5N1:*

- a. *for the Van Buynder study, the protocol, copies of the forms used to collect data, datasets, a clinical study report, descriptions of the statistical methods and information on the assays conducted;*
- b. *for the Skowronski study, a summary as described in the briefing package and the publication;*
- c. *for the Mahmud study, a summary and publication (currently in press) in the same format as described for the Skowronski study; and*
- d. *the GSK-sponsored clinical trial Q-Pan H5N1 safety and immunogenicity data.”*

We consider that the Van Buynder study provides important vaccine effectiveness data that **pending review** will support traditional approval of the Q-Pan H5N1 vaccine. However, we encourage you to continue your due diligence efforts to gain access to the data from the Mahmud study because these data will provide vaccine effectiveness data on an additional 3,744 participants (1,435 cases and 2,309 controls) 6 months of age and older, and are relevant to support licensure of Q-Pan H5N1. Please provide an update on your efforts to gain access to the raw data from the Mahmud study.”

In this context, the results of the Van Buynder study were carefully discussed during the Mid-Cycle Review meeting held on July 20, 2012. During this meeting, the statistical reviewer outlined several limitations of the study. The combined recommendation from the statistical, clinical, and epidemiological reviewers was that, because of the limitations of the Van Buynder study, this study cannot be considered as the pivotal study for traditional approval of the Q-Pan H5N1 vaccine. During the meeting, it was agreed that the Van Buynder study was not sufficient to serve as a pivotal study for traditional approval of the Q-Pan H5N1 vaccine. There was also agreement that the preliminary review of the safety and immunogenicity data provided in the BLA appeared to support licensure of the Q-Pan H5N1 vaccine in individuals ≥ 18 years of age via the accelerated approval regulations. Several scenarios were considered as possible confirmatory studies. One path discussed was

accelerated approval of the Q-Pan H5N1 vaccine using the results from the *FluLaval* efficacy study FLU Q-QIV-006 as a confirmatory study. Another path was accelerated approval using the results of a post-marketing vaccine effectiveness study conducted during an H5N1 outbreak as a confirmatory study.

One important outcome of the Mid-Cycle Review meeting was that GSK needed to be notified of the scientific assessment of the Van Buynder study and the overall conclusions and recommendations of the reviewers. With this objective, a conference call with GSK was held on August 10, 2012 (see item 3.0 DISCUSSION TOPICS).

3.0 DISCUSSION TOPICS

- CBER made reference to the VRBPAC meeting held on February 29, 2012, in which several pathways were outlined for licensure of pandemic influenza vaccines. One pathway involved effectiveness of the adjuvanted H5N1 vaccine being inferred from efficacy of the manufacturer's unadjuvanted seasonal influenza vaccine. Another approach discussed was based on effectiveness of the pandemic influenza vaccine being inferred from observational effectiveness data with adjuvanted H1N1 vaccine. To illustrate the latter pathway, GSK presented during the VRBPAC meeting an outline of the package for the Q-Pan H5N1 BLA, including a brief description of the Van Buynder study.
- GSK was informed that CBER reviewed the Van Buynder study and concluded that it was not sufficient to support effectiveness as a pivotal study for traditional approval of the Q-Pan H5N1 vaccine. A different path for licensure needed to be considered.
- CBER briefly outlined the issues with the Van Buynder study, including a very small sample size, missing vaccination status data, design methodology issues, all of which result in a high degree of uncertainty about the estimated vaccine effectiveness. Although GSK conducted a logistic regression analysis to adjust for potential confounders, there was only one vaccinated case. This analysis is not reliable when the data are so sparse. GSK asked for written comments in regards to the review of the Van Buynder study and CBER agreed to provide these comments.
- GSK asked whether CBER considered in the review the published results of the Mahmud study. CBER reminded GSK of a discussion held during the October 2011 Type C meeting (under BB-IND 13413) in which we stated that an assessment of the effectiveness of the Q-Pan vaccine would rely solely on data originating from the Van Buynder study because GSK was not able to obtain the necessary documentation for CBER to conduct a substantive review of the other observational vaccine effectiveness studies (i.e., Skowronski and Mahmud studies).
- CBER stated that the preliminary review of the safety and immunogenicity data appeared to be favorable to support licensure of the Q-Pan H5N1 vaccine via the accelerated approval regulations. Two approaches were briefly discussed as possibilities to fulfill the post-marketing confirmatory study requirement to demonstrate clinical benefit under

the accelerated approval regulations (21 CFR 601.41). One possibility was to use the *FluLaval* efficacy study FLU Q-QIV-006 as a confirmatory study (BLA supplement to be submitted in the fall of 2012). The other was to use the results of a post-marketing vaccine effectiveness study conducted during an H5N1 outbreak as a confirmatory study.

