Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

Application Type	BLA Supplement
STN	125285/194
CBER Received Date	December 8, 2015
PDUFA Goal Date	October 7, 2016
Division / Office	DVRPA /OVRR
Committee Chair	Timothy Fritz, PhD
Clinical Reviewer(s)	Cynthia Nolletti, MD
Project Manager	Helen Gemignani Josephine Resnick, PhD Rebekah Wiesmann, 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	Protein Sciences Corporation
Established Name	Influenza Vaccine
(Proposed) Trade Name	Flublok Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	45 μg of recombinant hemagglutinin of each strain per 0.5 mL dose
Dosage Form(s) and Route(s) of Administration	Sterile liquid, single dose vials or syringes, intramuscular injection
Indication(s) and Intended Population(s)	Active immunization of adults 18 years of age and older against influenza disease

Table of Contents

Glossary

AE	Adverse Event
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CSR	Clinical Study Report
GMT	Geometric Mean Titer
HAI	Hemagglutination Inhibition
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
IR	Information Request
MAE	Medically-Attended Adverse Event
PSC	Protein Sciences Corporation
rHA	Recombinant Hemagglutinin
rtPCR	Reverse Transcription Polymerase Chain Reaction
rVE	Relative Vaccine Efficacy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Seroconversion Rate
SPR	Seroprotection Rate

1. EXECUTIVE SUMMARY

Protein Sciences Corporation (PSC) submitted BLA supplement STN 125285/194 to seek licensure of a quadrivalent formulation of Flublok. Two observer-blinded, randomized, active-controlled clinical trials were submitted to support the application. Study PSC12 was conducted primarily to establish non-inferiority of the vaccine efficacy of Flublok Quadrivalent relative to a licensed quadrivalent inactivated influenza vaccine (IIV4) in protecting against reverse transcription polymerase chain reaction (rtPCR) -confirmed protocol-defined influenza-like illness (ILI) in adults ≥50 years of age. Study PSC16 was conducted primarily to establish non-inferior immunogenicity of Flublok Quadrivalent to that of IIV4 in adults 18-49 years of age as measured by post-vaccination Hemagglutination Inhibition (HAI) antibody geometric mean titers (GMTs) and seroconversion rates (SCRs).

Efficacy (PSC12, adults ≥50 years of age):
Flublok Quadrivalent met the pre-specified relative vaccine efficacy (rVE) criterion for non-inferiority with respect to rtPCR-confirmed protocol-defined ILI: the rVE was estimated to be 30%, (95% confidence interval [CI]: 10%, 47%), with the lower 95% CI bound greater than the criterion of -20%.

Immunogenicity (PSC16, adults 18-49 years of age):
The primary objective of demonstrating non-inferior immunogenicity of Flublok Quadrivalent to IIV4 was met for three of the four antigens (A/H1N1/California, A/H3N2/Texas, and B/Massachusetts [Yamagata lineage]) by GMT ratios and SCR differences. The post-vaccination HAI titers for B/Brisbane [Victoria lineage] were notably lower in the Flublok Quadrivalent group compared to the IIV4 group.

- The HAI GMT ratio (IIV4/Flublok Quadrivalent) and 95% CI for each of the four strains (A/H1N1/California, A/H3N2/Texas, B/Massachusetts, and B/Brisbane) were 0.81 (0.71, 0.92), 0.50 (0.44, 0.57), 0.86 (0.74, 0.99), and 1.49 (1.29, 1.71), respectively (criterion: upper bound ≤1.5).
- The HAI SCR difference (IIV4-Flublok Quadrivalent) and 95% CI for each of the four strains were -3.2 (-9.2, 2.8), -15.2 (-21.3, -9.1), 0.7 (-5.4, 6.9), and 17.6 (11.4, 23.9), respectively (criterion: upper bound ≤10%).

Overall, no notable safety concerns were identified comparing Flublok Quadrivalent to IIV4. In adults 18-49 years of age, the criteria for demonstrating non-inferiority of Flublok Quadrivalent compared to IIV4 were not met for all co-primary immunogenicity endpoints. I defer to the medical officer and other review committee members to determine whether the totality of the data support approval in adults 18-49 years of age.

2. CLINICAL AND REGULATORY BACKGROUND

Flublok, a trivalent recombinant hemagglutinin (rHA) influenza vaccine, was approved on January 16, 2013 for indication of active immunization against disease caused by influenza virus subtypes A and type B contained in the vaccine in adults 18-49 years of age; it was approved on October 29, 2014 for use in adults ≥50 years of age under the accelerated approval of biological products regulations. To be consistent with the

direction in which the field of seasonal influenza vaccines is moving, PSC submitted BLA supplement STN 125285/194 on December 8, 2015 to seek licensure of a quadrivalent formulation of Flublok. Two observer-blinded, randomized, active-controlled phase 3 clinical trials were conducted to support the application.

- Study PSC12 was conducted primarily to establish non-inferiority of vaccine efficacy of Flublok Quadrivalent relative to that of a licensed quadrivalent IIV4 in protecting against rtPCR-confirmed protocol-defined ILI in the ≥50 year age population.
- Study PSC16 was conducted primarily to establish non-inferior immunogenicity of Flublok Quadrivalent relative to that of IIV4 as measured by post-vaccination HAI antibody titers among adults 18-49 years of age.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission quality and completeness was adequate for conducting a statistical review.

3.2 Compliance With Good Clinical Practices And Data Integrity

NA

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

NA

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

5.1 Review Strategy

This review focuses on two clinical studies: PSC12 and PSC16. 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 125285/194/0 (received on December 8, 2015), as well as several subsequent amendments 2, 3, 9, and 19.

5.3 Table of Studies/Clinical Trials

Two clinical trials were submitted to support the application (Table 1).

