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Sponsor: Protein Sciences Corporation **Drug substances:** Quadrivalent Recombinant Influenza Vaccine	**Study Identifiers:** NCT02285998 **Study code:** PSC12
Title of the study: Comparison of the Protective Efficacy of Flublok® Quadrivalent versus Licensed Inactivated Influenza Vaccine (IIV4) in Healthy, Medically Stable Adults ≥50 Years of Age.	
Study centers: 41 centers in United States.	
Study period: Date first subject enrolled: 22/Oct/2014 Date last subject completed: 22/May/2015	
Phase of development: III	

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 influenza-like-illnesses (ILI) that begin at least 14 days after vaccination caused by any influenza viral types/subtypes

Secondary Objectives:

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

Methodology:

The study was an observer-blind, randomized, active-controlled, parallel design Phase 3 multi-center clinical trial designed to compare the relative vaccine efficacy (rVE), immunogenicity, reactogenicity and safety of Flublok Quadrivalent with that of US-licensed IIV4. The relative vaccine efficacy (1 – [Attack rate Flublok Quadrivalent/ Attack Rate IIV4] x 100) for the primary analysis was based on rtPCR-confirmed influenza infection associated with protocol-defined influenza-like illness (ILI). Non-inferiority was pre-defined as a lower limit of the two-sided 95% confidence interval around the rVE for Flublok Quadrivalent (compared to IIV4) of > -20%. If the non-inferiority criterion was met, the protocol specified an exploratory criterion for superiority of a lower bound of the two sided 95% CI for rVE of > +9%.

A total of 9003 subjects medically-stable adults ≥50 years of age were enrolled in the study. Fifteen subjects withdrew consent prior to receiving study vaccine and 25 subjects received a dose of study vaccine the identity of which could not be verified in site source documents. A total of 8963 subjects were randomized via an internet web-based response system (IWRS) in a 1:1 ratio to receive a single dose of Flublok Quadrivalent (n=4474) or a U.S.-licensed IIV4 (n=4489) on Day 0.

Surveillance for influenza-like illness was both passive and active. All subjects were instructed to call a central interactive voice response system (IVRS) twice weekly to report whether they had experienced any of the prespecified respiratory or systemic symptoms that might have defined ILI. If subjects responded "yes" they were instructed to contact their investigative site to determine whether they should return for an "ILI visit". In addition, sites contacted each subject at least once every two weeks to inquire as to ILI symptoms and to maintain subjects engagement in the study. Sites were notified by the IVRS system if subjects missed their twice weekly calls. If at any of the contacts, the subject's symptoms met protocol-defined criteria for ILI, they were instructed to return immediately or within 72 hours of onset of symptoms for evaluation and nasopharyngeal swab for rtPCR testing.

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: 8963

Evaluated:

Efficacy: 8604

Safety:8672

Immunogenicity: 614

Diagnosis and criteria for inclusion:

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.

Study treatments

Subjects were randomized 1:1 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, or

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's Vaccines and Related Biological Products Advisory Committee as the four strains (or "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:

- rtPCR-confirmed, protocol-defined Influenza-Like Illness (ILI) caused by any influenza strain that begins at least 14 days post-vaccination

Secondary endpoints:

- rtPCR-confirmed CDC-defined ILI that begins at least 14 days post-vaccination caused by any influenza strain.
- 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.
- 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 seroconversion rates (SCR) for all four antigens in a subset of subjects
    - ✧ The HAI titers were compared between the two vaccine groups using the criteria for non-inferiority defined by CBER for the difference in seroconversion rates and the ratio of GMTs of IIV4/Flublok Quadrivalent.
    - ✧ 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%. 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 30%.
- Solicited events of systemic and injection site reactogenicity reported during Day 0-7.
- Unsolicited adverse events reported in the 28 days following vaccine administration.
- Serious adverse events (SAEs) and medically-attended adverse events (MAEs) reported during the period of follow-up through the influenza season (at least 6 months post-vaccination).

