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Sponsor: Protein Sciences Corporation **Drug substances:** Quadrivalent Recombinant Influenza vaccine	**Study Identifiers:** NCT02290509 **Study code:** PSC16
Title of the study: 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.	
Study centers: 10 centers in United States.	
Study period: Date first subject enrolled: 22/Oct/2014 Date last subject completed: 14/May/2015	
Phase of development: III	

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. This was to be accomplished through the evaluation of:
  - ✧ the ratio of post-vaccination HAI Geometric Mean Titers (GMTs) to each of the four antigens

  and
  - ✧ the difference in HAI seroconversion rates to the same four antigens.

Evaluations utilized CBER criteria for non-inferiority of HAI Geometric Mean Titers (GMTs) and seroconversion rates.

- To compare the safety profiles of Flublok Quadrivalent and US-licensed IIV4.

Secondary Objectives:

- To evaluate the HAI seroconversion rates and proportion of subjects with a post-vaccination HAI titer ≥40 (%≥40) for 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

Methodology:

The study was an observer-blind, randomized, active-controlled, parallel design Phase 3 multi-center clinical trial designed to compare the immunogenicity, reactogenicity and safety of Flublok Quadrivalent with that of US-licensed IIV4 administered during the 2014-2015 influenza vaccination season. The immunogenicity of each of the antigens in Flublok Quadrivalent was compared with the corresponding antigen in IIV4 comparator. All comparisons will be designed to demonstrate non-inferior immunogenicity according to CBER criteria.
A total of 1350 ambulatory, medically stable adults 18 – 49 years of age were enrolled and were randomized 3:1 to receive Flublok Quadrivalent (1011 subjects) or US-Licensed IIV4 (339 subjects).

Serum samples for HAI serology were obtained pre- and post- vaccination on Days 0 and 28 from a subset of subjects enrolled at five sites (N=614). Immunogenicity of each of the four antigens in Flublok Quadrivalent was compared with the corresponding antigen in IIV4 comparator. All comparisons were designed to demonstrate non-inferior immunogenicity according to CBER criteria.
Solicited injections site and systemic Adverse Events (AEs) were recorded by subjects on Memory Aid -on the day of vaccination (Day 0) and for the next 7 days. Spontaneously reported AEs were recorded by subjects on Memory Aid from Day 0 to Day 28. Between Day 28 and the end of the study approximately 5 months later (6 months postvaccination), medically-attended and serious adverse events (MAEs and SAEs, respectively) were also recorded on the same tool as for the unsolicited, spontaneously reported AEs.

Number of subjects:

Randomized: 1350

Evaluated:

Immunogenicity:1292

Reactogenicity:1328

Safety: 1330

Diagnosis and criteria for inclusion:

The study population included ambulatory and medically stable adults 18-49 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 safety endpoint.

Study treatments

Subjects were randomized ~3:1 to one of the following vaccine groups:

Group A: Flublok Quadrivalent containing 4x45µg (180µg total) of rHA0 derived from influenza A/H1N1 and A/H3N2 and two influenza B viruses in a total volume of 0.5mL provided in pre-filled syringes.

Group B: IIV4 (Fluarix Quadrivalent®) containing 4x15µg (60 µg total), of quadrivalent, inactivated influenza vaccine (licensed IIV4) containing influenza antigen derived from A/H1N1 and A/H3N2 and two influenza B viruses in a total volume of 0.5mL provided in pre-filled syringes.

Flublok Quadrivalent and IIV4 contained the following influenza viruses that were identified by the FDA Vaccines and Related Biological Products Advisory Committee as the four strains ("-like viruses") to be included in quadrivalent influenza vaccines for the 2014-2015 season:

Flublok Quadrivalent	**IIV4 (Fluarix Quadrivalent)**
H1N1: A/California/07/2009	H1N1: A/ Christchurch/16/2010 (an A/California/7/2009-like virus)
H3N2: A/Texas/50/2012	H3N2: A/Texas/50/2012
B/Massachusetts/2/2012 (B/Yamagata-lineage)	B/Massachusetts/2/2012
B/Brisbane/60/2008 (B/Victoria-lineage)	B/Brisbane/60/2008

Duration of observation: 6 Months

Criteria for Evaluation

Primary endpoint: The study had two co-primary endpoints:

- HAI seroconversion rates at Day 28 to each of the four antigens contained in the study vaccine
- HAI GMTs at Day 28 to each of the four antigens contained in the study vaccine

These measurements were compared between the two vaccine groups according to CBER criteria for noninferiority. Seroconversion is 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 minimum fourfold rise in post-vaccination HI antibody titer.