Table 1: Overview of clinical trials

Study Number Number of Centers Location(s) Season	Study Objective(s)	Design and Type of Control	Test Product(s) Dosage Regimen	Subjects Population
PSC12 40 Centers, US only 2014-2015	Relative efficacy, immunogenicity, and safety/reactogenicity	Randomized, observer-blinded, active controlled	Flublok Quadrivalent seasonal vaccine ×1; Fluarix Quadrivalent seasonal vaccine ×1	Healthy, medically stable adults ≥50 years of age with no contraindication to either study vaccine; immunogenicity subset included all subjects enrolled at 5 sites.
PSC16 10 Centers, US only 2014-2015	Immunogenicity, and safety/reactogenicity	Randomized, observer-blinded, active controlled	Flublok Quadrivalent seasonal vaccine ×1; Fluarix Quadrivalent seasonal vaccine ×1	Healthy, medically stable adults 18-49 years of age with no contraindication to either study vaccine.

Source: adapted from Module 5.3.5.3 Integrated Summary of Efficacy

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 PSC12

Title: Comparison of the Protective Efficacy of Flublok® Quadrivalent versus Licensed Inactivated Influenza Vaccine in Healthy, Medically Stable Adults ≥50 Years of Age

6.1.1 Objectives

Primary Objectives:

- To compare the clinical efficacy of Flublok Quadrivalent to that of IIV4, with respect to the ratio of attack rates of rtPCR-confirmed protocol-defined ILIs that begin at least 14 days after vaccination caused by any influenza viral types/subtypes.

Secondary Objectives:

- To compare the relative protective efficacy in prevention of respiratory illness and influenza infection beginning at least 14 days after vaccination among Flublok Quadrivalent recipients versus IIV4 recipients using several alternative case definitions;
- To compare immunogenicity of Flublok Quadrivalent versus IIV4 in a preselected subset of subjects adequate to compare post-vaccination HAI GMTs and SCRs for all four antigens in each study vaccine;
- To compare the safety and reactogenicity of Flublok Quadrivalent versus IIV4.

6.1.2 Design Overview

This study was an observer-blinded, randomized, active controlled, multi-center trial. Subjects were randomized (without stratification) in a ratio of 1:1 to receive a single dose of Flublok Quadrivalent or US-licensed IIV4 (Fluarix Quadrivalent). The randomization was conducted to ensure reasonable balance across three age categories (50-64, 65-74, and ≥75 years) and to ensure balanced enrollment to two treatment groups across study sites.

- Surveillance of ILIs was both passive and active. These procedures included twice-weekly calls by subjects to a central interactive voice response system to report whether they had or were experiencing influenza-like symptoms. In addition, sites

contacted each subject every two weeks to inquire as to ILI symptoms, to maintain subjects' engagement in the study, and to remind subjects to return for testing in the event of influenza-like symptoms.

- Serum samples for HAI serology were obtained on Days 0 and 28 from all subjects who enrolled at pre-selected sites without further selection of subjects to participate in the serology subset.
- For safety data collection, solicited events of reactogenicity were recorded on Memory Aid A during the 7 days following vaccine administration and reported to the site by phone at 7-9 days after the vaccine administration. Unsolicited AEs occurring during 28 days following vaccine administration were recorded on a separate Memory Aid B and reviewed at the Day 28 contact. SAEs and MAEs continued to be captured on Memory Aid B through the period of follow-up to the end of the influenza season (at least 6 months post-vaccination).

Reviewer's comments:
Discrepancies were observed among the protocol, the CSR, and the data set, regarding the subpopulation from whom the serum samples were collected. The protocol stated that subjects at two to three pre-selected study sites were to have serum samples drawn for HAI serology. The CSR stated that serum samples for HAI serology were obtained from all subjects at five sites which were identified at the initiation of the study as having the capabilities for managing serologic sample collection and handling, and no further selection of subjects to participate in the serology subset was performed. However, the data showed that, for two of the five study sites, fewer than 30% of the subjects were included in the serology subset.

An IR was therefore sent to the applicant requesting clarification. The response (STN 125285/194/19) explained that by early November 2014, the pace of enrollment suggested that the three pre-selected sites might not fully enroll the serology subset by the time the overall enrollment was complete. Thus, two additional sites were asked to participate since then, and all subsequently randomized subjects at those two sites were included in the serology subset, with no further selection. This procedure appears to be supported by the enrollment information provided in the data.

6.1.3 Population

The study population included ambulatory and medically stable adults ≥50 years of age for whom the study vaccines were not contraindicated, and who did not have underlying conditions that might complicate the evaluation of the primary efficacy endpoint.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were randomized to receive one of the two vaccines by intramuscular injection:

- Flublok Quadrivalent (0.5 mL volume): 45µg (180µg total) of rHA derived from each of four influenza antigen strains: A/California/07/2009 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/2/2012 (B/Yamagata-lineage), and B/Brisbane/60/2008 (B/Victoria-lineage);
- IIV4 (Fluarix Quadrivalent) (0.5 mL volume): 15µg (60µg total) of HA from each of the four influenza antigen strains: A/Christchurch/16/2010 (an A/California/7/2009-

like virus) (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/2/2012, and B/Brisbane/60/2008.

6.1.6 Sites and Centers

The study was conducted in 40 sites in the US.

6.1.7 Surveillance/Monitoring

NA

6.1.8 Endpoints and Criteria for Study Success

Primary endpoint:

- rtPCR-confirmed, protocol-defined ILI caused by any influenza strain that begins at least 14 days post-vaccination.
  - The primary objective was evaluated by assessing non-inferiority of the relative efficacy of Flublok Quadrivalent as compared to that of IIV4. The non-inferiority criterion was that the lower bound of the two-sided 95% CI of the rVE > -20%.

Secondary efficacy and immunogenicity endpoints:

- Culture-confirmed protocol-defined ILI that begins at least 14 days post-vaccination caused by an influenza strain (identified from the same clinical sample) antigenically matched to those strains represented in the study vaccines;
- rtPCR-confirmed CDC-defined ILI that begins at least 14 days post-vaccination caused by any influenza strain;
- Culture-confirmed CDC-defined ILI that begins at least 14 days post-vaccination caused by an influenza strain (identified from the same clinical sample) antigenically matched to those in the study vaccines;
- Post-vaccination HAI GMTs and SCRs for all four antigens in a preselected subset of subjects.