Summary

Clinical Efficacy

Primary Endpoints

The primary endpoint of this study, the relative vaccine efficacy for rtPCR-confirmed protocol-defined ILI due to any influenza strain, demonstrated a positive relative VE of +31% (Table 1). The lower bound of the two-sided 95% confidence interval met the pre-specified non-inferiority criterion of > -20%. Having met the primary efficacy endpoint of the study, the test for superiority of Flublok Quadrivalent over IIV4, as a pre-specified exploratory analysis, was also met by the lower bound of the two-sided 95% CI > +9%.

Table 1. PSC12 -- rVE for rtPCR-confirmed Protocol-defined ILI* – Efficacy Population (Primary Analysis)

Flublok Quadrivalent (N=4303)		IIV4 (N=4301)			
n	Attack Rate (%)	n	Attack Rate (%)	Relative Risk (RR)	rVE (95% CI)
96	2.2	138	3.2	0.69	+31 (+10, 47%)

The rVE reported above was calculated using attack rate data that were rounded to a single decimal place.

*Meets case definition of protocol-defined influenza-like illness: At least one of the following respiratory symptoms (sore throat, cough, sputum production, wheezing or difficulty breathing) accompanied by at least one of the following systemic (temperature of >99º F [>37.2º C], chills, fatigue, headache or myalgia).

Secondary and Additional endpoints

Secondary analyses and additional analyses evaluated clinical efficacy using several definitions of the primary endpoint, including either culture confirmation of ILI or ILI as defined by CDC criteria. Aliquots of all rt-PCR-positive NP swabs were automatically processed for culture in MDCK cells. A secondary efficacy endpoint of the study was the occurrence of culture-confirmed influenza caused by viral types/subtypes antigenically similar ("matched") to those contained in the respective vaccine formulations in association with protocol-defined ILI. However, the virus cultures did not provide an adequate titer of viruses to be tested for antigenic similarity. However, in an additional analysis, the rVE for culture-confirmed protocol-defined ILI due to any influenza strain also met the predefined lower bound of 95% CI for both non-inferiority (> -20%) and superiority (> +9%), even though there were notably fewer ILI cases confirmed by positive culture of an influenza virus than by rtPCR. (Table 2).

Table 2. PSC12 -- rVE against Culture-Confirmed Protocol-defined ILI – Efficacy Population

Flublok Quadrivalent (N=4303)		IIV4 (N=4301)			
n	Attack Rate (%)	n	Attack Rate (%)	Relative Risk (RR)	rVE (95% CI)
58	1.3	101	2.3	0.57	+43 (+21, 59%)

The rVE reported above was calculated using attack rate data that were rounded to a single decimal place.

One of the secondary endpoints was rtPCR-confirmed CDC-ILI that begins at least 14 days postvaccination caused by any influenza strain. Even fewer of the ILI cases met the criteria for CDC-defined ILI, largely due to the absence of fever >100°F [37.8°C]. The rVE for rtPCR-confirmed CDC-defined ILI also met the criterion for non-inferiority, but barely missed the criterion for superiority due to wider a confidence interval (Table 3). Using the CDC criteria for ILI that includes fever may be inappropriately rigid for the older adult population that is less likely than younger individuals to mount a febrile response to infection.

Table 3. PSC12 -- rVE against rtPCR-confirmed CDC-ILI – Efficacy Population (Secondary analysis)

Flublok Quadrivalent (N=4303)		IIV4 (N=4301)			
n	Attack Rate (%)	n	Attack Rate (%)	Relative Risk (RR)	rVE (95% CI)
54	1.3	83	1.9	0.68	+32 (+8, 54%)

The rVE reported above was calculated using attack rate data that were rounded to a single decimal place.

The rVE for culture-confirmed CDC-defined ILI due to any influenza strain demonstrated the superior efficacy of Flublok Quadrivalent over IIV4 (Table 4).