Secondary endpoints:

- Seroconversion rates and % ⩾40 to all four antigens in Flublok Quadrivalent, assessed according to CBER criteria for licensure under accelerated approval regulations
  - ✧ 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
- Serious adverse events (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

Summary

Primary Endpoints

HAI seroconversion rates – non-inferiority comparison

Seroconversion rates (SCRs) calculated for each treatment group for each of the four antigens represented in both vaccines are shown in Table 1. The criterion for non-inferiority (upper bound of 95% confidence interval for the difference in SCR between IIV4 and Flublok Quadrivalent ≤10%) was met for both A antigens and for B/Massachusetts.

Table 1. PSC16 -- HAI Seroconversion Rates at Day 28 – Immunogenicity population

Category	Parameter	Flublok Quadrivalent N=969	IIV4 N=323	Difference	95% CI for Difference
A/H1/California	n (%) 95% CI	646 (66.7) (63.6, 69.6)	205 (63.5) (58.0, 68.7)	-3.2	(-9.2, **2.8**)
A/H3/Texas	n (%) 95% CI	699 (72.1) (69.2, 74.9)	184 (57.0) (51.4, 62.4)	-15.1	(-21.3, **-9.1**)
B/Massachusetts	n (%) 95% CI	578 (59.6) (56.5, 62.8)	195 (60.4) (54.8, 65.7)	0.8	(-5.4, **6.9**)
B/Brisbane	n (%) 95% CI	393 (40.6) (37.4, 43.7)	188 (58.2) (52.6, 63.6)	17.6	(11.4, 23.9)

Figures in **bold** meet CBER criteria for non-inferiority
Rounding with one decimal digit after log-transformation

Non-inferiority was not met for B/Brisbane. In contrast, for A/H3/Texas, the seroconversion rate was notably higher (upper bound of 95% confidence interval for the difference in SCR [IIV4 minus Flublok Q] of < 0)) for Flublok Quadrivalent recipients as compared with IIV4 recipients.

Post-vaccination HAI GMTs – non-inferiority ratios

The post-vaccination HAI GMTs calculated for each treatment group against each of the four antigens represented in the vaccines are shown in Table 2. The criterion for non-inferiority (upper bound of 95% confidence interval of the ratio of IIV4 to Flublok Quadrivalent $\leqslant$1.5) was met for both A antigens and for B/Massachusetts. Similar to seroconversion rates, non-inferiority for Flublok Quadrivalent GMTs was not met for B/Brisbane.

Table 2. PSC16 – Pre- and Post-vaccination HAI GMTs - Immunogenicity population

Antigen	Visit	Parameter	Flublok Quadrivalent (N=969)	IIV4 (N=323)	GMR	95% CI for GMR
A/H1/California	Day 0					
		GMT	60	54	0.90	(0.75, 1.09)
		95% CI for GMT	(54, 65)	(46, 63)		
	Day 28					
		GMT	502	407	0.81	(0.71, **0.92)**
		95% CI for GMT	(469, 537)	(367, 451)		
A/H3/Texas	Day 0					
		GMT	75	70	0.93	(0.78, 1.13)
		95% CI for GMT	(68, 83)	(60, 82)		
	Day 28					
		GMT	757	385	0.51	(0.45**, 0.58**)
		95% CI for GMT	(709, 808)	(348, 425)		
B/Massachusetts	Day 0					
		GMT	27	24	0.89	(0.77, 1.06)
		95% CI for GMT	(25, 29)	(21, 28)		
	Day 28					
		GMT	159	136	0.86	(0.74, **1.00**)
		95% CI for GMT	(147, 171)	(121, 153)		
B/Brisbane	Day 0					
		GMT	12	11	0.92	(0.82, 1.05)
		95% CI for GMT	(11, 13)	(10, 12)		
	Day 28					
		GMT	43	64	1.49	(1.30, 1.71)
		95% CI for GMT	(40, 46)	(58, 72)		

Figures in **bold** meet CBER criteria for non-inferiority
Rounding with one decimal digit after log-transformation

For both A antigens, the post-vaccination HAI GMTs were notably higher among Flublok Quadrivalent recipients (upper bound of 95% confidence interval for the GMT ratio [IIV4/ Flublok Q] of < 1) than among IIV4 recipients. The post-vaccination GMTs for B/Brisbane were very low in both treatment groups (43 versus 64), and were within the 2-fold dilution validated for the HAI assay.