Secondary safety endpoints:

- Solicited events of systemic and injection site reactogenicity during Days 0-7;
- Unsolicited AEs reported within 28 days following vaccine administration;
- SAEs and MAEs occurring during the period of follow-up through the influenza season (at least 6 months post-vaccination).

6.1.9 Statistical Considerations & Statistical Analysis Plan

Efficacy analyses

The rVE was calculated as 100×(1-Attack rate [Flublok Quadrivalent]/Attack Rate [IIV4]). Farrington and Manning's score method was used to compute the two-sided 95% CI.

Immunogenicity analyses

The post-vaccination HAI titers were compared between Flublok Quadrivalent recipients and IIV4 recipients using CBER's criteria for non-inferiority: the upper bound of the two-sided 95% CI on SCR difference (IIV4-Flublok Quadrivalent) ≤10%; the upper

bound of the 95% CI on the GMT ratio (IIV4/Flublok Quadrivalent) ≤1.5. The GMT ratios were to be calculated as the antilog of the difference between two mean log-transformed titers. The CI for the SCR difference was based on Farrington and Manning's score method.

Reviewer's comments:
The Statistical Analysis Plan (SAP) stated that "Non-inferiority of immune responses across the entire age spectrum will be concluded if the criteria specified above are met using the Bonferroni adjustment for multiple comparisons. The Bonferroni adjusted significance level (two sided) is 0.00625 for the eight co-primary immunogenicity endpoint HAI comparisons." Since the immunogenicity endpoints were to be evaluated as "co-primary," all endpoints must meet the criterion to conclude non-inferiority and thus the Bonferroni adjustment is unnecessary.

Major changes in study conduct or planned analyses
Cultures of influenza viruses from rtPCR positive nasopharyngeal swabs could not be processed to generate adequate titers of virus to be tested against ferret antiserum for antigenic identification. Thus, the analyses of rVE for ILI due to strains that matched the HAs in the study vaccines were not available.

Reviewer's comments:
During the review of both study PSC12 and study PSC16, the reviewer found that the applicant calculated the rVEs, GMT ratios, and SCR differences based on rounded attack rates, GMTs, and SCRs, respectively. In addition, the log-transformed HAI titers used for GMT analyses were also rounded values. All of these intermediate roundings could lead to inaccurate analysis results; thus, an IR was sent to the applicant requesting recalculations. This review presents the applicant's results from recalculations for both studies, which were submitted to STN 125285/194/9.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

The efficacy population included all randomized subjects who received study vaccine and provided follow-up for ILI beginning at least 14 days following vaccine administration. The efficacy population excluded subjects with significant protocol deviations that could adversely impact efficacy, e.g., disease or therapeutic intervention that might cause suboptimal response to study vaccine. The efficacy population was used for all efficacy analyses.

The immunogenicity population included all randomized subjects at the specific sites pre-selected for serology who received study vaccine and provided serum samples on Days 0 and 28 for serologic testing. The immunogenicity population did not include subjects with significant protocol deviations that could adversely impact the immune response, e.g., disease or therapeutic intervention that might cause immunocompromise.

The safety population included all randomized and vaccinated subjects that provided any safety data following administration of study vaccine. The reactogenicity population included all randomized subjects who received study vaccine and provided data on at least one day of the 7-day Memory Aid A for reactogenicity. There were three reactogenicity subpopulations: (1) subjects with at least 1 injection site reaction recorded in Memory Aid A; (2) subjects with at least 1 systemic reaction recorded in Memory Aid A; and (3) subjects with at least one body temperature measurement recorded in Memory Aid A.

For all the study populations, subjects were analyzed according to the vaccine received, regardless of the vaccine group to which they were randomized.

6.1.10.1.1 Demographics

Table 2 shows the demographics by treatment group for the safety population. The demographical characteristics were comparable between treatment groups. The demographic profile for the efficacy population was similar.

Table 2: PSC12 – Demographics (Safety Population)

	Flublok Quadrivalent N=4328	IIV4 N=4344
Age (years) mean (range)	62.7 (50 – 96)	62.6 (50 - 94)
Age Group n (%)		
50-64 years	2569 (59.4)	2617 (60.2)
≥65 years	1759 (40.6)	1727 (39.8)
65-74 years	1234 (28.5)	1254 (28.9)
≥75 years	525 (12.1)	473 (10.9)
Sex, n (%)		
Male	1796 (41.5)	1807 (41.6)
Female	2532 (58.5)	2537 (58.4)
Race, n (%)		
Black or African American	773 (17.9)	753 (17.3)
White or Caucasian	3467 (80.1)	3493 (80.4)
Other [a]	88 (2.0)	98 (2.3)
Ethnicity, n (%)		
Hispanic	206 (4.8)	219 (5.0)
Non-Hispanic	4122 (95.2)	4123 (94.9)
Other	0	2 (0.0)

[a] Other = American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Asian or other
Source: Table 19 of PSC12 CSR

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
NA

6.1.10.1.3 Subject Disposition

A total of 9003 subjects were enrolled and randomized. Among them 15 subjects withdrew consent prior to receiving study vaccine, and 25 subjects received a dose of study vaccine for which the identity could not be verified. Table 3 summarizes the study subject disposition excluding these 40 subjects based on the actual treatment received per subject.