Table 4. PSC12 -- rVE against culture-confirmed CDC-ILI – Efficacy Population

Flublok Quadrivalent (N=4303)		IIV4 (N=4301)			
n	Attack Rate (%)	n	Attack Rate (%)	Relative Risk (RR)	rVE (95% CI)
38	0.9	64	0.15	0.60	+40 (+11, 61%)

The rVE reported above was calculated using attack rate data that were rounded to a single decimal place.

A *post- hoc* analysis was performed to assess the rVE for influenza A and B strains, separately (Table 5). This was of interest since the estimated vaccine effectiveness for the licensed vaccines for the 2014-2015 season was low for influenza A (<20%), but satisfactory for influenza B.

Table 5. PSC12 – rVE against rtPCR-confirmed protocol-defined ILI caused by Influenza A and B

Type	Flublok Quadrivalent (N=4303)		IIV4 (N=4301)		Relative Risk (RR)	rVE (95% CI)
	n	Attack Rate (%)	n	Attack Rate (%)		
Influenza Type A	73	1.7	114	2.7	0.63	+37 (+14, 53%)
Influenza B	23	0.5	24	0.6	0.83	+17 (-72, +46%)

The rVE reported above was calculated using attack rate data that were rounded to a single decimal place.

The robust relative efficacy of Flublok Quadrivalent against culture-confirmed ILI further supported the efficacy against the predominating Influenza A strain during the 2014-2015 season (Table 6).

Table 6. PSC12 – rVE against cell culture-confirmed protocol-defined ILI caused by Influenza A and B

Type	Flublok Quadrivalent (N=4303)		IIV4 (N=4301)		Relative Risk (RR)	rVE (95% CI)
	n	Attack Rate (%)	n	Attack Rate (%)		
Influenza Type A	52	1.2	93	2.2	0.55	+45 (+22, 61%)
Influenza B	6	0.1	8	0.2	0	+50 (-121, +75%)

The rVE reported above was calculated using attack rate data that were rounded to a single decimal place.

Overall, Flublok Quadrivalent demonstrated encouraging efficacy relative to the licensed inactivated vaccine, especially, against the influenza A/H3 strain that was responsible for a particularly severe influenza season.

Immunogenicity

Serum samples for hemagglutination inhibition (HAI) titers were obtained on Day 0 prior to vaccination and on Day 28 after vaccination from 614 subjects enrolled at five clinical sites selected to participate in the immunogenicity subset of the study. There was no further selection at the subject level with respect to which subjects would participate in the immunogenicity subset. The projected sample size for the Immunogenicity subset was based on the entire study population aged ≥50 years. However, HAI seroconversion rates were calculated by Age Category and several other pre-specified subsets, even though the sample sizes for the subsets are not adequately powered for the non-inferiority analysis.

Seroconversion rates for Flublok Quadrivalent recipients met the criterion for non-inferiority (upper bound of the two-sided 95% CI around the difference between IIV4 and Flublok Quadrivalent <10) for two of the four antigens (A/Texas and B/Massachusetts) (Table 7). The HAI response to B/Brisbane was less robust following Flublok Quadrivalent and did not meet non-inferiority, while the response to A/California was very similar in both vaccine groups, suggesting that the failure to meet non-inferiority was related to the sample size and the resultant wide 95% CI.

Table 7. PSC12 – Comparison of HAI Seroconversion Rates – Immunogenicity Population

Antigen	Flublok Quadrivalent N=314 N (%)	IIV4 N=300 N (%)	Difference (95% CI)
A/California	141 (44.9)	147 (49.0)	4.1 (-3.8, 12.0)
A/Texas	171 (54.5)	130 (43.3)	-11.2 (-19.0, -**3.3***)
B/Massachusetts	122 (38.9)	115 (38.3)	- 0.6 (-8.2, **7.2***)
B/Brisbane	66 (21.0)	103 (34.3)	13.3 (6.3, 20.3)

* Figures in **bold** meet criterion for non-inferiority

The post-vaccination HAI GMTs showed that robust immune responses were observed to three of the four antigens (A/California, A/Texas and B/Massachusetts) and that the ratios of GMT met the criterion for non-inferiority for those three antigens (Table 8). Again, the GMT responses for B/Brisbane were relatively low in both treatment groups compared to the other strains. While Flublok Quadrivalent did not meet the GMT ratio criterion for non-inferiority for B/Brisbane, the absolute values for GMT in each treatment group was within the limits of sensitivity for which this assay is validated (2-fold dilution).