Secondary endpoints

Seroconversion rates

Seroconversion rates to all four antigens represented in the vaccines were compared for both vaccine groups to the CBER criterion for approval under accelerated approval regulations (lower bound of the 95% confidence interval ≥40%) was met in Flublok Quadrivalent recipients for both A antigens and for B/Massachusetts (Table 3). In this analysis, as well, the criterion was not met for B/Brisbane among Flublok Quadrivalent recipients.

Table 3. PSC16 – Seroconversion rates at Day 28 – Immunogenicity population

Antigen	Parameter	Flublok Quadrivalent N=969	IIV4 N=323
A/H1/California	Seroconversion Rate 95% CI	66.7 (**63.6,** 69.6)	63.5 (**58.0**, 68.7)
A/H3/Texas	Seroconversion Rate 95% CI	72.1 (**69.2**, 74.9)	57.0 (**51.4**, 62.4)
B/Massachusetts	Seroconversion Rate 95% CI	59.6 (**56.5,** 62.8)	60.4 (**54.8**, 65.7)
B/Brisbane	Seroconversion Rate 95% CI	40.6 (37.4, 43.7)	58.2 (**52.6**, 63.6)

Figures in **bold** meet CBER criteria for licensure under accelerated approval regulations.
Rounding with one decimal digit after log-transformation

Proportion of Subjects with Post-vaccination titer ≥40 (%≥40)

The CBER criterion for licensure under accelerated approval regulations for the proportion of subjects with post-vaccination HAI titers ⩾40, sometimes referred to as "seroprotection" (lower bound of the confidence interval ⩾70%), was met among Flublok Quadrivalent recipients for both A antigens and for B/Massachusetts, but not for B/Brisbane (Table 4). In comparing 95% confidence limits for the proportions of subjects with titers %⩾40, all were overlapping between Flublok Quadrivalent and IIV4 recipients, except those for B/Brisbane.

Table 4. PSC16 -- Proportion of Subjects with Post-vaccine HAI titers ⩾40 – Immunogenicity population\

Category	Visit	Parameter	Flublok Quadrivalent N=969	IIV4 N=323
A/H1/California	Day 0	% ≥40, n (%) 95% CI	666 (68.7) (65.7, 71.6)	215 (66.6) (61.1, 71.7)
	Day 28	% ≥40, n (%) 95% CI	952 (98.2) (**97.2**, 99.0)	320 (99.1) (**97.3**, 99.8)
A/H3/Texas	Day 0	% ≥40, n (%) 95% CI	713 (73.6) (70.7, 76.3)	241 (74.6) (69.5, 79.3)
	Day 28	% ≥40, n (%) 95% CI	966 (99.7) (**99.1**, 99.9)	320 (99.1) (**97.3**, 99.8)
B/Massachusetts	Day 0	% ≥40, n (%) 95% CI	446 (46.0) (42.9, 49.2)	145 (44.9) (39.4, 50.5)
	Day 28	% ≥40, n (%) 95% CI	882 (91.0) (**89.0**, 92.7)	297 (92.0) (**88.4,** 94.7)
B/Brisbane	Day 0	% ≥40, n (%) 95% CI	175 (18.1) (15.7, 20.6)	53 (16.4) (12.5, 20.9)
	Day 28	% ≥40, n (%) 95% CI	623 (64.3) (61.2, 67.3)	257 (79.6) (**74.8**, 83.8)

Figures in **bold** meet CBER criteria for licensure under accelerated approval regulations.
Rounding with one decimal digit after log-transformation

Solicited Reactogenicity Events

Incidence and severity of solicited events of reactogenicity were compiled from the data recorded on subjects' Memory Aid A and reported to the sites during the remote contact Days 7 - 9 following vaccination. Local events of reactogenicity show largely mild to moderate complaints (Grade 1-2) and little difference between the treatment groups (Table 5). Only the incidence of erythema (reported as "redness") at the site of injection was higher among Flublok Quadrivalent recipients than among IIV4 recipients (p=0.002).