Table 3: PSC12 – Subject disposition

	Flublok Quadrivalent N = 4474	IIV4 N = 4489
	n (%)	n (%)
Efficacy Population	4303 (96.2)	4301 (95.8)
Immunogenicity Population	314 (7.0)	300 (6.7)
Safety Population	4328 (96.7)	4344 (96.8)
Reactogenicity Population	4312 (96.4)	4327 (96.4)
Reactogenicity Population 1[a]	4307 (96.3)	4319 (96.2)
Reactogenicity Population 2[b]	4306 (96.2)	4318 (96.2)
Reactogenicity Population 3[c]	4262 (95.3)	4282 (95.4)
Subjects with any Major Protocol Deviation	124 (2.8)	127 (2.8)
Subjects with any Major Protocol Deviation For Immunogenicity	24 (0.5)	25 (0.6)
Completed study	4228 (94.5)	4236 (94.4)
Primary Reason for Early Withdrawal		
Adverse Event	9 (0.2)	8 (0.2)
Investigator Decision	1 (0.0)	2 (0.0)
Lost to Follow-up	176 (3.9)	172 (3.8)
Sponsor Request	0	0
Voluntary withdrawal unrelated to AE	53 (1.2)	61 (1.4)
Other	7 (0.2)	10 (0.2)

[a] Subjects with any injection site reactogenicity data, Days 0-7
[b] Subjects with any systemic reactogenicity data, Days 0-7
[c] Subjects with any body temperature data, Days 0-7
Source: Tables 16 and 17 of PSC12 CSR

Reviewer's comments:
The medical officer issued an IR to the applicant because inconsistencies were observed between the study disposition table and the AE/death data, regarding the distribution of subjects who discontinued the study due to AEs and/or deaths. In the response (submitted to STN 125285/194/3), the applicant listed 10 (0.2%) and 11 (0.2%) subjects in the Flublok Quadrivalent group and IIV4 group, respectively, who discontinued the study due to AEs, including deaths. In addition, one IIV4 recipient completed the study but died in a motor vehicle accident beyond the 6 months follow-up period.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Table 4 summarizes the results for the primary objective on the rVE regarding the rtPCR-confirmed protocol-defined ILI with onset ≥14 days after vaccination due to any strain of influenza. The lower bound of the two-sided 95% confidence interval met the pre-specified non-inferiority criterion of > -20%.

Table 4: PSC12 – Relative vaccine efficacy for rtPCR-confirmed protocol-defined ILI (Efficacy Population)

Flublok Quadrivalent (N=4303)		IIV4 (N=4301)		
n	Attack Rate (%)	n	Attack Rate (%)	rVE (95% CI)
96	2.2	138	3.2	30% (10%, 47%)

Source: Table 1R of IR response STN 125285/194/9

6.1.11.2 Analyses of Secondary Endpoints

Secondary efficacy endpoints

Table 5 shows the analysis results on one of the secondary endpoints, rtPCR-confirmed CDC-defined ILI that begins at least 14 days post-vaccination caused by any influenza strain. Analyses on the other two secondary efficacy endpoints of culture-confirmed ILIs could not be performed because the antigenic similarity of cultured viruses to the vaccine strains could not be assessed in this trial, as noted in Section 6.1.9.

Table 5: PSC12 – Relative vaccine efficacy against rtPCR-confirmed CDC-defined ILI (Efficacy Population)

Flublok Quadrivalent (N=4303)		IIV4 (N=4301)		
n	Attack Rate (%)	n	Attack Rate (%)	rVE (95% CI)
54	1.3	83	1.9	35% (8%, 54%)

Source: Table 3R of IR response STN 125285/194/9

Secondary immunogenicity endpoints

The HAI titers were compared between the two treatment groups according to the non-inferiority criteria described in Section 6.1.9. As shown in Table 6, the HAI titer against A/H1N1/California did not meet the criterion for SCR difference, and the titer against B/Brisbane did not meet the criteria for either GMT ratio or SCR difference. The post-vaccination HAI GMTs for the influenza B strains were notably lower than those for the A strains.

Table 6: PSC12 – Comparison of HAI GMT responses and seroconversion rates (Immunogenicity Population)

	Post-vaccination GMT			Seroconversion rate		
Antigen	Flublok Quadrivalent N=314	IIV4 N=300	GMT ratio (95% CI)	Flublok Quadrivalent N=314	IIV4 N=300	SCR Difference (95% CI)
A/H1N1/California	190	220	1.15 (0.95, **1.41**)	44.9	49.0	4.1 (-3.8, 12.0)
A/H3N2/Texas	522	358	0.69 (0.58, **0.81**)	54.5	43.3	-11.1 (-19.0, **-3.3**)
B/Massachusetts	55	57	1.03 (0.86, **1.24**)	38.9	38.3	-0.5 (-8.2, **7.2**)
B/Brisbane	29	43	1.47 (1.23, 1.76)	21.0	34.3	13.3 (6.3, 20.3)

Figures in bold met the non-inferiority criteria.
Source: Table 7R and Table 8R of IR response STN 125285/194/9

Reviewer's comments:

For the design of this study with regard to the HAI serology subset, it appears that the study sites were not randomly selected to participate in the subset. In addition, the randomization was not stratified by site. Therefore, the immunogenicity results need to be interpreted with caution when attempting to draw firm conclusions regarding the entire study population.

6.1.11.3 Subpopulation Analyses

The rtPCR-confirmed protocol-defined ILIs beginning at least 14 days post-vaccination were predominately reported among non-Hispanic subjects with respect to the ethnic subgroups, and among white or Caucasian subjects with respect to the race subgroups; therefore, those subpopulations showed similar rVE results as in the overall population. Female and male subjects had similar rVE estimates. The rVE among adults 50-64 years of age was estimated as 42% (95% CI: 15%, 61%), as compared to 17% (95% CI: -20%, 43%) among adults ≥65 years of age. The number of cases was too small to support meaningful comparisons of rVE between subgroups.

6.1.11.4 Dropouts and/or Discontinuations

The proportions of subjects who withdrew from the study were small and similar between treatment groups; therefore, missing data were not expected to have significant impact on the comparison of efficacy endpoints between treatment groups.

6.1.11.5 Exploratory and Post Hoc Analyses

Table 7 shows the results from post-hoc analyses assessing the rVE of Flublok Quadrivalent to IIV4 based on rtPCR-confirmed protocol-defined ILI caused by influenza A and B strains separately, as well as based on culture-confirmed protocol-defined ILI caused by any strain. The number of cases caused by influenza B was too small to provide meaningful information regarding the relative efficacy of Flublok Quadrivalent against IIV4.