- CBER advised that both approaches to licensure would be deliberated at the VRBPAC meeting scheduled for November 2012. A general discussion regarding the VRBPAC meeting presentation ensued. The VRBPAC presentation would center on the safety and immunogenicity data of the Q-Pan H5N1 vaccine that support accelerated approval with two approaches outlined as possible post-marketing confirmatory studies. CBER discussed that we would present first and provide our review of the data, including the findings of the Van Buynder study. CBER would also delineate a path forward describing the two approaches for inferring effectiveness of the Q-Pan H5N1 vaccine. GSK would then present the data and discuss the company's perspective on the two approaches, identifying pros and cons for each one. VRBPAC would also have to have an understanding of what the studies would look like. It was agreed that there would not be a debate on the Van Buynder study at the VRBPAC. CBER stated that the Van Buynder study has supportive value in terms of illustrating how the adjuvanted vaccine works.
- GSK made reference to an e-mail communication of August 7, 2012 (see Attachment 1) in which the applicant asked about the possibility of including data from two studies, Q-Pan H1N1-035 and FLU Q-QIV-006, to support efficacy of the Q-Pan H5N1 vaccine. CBER responded that we are discussing internally the feasibility of considering study Q-Pan H1N1-035. Regarding study FLU Q-QIV-006, GSK could provide a summary of the study during the VRBPAC meeting presentation and acknowledge that these data are still under review by the FDA.

4.0 ACTION ITEMS

- Arrange an internal meeting to discuss the role of study Q-Pan H1N1-035 as a study to support efficacy of the Q-Pan-H5N1 vaccine.
- Prepare a discipline review letter outlining the deficiencies identified in the Van Buynder study.

Post-meeting communication: Ms. Katalin Abraham called Dr. Carmen Collazo-Custodio on August 13, 2012, to indicate that GSK is expecting to receive comments from CBER on the review of the Van Buynder study.

Attachment 1: August 7, 2012, E-mail Correspondence from GSK to CBER

From: Michael Schwartz [mailto:michael.p.schwartz@gsk.com]
Sent: Tuesday, August 07, 2012 5:15 PM
To: Collazo, Carmen
Cc: Prutzman, Kirk C; Wally, Jeremy; Kati Abraham
Subject: Pathway for inclusion of supportive Q-H5N1 data to VRBPAC

Dear Carmen,

Thank you for providing clarification that GSK can expect to receive additional information with respect to the anticipated November VRBPAC for Q-Pan, approximately 55 days before the meeting is scheduled to occur. As we had mentioned, GSK is actively preparing for that VRBPAC. We have identified that subsequent to the submission of the BLA, additional clinical data supportive of Q-Pan H5N1 have become available that may be of benefit for the Committee's deliberation.

Details of the supportive data are below.

At the February 2011 Type A meeting to discuss regulatory pathways for Q-Pan H5N1 licensure, CBER noted that traditional approval was the preferred regulatory pathway for licensure of Q-Pan H5N1 vaccine and offered GSK two pathways. These were, in addition to safety and immunogenicity data for Q-Pan H5N1, 1) Canadian Q-Pan H1N1 vaccine effectiveness data or 2) once traditional approval is obtained for FluLaval vaccine by demonstration of adequate efficacy. As you know, GSK chose to pursue the first option and submitted the BLA containing a pathway for licensure of Q-Pan H5N1 through use of a surrogate influenza antigen that was manufactured using the same process. The relevant data from the vaccine effectiveness study conducted by Van Buynder and carried out by the New Brunswick Department of Public Health are included in the BLA.

Subsequent to submission of the BLA, additional data from two studies that support efficacy of the Q-Pan H5N1 vaccine became available.

- Q-Pan H1N1-035, *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*
- FLU Q-QIV-006, *Efficacy study of GSK Biologicals' quadrivalent influenza vaccine, GSK2282512A, (FLU Q-QIV) when administered in children*

Q-Pan H1N1-035

As you will recall, at CBER's request, GSK plans to integrate this study into the pediatric plan for Q-Pan H5N1. The protocol for the study was included in the Q-Pan BLA submission and GSK proposed to provide the statistical analysis plan and the study report post approval.

The efficacy results for this study are available and the primary objective, to evaluate the relative protective efficacy of two doses of AS03-adjuvanted A/California vaccine (Group A) compared to two doses of unadjuvanted vaccine (Group C) beginning 14 days after dose 1 vaccination (for each subject enrolled) and continuing until study conclusion on Day 385, was met. (In brief, the secondary objectives were: Relative protective efficacy of Group B to Group C (Day 14-385). If NI of Group B to Group A is shown, evaluate the relative protective efficacy of Groups A + B compared to Group C; To estimate incidence of pneumonia and ILI cases for all treatment groups, and VEI of the adjuvanted vaccine versus unadjuvanted vaccine from study Days 0, 14, and 42 until study conclusion on Day 385 for a) RT-qPCR and b) culture confirmed cases; To evaluate HI antibody responses in a subcohort; To assess (Group A versus Group C, and Group B versus

Group C) at Day 42 in terms of geometric mean titer (GMT) ratio and difference in SCR; To assess antibody persistence at Day 182 and Day 385 in all vaccine groups; To describe the reactogenicity and safety of AS03-adjuvanted and unadjuvanted vaccine groups.)