Table 8. PSC12 - Comparison of HAI GMT Responses - Immunogenicity Population

Antigen	Visit	Flublok Quadrivalent (N=314) GMT (95% CI)	IIV4 N=300 N (%)	GMR (95% CI)
A/H1N1/California	Day 0	45 (38, 52)	49 (42, 57)	1.15 (0.95, **1.41***)
	Day 28	194 (167, 226)	224 (197, 255)	
A/H3N2/Texas	Day 0	88 (74, 104)	100 (84, 119)	0.69 (0.58, **0.82***)
	Day 28	530 (470, 597)	366 (325, 412)	
B/Massachusetts	Day 0	17 (15, 20)	18 (16, 21)	1.04 (0.86, **1.24***)
	Day 28	56 (49, 64)	18 (51, 66)	
B/Brisbane	Day 0	14 (12, 15)	15 (13, 16)	1.47 (1.24, 1.77)
	Day 28	30 (26, 34)	44 (39, 50)	

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

Seroconversion rates were also calculated for each antigen in the two age categories (50-64 and ≥65 years) in an exploratory analysis to be evaluated according to CBER criteria for accelerated approval. For both groups, the SCR met the CBER criterion (lower bound of two-sided 95% CI ≥40%) for A/California and A/Texas in the 50-64 year age subset and came somewhat close for B/Massachusetts. SCR for 50-64 years old subjects did not pass for B/Brisbane in both treatment groups.

Table 9. PSC12 -- Seroconversion Rates by Age Category

Antigen	Age Group	Flublok Quadrivalent N=314 N (SCR %) (95% CI)	IIV4 N=300 N (SCR %) (95% CI)
A/H1N1/California	50-64	196 109 (55.6) (**48.4**[*], 62.7)	209 113 (54.1) (**47.1**[*], 61.0)
	≥65	118 32 (27.1) (19.3, 36.1)	91 34 (37.4) (27.4, 48.1)
A/H3N2/Texas	50-64	123 (62.8) (**55.6**[*], 69.5)	107 (51.2) (**44.2**[*], 58.2)
	≥65	48 (40.7) (**31.7**[*], 50.1)	23 (25.3) (16.7, 35.5)
B/Massachusetts	50-64	84 (42.9) (35.8, 50.1)	91 (43.5) (36.7, 50.6)
	≥65	38 (32.2) (23.9, 41.4)	24 (26.4) (17.7, 36.7)
B/Brisbane	50-64	50 (25.5) (19.6, 32.2)	89 (42.6) (35.8, 49.6)
	≥65	16 (13.6) (8.0, 21.1)	14 (15.4) (8.7, 24.5)

[*]Figures in **bold** meet CBER criterion for accelerated approval.

As noted above, the age category subset sample sizes were not adequately powered for this analysis. In the ≥65 year age subset, only the SCR for Flublok Quadrivalent against A/Texas met the CBER licensure criterion (lower bound of the 95% CI ≥30%). IIV4 did not meet the criterion for any of the four antigens in this age group. In this age subset, the point estimates for SCRs were usually low, especially for B/Brisbane but similar in both vaccine groups, although subjects in the Flublok group did meet the CBER criterion for seroconversion to influenza A/H3.

Solicited Reactogenicity Events

Solicited events of local injection site reactions were reported overall less frequently among Flublok Quadrivalent recipients than among IIV4 recipients.