Table 7: PSC12 – Post-hoc analyses on relative vaccine efficacy

	Flublok Quadrivalent (N=4303)		IIV4 (N=4301)		
	n	Attack Rate (%)	n	Attack Rate (%)	rVE (95% CI)
rtPCR-confirmed protocol-defined ILI caused by Influenza A	73	1.7	114	2.7	36% (14%, 53%)
rtPCR-confirmed protocol-defined ILI caused by Influenza B	23	0.5	24	0.6	4% (-72%, 46%)
All culture-confirmed Protocol-defined ILI	58	1.3	101	2.3	43% (21%, 59%)

Source: Tables 2R and 5R of IR response STN 125285/194/9

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety endpoints were primarily summarized by frequency counts and percentages for each treatment group. Overall, no notable difference was observed regarding the proportions of subjects reporting solicited adverse reactions, unsolicited AEs, or MAEs between treatment groups.

- The proportions of subjects reporting solicited local injection site reactions or systemic adverse reactions in the Flublok Quadrivalent group were generally comparable to those in the IIV4 group (Table 8). The proportions of subjects reporting Grade 3 or Grade 4 solicited adverse reactions were small in both treatment groups (≤1%).
- The proportion of Flublok Quadrivalent recipients reporting any unsolicited AEs within 28 days following vaccination was similar to that of IIV4 recipients (13.9% versus 14.1%). Severe unsolicited AEs were reported in 1.0% of subjects in each treatment group.
- MAEs were reported in 17.9% and 18.1% of subjects in Flublok Quadrivalent and IIV4 groups during the six months of follow-up after vaccination, respectively.

Table 8: PSC12 – Solicited events of local injection site reactions and systemic adverse reactions

	Flublok Quadrivalent n (%)			IIV4 n (%)		
Local Reactogenicity Event[a]	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Local Pain	813 (18.9)	5 (0.1)	0	950 (22.0)	8 (0.2)	1 (0.0)
Local Tenderness	1479 (34.3)	6 (0.1)	1 (0.0)	1604 (37.1)	10 (0.2)	2 (0.0)
Redness	122 (2.8)	2 (0.0)	0	87 (2.0)	1 (0.0)	0
Firmness / Swelling	142 (3.3)	1 (0.0)	0	115 (2.7)	2 (0.0)	0
Systemic Reactogenicity Event[b]	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Fatigue	526 (12.2)	19 (0.4)	0	521 (12.1)	15 (0.3)	6 (0.1)
Shivering / Chills	204 (4.7)	10 (0.2)	0	187 (4.3)	15 (0.3)	2 (0.0)
Joint Pain	324 (7.5)	9 (0.2)	0	346 (8.0)	18 (0.4)	2 (0.0)
Muscle Pain	366 (8.5)	12 (0.3)	2 (0.0)	378 (8.8)	13 (0.3)	1 (0.0)
Headache	549 (12.7)	11 (0.3)	1 (0.0)	582 (13.5)	21 (0.5)	2 (0.0)
Nausea	212 (4.9)	7 (0.2)	0	213 (4.9)	9 (0.2)	1 (0.0)
Fever[c]	19 (0.4)	7 (0.2)	0	21 (0.5)	6 (0.1)	0

[a] Denominators for local injection reactions were Reactogenicity Population 1: Flublok Quadrivalent N=4307, IIV4 N=4319.
[b] Denominators for systemic reactions were Reactogenicity Population 2: Flublok Quadrivalent N=4306, IIV4 N=4318.
[c] Denominators for fever were Reactogenicity Population 3: Flublok Quadrivalent N=4262, IIV4 N=4282.
Source: Tables 30-32 of PSC12 CSR

Reviewer's comments:
The medical officer determined that the analyses on unsolicited AEs presented in CSRs for PSC12 and PSC16 included events occurring up to Day 180. An IR was sent to the applicant requesting reanalyses focusing on events occurring up to Day 28. This review presents the results from the applicant's reanalyses for both studies, which were submitted to STN 125285/194/2.

6.1.12.3 Deaths

There were 20 deaths throughout the duration of the study: 8 (0.2%) among Flublok Quadrivalent recipients and 12 (0.3%) among IIV4 recipients. The investigators did not think any of the deaths were related to study vaccines.

6.1.12.4 Nonfatal Serious Adverse Events

No notable difference was observed between the Flublok Quadrivalent group and IIV4 group with respect to the proportion of subjects reporting any SAE during the six months of follow-up after vaccination (3.4% versus 3.0%).

6.1.12.5 Adverse Events of Special Interest (AESI)

NA

6.1.12.6 Clinical Test Results

NA

6.1.12.7 Dropouts and/or Discontinuations

Please refer to Section 6.1.10.1.3.

6.2 PSC16

Title: Double-Blind, Randomized, Active-Controlled Comparison of the Immunogenicity and Safety of Flublok® Quadrivalent versus IIV4 in Healthy, Medically Stable Adults 18-49 Years of Age

6.2.1 Objectives

Primary Objectives:

- To demonstrate non-inferior immunogenicity of the four antigens in the Flublok Quadrivalent formulation to the corresponding antigens in the licensed IIV4.

Secondary Objectives:

- To evaluate the HAI SCRs and seroprotection rates (SPR; the proportion of subjects with post-vaccination HAI titers ≥1:40) against the four rHA antigens contained in the quadrivalent formulation, with respect to CBER criteria for licensure under accelerated approval regulations;
- To evaluate the safety and reactogenicity of Flublok Quadrivalent in adults 18-49 years of age.