For reference, the study design was:

Group*	Dose 1 (Day 0)	Dose 2 (Day 21)
A=A1+A2	1.9µg + AS03 _B	1.9µg + AS03 _B
B=B1+B2	1.9µg + AS03 _B	Saline
C=C1+C2	7.5µg or 15µg	7.5µg or 15µg

*Groups A1, B1, C1: 6<36 months

*Groups A2, B2, C2: 3<10 years

Group	Vaccine Regimen	Subjects with RT-qPCR confirmed H1N1					
		N (TVC)	Day 0-385 (TVC)	Day 14-385 (TVC)	Day 42-385 (TVC)	N (ATP-TE)	Day 0-385 (ATP-TE)
A	Adjuvanted x2	2048	4	3	3	1940	4
B	Adjuvanted x1	2048	9	7	5	1933	9
C	Plain antigen x2	2049	14	14	10	1930	13**
	Censored before events		1*	1*	1*		1*
	Totals	6145	28	25	19	5803 (94%)	27

3 subjects were RT-qPCR positive prior to Day 14; 9 subjects were RT-qPCR positive prior to Day 42

*1 subject with H1N1 disease was censored from Group C: the subject received seasonal flu vaccine approximately 8 months post dose 1 and 3 months prior to onset of H1N1 disease.

**1 subject with H1N1 disease was eliminated from Group C: the subject received the second dose of vaccine 4 days late

The efficacy results are:

- Primary objectives were met:
 - Non-inferiority Group A versus C: LL 95% CI VEI >-33%
 - Superiority Group A versus C: LL 95% CI VEI >0%
 - Criteria met both the ATP cohort (primary objective) and TVC

- VEI Day 14 to Day 385 for Group A versus Group C:

Group	Endpoint	VEI & 95% CI
A vs. C (ATP cohort)	RT-qPCR confirmed: D14-385	76.79 (18.53-93.39)
A vs. C (TVC cohort)	RT-qPCR confirmed: D14-385	78.47 (25.07-93.81)

- Secondary objectives Group B versus C not met:
 - ATP RT-qPCR-confirmed D14-385 VEI = 46.38 (-34.40-78.61)
 - TVC RT-qPCR-confirmed D14-385 VEI = 50.14 (-23.54-79.88)
- Secondary objectives NI for Group A2 versus C2 met:
 - ATP RT-qPCR-confirmed D14-385 VEI = 77.53% (-4.02, 95.15)
 - TVC RT-qPCR-confirmed D14-385 VEI = 80.07% (9.04-95.63)

FLU Q-QIV-006

Q-QIV-006 is a pediatrics efficacy study of quadrivalent seasonal unadjuvanted influenza vaccine manufactured following the FluLaval process (BB-IND 14466). The study has met its primary endpoints (Primary endpoint. Efficacy: Occurrence of RT-PCR-confirmed influenza A and/or B disease. The primary endpoint will require a positive RTPCR result for influenza A or B virus from a nose and throat swab obtained concurrently with ILI. *Influenza-like illness (ILI) will be defined by the presence of an oral or axillary temperature $\geq 37.8^{\circ}\text{C}$ in the presence of at least one of the following symptoms on the same day: cough, sore throat, runny nose or nasal congestion.*)

Table 1 FLU Q-QIV 006 Primary Objective Result: Vaccine efficacy for total number of RT-PCR confirmed influenza A and or B disease presenting as influenza-like illness (ILI) reported from 14 days post vaccination through the end of the ILI surveillance period (ATP cohort for efficacy - Time to event)

Event Type	Group	N	n	AR			T		VE		
				%	LL	UL	(month)	T/N	%	LL	UL
RT-PCR confirmed influenza cases	FLUQQIV	2379	58	2.44	1.86	3.14	12168.3	5.1	55.383	39.148	67.286
	HAVRIX	2398	128	5.34	4.47	6.31	12017.5	5.0	-	-	-

FLUQQIV = Flu Q-QIV Vaccine

HAVRIX = Havrix Vaccine

N = number of subjects included in each group

n = number of subjects reporting at least one event in each group

AR = attack rate = n/N (%) = percentage of subjects reporting at least one event

T (month) = sum of follow-up periods expressed in months in each group

T/N = mean follow-up period in each group

VE (%) = Vaccine efficacy (Cox regression model adjusted for covariates age category, region, priming status)

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

Could you please offer guidance regarding the possibility of including these relevant supportive data (summaries above) to the VRBPAC when these data are not detailed in the BLA since they were not available until after that submission?

Kind Regards,

Mike

Michael P. Schwartz, PhD

U.S. Regulatory Affairs - Adjuvanted Influenza Vaccines

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