Table 5. PSC16-Comparison of Incidence and Severity of Local Events of Reactogenicity Days 0-7- Reactogenicity population A

	Flublok Quadrivalent N=996 N (%)			IIV4 N=332 N (%)		
Reactogenicity Event	Any	Gr 3	Gr 4	Any	Gr 3	Gr 4
At least one local reactogenicity event	510 (51.2)	11 (1.1)	1 (0.1)*	172 (51.8)	5 (1.5)	0
Local Pain	367 (36.8)	9 (0.9)	0	121 (36.4)	3 (0.9)	0
Local Tenderness	478 (48.0)	9 (0.9)	1 (0.1)*	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

Reactogenicity population with at least one non-missing data point for injection site reactions – Days 0-7

Subjects with at least one value on the Memory Aid A during Days 0-7 following vaccine administration are included in the analysis
*This datapoint was determined upon review of the subject's Memory Aid A to have been a transcription error; the correct number is 0.

Systemic reactogenicity was also compiled from the same sources and, again, showed no events of concern or notable difference between the treatment groups (Table 6).

Table 6. Comparison of Incidence and Severity of Systemic Events of Reactogenicity – Days 0-7- Reactogenicity population B

	Flublok Quadrivalent N=996 N (%)[1]			IIV4 N=332 N (%)		
Reactogenicity Event	Any	Gr 3	Gr 4	Any	Gr 3	Gr 4
At least one systemic reactogenicity event	339 (34.1)	23 (2.3)	1 (0.1)	119 (35.8)	9 (2.7)	1 (0.3)
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

Reactogenicity population with at least one non-missing data point for systemic reactions – Days 0-7
The denominator in the Flublok Quadrivalent group was 994 due to 2 subjects with no systemic event data on their Memory Aid A

Daily body temperatures were measured with a digital thermometer provided to subjects and recorded on Memory Aid A. Temperatures (in °F) were categorized as fever according to grades of severity as defined in the protocol (Table 7).

Table 7. PSC16 -- Comparison of Incidence and Severity of Fever - Days 0-7 – Reactogenicity population C

	Flublok Quadrivalent N=996 N(%)[1]			IIV4 N=332 N(%)[2]		
	Any[3]	Grade 3	Grade 4	Any	Grade 3	Grade 4
Fever	15 (1.5)	4 (0.4)	0	2 (0.6)	1 (0.3)	0

Reactogenicity population with at least one non-missing data point for body temperature – Days 0-7
[1]The denominator in the Flublok Quadrivalent group was 990 due to 6 subjects with no body temperature recorded on their Memory Aid A
[2]The denominator for fever in the IIV4 group was 327 due to 5 subjects with no body temperature on their Memory Aid A
[3]Grade 1: 100.4 – 101.1 °F; Grade 2: 101.2 – 102.0 °F; Grade 3: 102.1 – 104 °F; Grade 4: >104 °F

Few subjects experienced elevated body temperatures and none reached Grade 4 or were of significant medical concern.

Unsolicited AEs

The only unsolicited adverse events that were reported from ⩾1% of subjects in either treatment group were nasopharyngitis, upper respiratory tract infection, sinusitis, cough and headache, all of which were reported with similar frequency in both treatment groups.

Serious and Medically-Attended Adverse Events (SAEs and MAEs):

There were 14 SAEs reported from 12 subjects (10 Flublok Quadrivalent and 2 IIV4 recipients) throughout the duration of the study. None was considered related to study vaccine and myocardialinfarction was the only event that occurred in more than one subject (n=2). These 2 subjects experienced a myocardial infarction >60 days post-vaccination. Medically-attended adverse events (MAEs) were reported from 80 (8.0%) Flublok Quadrivalent recipients and 24 (7.2%) IIV4 recipients. The only MAE (preferred term) that was reported from ⩾1% of subjects in a treatment group was sinusitis, reported from 5 (1.5%) IIV4 recipients.

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