6.2.2 Design Overview

The study was an observer-blind, randomized, active-controlled phase 3 trial in adults 18-49 years of age. Subjects were randomized approximately in a ratio of 3:1 to receive a single dose of Flublok Quadrivalent or US-licensed IIV4 (Fluarix Quadrivalent). All subjects who received the study vaccine had blood draws obtained for serum HAI titer at Day 0 and Day 28. For safety data collection, subjects were given Memory Aid A to record reactogenicity events during the 7 days following vaccination and Memory Aid B to record any unsolicited AEs. SAEs and MAEs were collected by remote follow-up for 6 months following vaccination.

6.2.3 Population

The study enrolled ambulatory, medically stable, non-pregnant adults 18-49 years of age.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Please refer to Section 6.1.4.

6.2.6 Sites and Centers

The study was conducted at 10 sites in the US.

6.2.7 Surveillance/Monitoring

NA

6.2.8 Endpoints and Criteria for Study Success

Primary endpoints:

- The co-primary endpoints included HAI GMT and SCR at Day 28 to each of the four antigens contained in the study vaccine, which were compared between the two

vaccine groups according to CBER criteria for non-inferiority described in Section 6.1.9.

Secondary endpoints:

- SCRs and the SPRs to each of the four antigens in Flublok Quadrivalent, assessed according to CBER criteria for adults <65 years of age:
    - The lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HAI antibody should meet or exceed 40%;
    - The lower bound of the two-sided 95% CI for the percent of subjects achieving an HAI antibody titer ≥1:40 should meet or exceed 70%.
- Incidence and severity of solicited local and solicited systemic events of reactogenicity and body temperature reported via Memory Aid A during Days 0-7 following vaccine administration.
- SAEs and other unsolicited AEs and MAEs occurring during the 28 days following vaccine administration.
- SAEs and MAEs occurring up to 6 months post-vaccination.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Immunogenicity analyses

Non-inferior immunogenicity of Flublok Quadrivalent compared to IIV4 was to be concluded if all eight comparisons met the criteria; no adjustment for multiple comparisons was implemented. The GMT ratios were calculated as the antilog of the difference between two mean log-transformed titers. The CI for the SCR difference was based on Farrington and Manning's score method. The 95% CI for SCRs and SPRs in each treatment group were computed using the Clopper-Pearson exact method.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

The immunogenicity population included all randomized subjects who received a dose of study vaccine, provided serum samples for HAI titers on Days 0 and 28 (within the specified windows), and had no major protocol deviations that might be expected to adversely impact the immune response.

Please refer to Section 6.1.10.1 for definitions of safety population, reactogenicity population, and reactogenicity subpopulations. For all the study populations defined, subjects were analyzed according to the vaccine received regardless of the vaccine group to which they were randomized.

6.2.10.1.1 Demographics

Table 9 summarizes the demographic characteristics by treatment group for the safety population. No notable difference between treatment groups was observed. The immunogenicity population had a similar demographic profile.

Table 9: PSC16 – Demographics (Safety Population)

Characteristic	Flublok Quadrivalent N=998	IIV4 N=332
Age (years)		
Mean	33.3	34.0
Range	18, 50	18, 49
Sex, n (%)		
Female	639 (64.0)	222 (66.9)
Male	359 (36.0)	110 (33.1)
Race, n (%)		
White or Caucasian	589 (59.0)	202 (60.8)
Black or African American	376 (37.7)	114 (34.3)
Native Hawaiian/Pacific Islander	11 (1.1)	2 (0.6)
American Indian or Alaska Native	7 (0.7)	3 (0.9)
Asian	3 (0.3)	4 (1.2)
Other	12 (1.2)	7 (2.1)
Ethnicity, n (%)		
Non-Hispanic	836 (83.8)	275 (82.8)
Hispanic	162 (16.2)	57 (17.2)

Source: Table 14 of PSC16 CSR

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
NA

6.2.10.1.3 Subject Disposition
Of the 1350 subjects who were enrolled and randomized, all received a dose of study vaccine. Table 10 summarizes the study subject disposition based on the actual treatment received per subject. Similar withdrawal rates were observed between the two treatment groups. The most common reason for major protocol deviation that excluded a subject from the immunogenicity population was missing study visit.

Table 10: PSC16 - Subjects disposition

	Flublok Qudrivalent N=1011	IIV4 N=339
	n (%)	n (%)
Immunogenicity Population	969 (95.8)	323 (95.3)
Safety Population	998 (98.7)	332 (97.9)
Reactogenicity Population	996 (98.5)	332 (97.9)
Reactogenicity Population 1[a]	996 (98.5)	332 (97.9)
Reactogenicity Population 2[b]	994 (98.3)	332 (97.9)
Reactogenicity Population 3[c]	990 (97.9)	327 (96.5)
Completed study	962 (95.2)	325 (95.9)
Primary Reason for Early Withdrawal		
Adverse Event	0	0
Investigator Decision	0	0
Lost to Follow-up	38 (3.8)	11 (3.2)
Sponsor Request	0	0
Voluntary withdrawal unrelated to AE	9 (0.9)	2 (0.6)
Other	2 (0.2)	1 (0.3)

[a] Reactogenicity Population 1 included subjects who recorded any injection site reaction data in Memory Aid A.
[b] Reactogenicity Population 2 included subjects who recorded any systemic reaction data in Memory Aid A.
[c] Reactogenicity Population 3 included subjects who recorded any body temperature measurement in Memory Aid A.
Source: Table 12 of PSC16 CSR

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The evaluation of the primary objective of non-inferior immunogenicity is summarized in Table 11. Among the eight co-primary endpoints, HAI titer against the B/Brisbane strain did not meet the criteria for either GMT ratio or SCR difference. The post-vaccination HAI GMT and SCR for B/Brisbane were notably lower in the Flublok Quadrivalent group compared to the IIV4 group.

Table 11: PSC16 – Comparison of HAI GMT responses and seroconversion rates (Immunogenicity Population)

	Post-vaccination GMT			Seroconversion rate		
Antigen	Flublok Quadrivalent N=969	IIV4 N=323	GMT ratio (95% CI)	Flublok Quadrivalent N=969	IIV4 N=323	SCR Difference (95% CI)
A/H1N1/California	493	397	0.81 (0.71, **0.92**)	66.7	63.5	-3.2 (-9.2, **2.8**)
A/H3N2/Texas	748	377	0.50 (0.44, **0.57**)	72.1	57.0	-15.2 (-21.3, **-9.1**)
B/Massachusetts	156	134	0.86 (0.74, **0.99**)	59.6	60.4	0.7 (-5.4, **6.9**)
B/Brisbane	43	64	1.49 (1.29, 1.71)	40.6	58.2	17.6 (11.4, 23.9)

Figures in bold met the non-inferiority criteria.
Source: Tables 9R and 10R of IR response STN 125285/194/9

Reviewer's comments:
The 95% CIs of SCR difference reported by the applicant appear to be computed by using the Wald method. The SAP-specified Farrington-Manning method would give very similar results with lower or equal upper limits. Results in Table 11 are thus considered acceptable considering their conservativeness.

6.2.11.2 Analyses of Secondary Endpoints

As shown in Table 12, the lower 95% CI limit of the SPR and SCR against B/Brisbane for the Flublok Quadrivalent group did not exceed the CBER criteria (70% for SPR and 40% for SCR).

Table 12: PSC16 – Day 28 HAI seroprotection rates and seroconversion rates (Immunogenicity population)

	Seroprotection rate (95% CI)		Seroconversion rate (95% CI)	
Antigen	Flublok Quadrivalent N=969	IIV4 N=323	Flublok Quadrivalent N=969	IIV4 N=323
A/H1N1/California	98.2 (**97.2**, 99.0)	99.1 (**97.3**, 99.8)	66.7 (**63.6**, 69.6)	63.5 (**58.0**, 68.7)
A/H3N2/Texas	99.7 (**99.1**, 99.9)	99.1 (**97.3**, 99.8)	72.1 (**69.2**, 74.9)	57.0 (**51.4**, 62.4)
B/Massachusetts	91.0 (**89.0**, 92.7)	92.0 (**88.4**, 94.7)	59.6 (**56.5**, 62.8)	60.4 (**54.8**, 65.7)
B/Brisbane	64.3 (61.2, 67.3)	79.6 (**74.8**, 83.8)	40.6 (37.4, 43.7)	58.2 (**52.6**, 63.6)

Figures in bold met CBER criteria for SPR and SCR in adults <65 years old.
Source: Table 18 of PSC16 CSR and Table 14.2.1.2 of IR response STN 125285/194/9

6.2.11.3 Subpopulation Analyses

Table 13 summarizes the post-vaccination HAI GMTs and SCRs among Flublok Quadrivalent recipients for subpopulations with at least moderate numbers of subjects. Black or African American subjects tended to show higher post-vaccination HAI titers

against A strains than white or Caucasian subjects; otherwise, no apparent differences were observed between subpopulations defined by sex, race, or ethnicity.

Table 13: PSC16 – Post-vaccination HAI GMTs and SCRs for Flublok Quadrivalent recipients by sex, race, and ethnicity (Immunogenicity Population)

Strain	Female N=623	Male N=346	Black or African American N=362	White or Caucasian N=575	Hispanic N=160	Not Hispanic N=809
Post-vaccination GMT (95% CI)						
A/H1N1/California	494 (453, 537)	491 (438, 549)	513 (456, 577)	477 (438, 519)	541 (454, 645)	483 (449, 520)
A/H3N2/Texas	738 (679, 803)	767 (688, 855)	790 (714, 875)	721 (660, 789)	725 (603, 871)	753 (702, 809)
B/Massachusetts	148 (135, 162)	172 (152, 195)	176 (156, 198)	148 (134, 163)	137 (113, 165)	160 (148, 174)
B/Brisbane	44 (40, 48)	40 (36, 45)	40 (35, 45)	46 (42, 50)	43 (36, 51)	43 (40, 46)
Seroconversion rate % (95% CI)						
A/H1N1/California	66.9 (63.1,70.6)	66.2 (60.9,71.2)	71.0 (66.0,75.6)	64.2(60.1,68.1)	66.3(58.4,73.5)	66.7 (63.4,70.0)
A/H3N2/Texas	70.1 (66.4,73.7)	75.7 (70.9,80.1)	77.1 (72.4,81.3)	69.0(65.1,72.8)	72.5(64.9,79.3)	72.1 (68.8,75.1)
B/Massachusetts	59.2 (55.3,63.1)	60.4 (55.0,65.6)	62.7 (57.5,67.7)	58.3(54.1,62.3)	60.0(52.0,67.7)	59.6 (56.1,63.0)
B/Brisbane	42.4 (38.5,46.4)	37.3 (32.2,42.6)	41.2 (36.0,46.4)	40.7(36.7,44.8)	43.8(35.9,51.8)	39.9 (36.5,43.4)

Source: Tables 14.2.1.2 and 14.2.1.1.1 of IR response STN 125285/194/9

6.2.11.4 Dropouts and/or Discontinuations

Please refer to Section 6.2.10.1.3.

6.2.11.5 Exploratory and Post Hoc Analyses

NA

6.2.12 Safety Analyses

6.2.12.1 Methods

The safety and reactogenicity profiles were described and compared descriptively between the Flublok Quadrivalent and IIV4 groups. In summary, the safety of Flublok Quadrivalent and IIV4 were comparable with respect to the overall solicited local and systemic reactogenicity events, unsolicited AEs during Days 0-28, and MAEs/SAEs through 6 months following vaccination.

- Generally, the proportion of subjects reporting each solicited local injection site reaction or systemic adverse reaction in the Flublok Quadrivalent group was similar to that in the IIV4 group, except that the Flublok Quadrivalent group tended to have higher incidence of redness (4.2% versus 0.9%); however, all of them were mild or moderate in severity (Table 14). The proportions of subjects reporting Grade 3 or Grade 4 solicited adverse reactions were low in the Flublok Quadrivalent group (<1.5%).
- The proportion of Flublok Quadrivalent recipients reporting any unsolicited AEs within 28 days following vaccination was similar to that of IIV4 recipients (10.3% versus 10.5%). Severe unsolicited AEs were reported in 1.1% and 0.9% of subjects in the Flublok Quadrivalent and IIV4 groups, respectively.
- MAEs were reported in 8.0% and 7.2% of subjects in the Flublok Quadrivalent and IIV4 groups during the six months of follow-up after vaccination, respectively.

Table 14: PSC16 – Comparison of Incidence and Severity of Local and Systemic Events of Reactogenicity and Fever (Days 0-7)

	Flublok Quadrivalent n (%)			IIV4 n (%)		
Local Reactogenicity Event[a]	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Local Pain	367 (36.8)	9 (0.9)	0	121 (36.4)	3 (0.9)	0
Local Tenderness	478 (48.0)	9 (0.9)	0[d]	155 (46.7)	4 (1.2)	0
Redness	42 (4.2)	0	0	3 (0.9)	0	0
Firmness / Swelling	49 (4.9)	0	0	10 (3.0)	0	0
Systemic Reactogenicity Event[b]	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Fatigue	164 (16.5)	5 (0.5)	0	55 (16.6)	4 (1.2)	0
Shivering / Chills	69 (6.9)	5 (0.5)	0	20 (6.0)	4 (1.2)	0
Joint Pain	94 (9.5)	9 (0.9)	0	34 (10.2)	2 (0.6)	0
Muscle Pain	127 (12.8)	9 (0.9)	0	39 (11.7)	3 (0.9)	0
Headache	202 (20.3)	13 (1.3)	0	70 (21.1)	6 (1.8)	1 (0.3)
Nausea	89 (9.0)	6 (0.6)	1 (0.1)	31 (9.3)	4 (1.2)	0
Fever[c]	15 (1.5)	4 (0.4)	0	2 (0.6)	1 (0.3)	0

[a] The denominator for local reactogenicity events was Flublok Quadrivalent = 996 and IIV4 = 332.
[b] The denominator for systemic reactogenicity events was Flublok Quadrivalent = 994 and IIV4 = 332.
[c] The denominator for fever was Flublok Quadrivalent = 990 and IIV4 = 327.
[d] This data point was corrected to eliminate a data entry error according to the IR response.
Source: Table 14.3.2.7.1 of PSC16 CSR and Table 1 of IR response STN 125285/194/2

6.2.12.3 Deaths

There were no deaths throughout the duration of the study.

6.2.12.4 Nonfatal Serious Adverse Events

There were 15 SAEs reported overall from 10 (1.0%) Flublok Quadrivalent recipients and 2 (0.6%) IIV4 recipients during the six months of follow up. No SAEs were considered related to study vaccine in the investigators' opinions.

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

Please refer to Section 6.2.10.1.3.

7. INTEGRATED OVERVIEW OF EFFICACY

Not applicable since the populations enrolled in the two trials were mutually exclusive with respect to age range.

8. INTEGRATED OVERVIEW OF SAFETY

See Section 7.

9. ADDITIONAL STATISTICAL ISSUES

NA

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Efficacy (PSC12, adults ≥50 years of age):

- Flublok Quadrivalent met the pre-specified rVE non-inferiority criterion as compared to IIV4 with respect to rtPCR-confirmed protocol-defined ILI beginning at least 14 days post-vaccination. The rVE was estimated as 30% (95% CI: 10%, 47%), with the lower 95% CI bound greater than the non-inferiority criterion of -20%.

Immunogenicity:

- In adults 18-49 years of age (study PSC16), the primary objective of demonstrating non-inferior immunogenicity of Flublok Quadrivalent to IIV4 was met for three of the four antigens (A/H1N1/California, A/H3N2/Texas, and B/Massachusetts) by GMT ratios and SCR differences. The post-vaccination HAI titers for B/Brisbane were notably lower in the Flublok Quadrivalent group than in the IIV4 group.
    - The HAI GMT ratio (IIV4/Flublok Quadrivalent) and 95% CI for each of the four strains (A/H1N1/California, A/H3N2/Texas, and B/Massachusetts, and B/Brisbane) were 0.81 (0.71, 0.92), 0.50 (0.44, 0.57), 0.86 (0.74, 0.99), and 1.49 (1.29, 1.71), respectively (non-inferiority criterion: upper bound ≤1.5).
    - The HAI SCR difference (IIV4-Flublok Quadrivalent) and 95% CI for each of the four strains were -3.2 (-9.2, 2.8), -15.2 (-21.3, -9.1), 0.7 (-5.4, 6.9), and 17.6 (11.4, 23.9), respectively (non-inferiority criterion: upper bound ≤10%).
- In adults ≥50 years of age (study PSC12), immunogenicity non-inferiority was evaluated as a secondary objective. The criterion was met for three of the four antigens (A/H1N1/California, A/H3N2/Texas, and B/Massachusetts) by GMT ratios, and for two of the four antigens (A/H3N2/Texas and B/Massachusetts) by SCR differences. The post-vaccination HAI titers for B/Brisbane were also notably lower in the Flublok Quadrivalent group than in the IIV4 group.

Safety:

- In both PSC12 and PSC16, the safety of Flublok Quadrivalent was comparable to that of IIV4 with respect to overall solicited local and systemic reactogenicity events, unsolicited AEs during Days 0-28, and MAEs/SAEs through 6 months following vaccination.
- Twenty deaths were reported in PSC12 (adults ≥50 years), similarly distributed across the two treatment groups; the investigators considered none of them to be related to vaccination. No deaths were reported in PSC16 (adults 18-49 years).

10.2 Conclusions and Recommendations

The submitted data support the primary non-inferior relative efficacy objective being met in adults ≥50 years of age. In adults 18-49 years of age, the criteria for demonstrating non-inferiority of Flublok Quadrivalent compared to IIV4 were not met for all co-primary immunogenicity endpoints. I defer to the medical officer and other review committee members to determine whether the totality of the data support approval in adults 18-49 years of age.