Table 10. PSC12 -- Comparison of Incidence of Local Reactogenicity -- Reactogenicity Population A

Event Term	Flublok Quadrivalent N=4307 N (%)	IIV4 N=4319 N (%)	p - value for difference
Subjects with ≥ one local event	1621 (37.6)	1745 (40.4)	0.009
Local Pain	813 (18.9)	950 (22.0)	<0.001
Local Tenderness	1479 (34.3)	1604 (37.1)	0.007
Redness	122 (2.8)	87 (2.0)	0.014
Firmness / Swelling	142 (3.3)	115 (2.7)	0.09

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

Specifically, injection site pain and tenderness were significantly less frequent among Flublok Quadrivalent recipients. By contrast, erythema and induration ("redness" and "firmness/swelling", respectively) were slightly more commonly reported among Flublok Quadrivalent recipients. Injection site redness was more frequent in Flublok Quadrivalent recipients compared to IIV4 recipients, but these reactions occurred in fewer than 3% of subjects per group.
Systemic reactogenicity events of any type, by contrast, were reported overall less frequently than injection site reactions and the incidence was not notably different between the two vaccines.

Table 11. PSC12 -- Comparison of Incidence of Systemic Reactogenicity -- Reactogenicity Population B

Event Term	Flublok Quadrivalent N=4306 N (%)	IIV4 N=4318 N (%)	p-value
Subjects with ≥ one systemic event	1077 (25.0)	1106 (25.6)	0.54
Fatigue	526 (12.2)	521 (12.1)	0.84
Shivering / Chills	204 (4.7)	187 (4.3)	0.38
Joint Pain	324 (7.5)	346 (8.0)	0.40
Muscle Pain	366 (8.5)	378 (8.8)	0.70
Headache	549 (12.7)	582 (13.5)	0.32
Nausea	212 (4.9)	213 (4.9)	>0.99

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

Body temperature was collected daily during Days 0-7 and, although reported by slightly fewer subjects, elevations of body temperature ≥100.4° F (38.0° C), were reported rarely, with no difference between vaccine groups (Table 12).

Table 12. PSC12 -- Comparison of Incidence of Fever -- Reactogenicity Population C

Event Term	Flublok Quadrivalent N=4262 N (%)	IIV4 N=4282 N (%)	p-value
Fever*	19 (0.4)	21 (0.5)	0.87

*≥100.4° F (38.0° C)

Reactogenicity population with at least one non-missing data point for body temperature – Days 0-7

Unsolicited AEs

The most common unsolicited adverse events that were reported from ≥2% of subjects in either treatment group during Days 0-28 were common complaints for the winter season and were no generally different in frequency between the two vaccine groups (Table 13).

Table 13. PSC12 -- Most Common Unsolicited AEs (>= 2% of subjects in either treatment group)

Preferred Term	Flublok Quadrivalent N=4328 N (%)	IIV4 N=4344 N (%)
Cough	226 (5.2)	253 (5.8)
Influenza like illness	186 (4.3)	199 (4.6)
Oropharyngeal pain	178 (4.1)	177 (4.1)
Headache	143 (3.3)	145 (3.3)
Upper respiratory tract infection	129 (3.0)	156 (3.6)
Fatigue	106 (2.4)	100 (2.3)
Myalgia	95 (2.2)	79 (1.8)
Productive cough	59 (1.4)	97 (2.2)

Medically-Attended Adverse Events (MAEs):

Medically-attended adverse events, defined as any adverse event that prompted a subjects to seek medical attention, were common through the six months of follow-up during this study, reported from 774 (17.9%) and 785 (18.1%) subjects in the Flublok Quadrivalent and IIV4 vaccine groups, respectively (p=0.82). Many were reported from only one or two individuals; the only MAEs that were reported from ≥1% of subjects in either treatment group were upper respiratory infection, sinusitis, bronchitis, cough and influenza-like illness. Each of these events was reported by fewer subjects in the Flublok Quadrivalent group, but none of the differences were statistically significant.

There were no reports of anaphylaxis, two reports of urticaria (1 in the Flublok Quadrivalent group and 1 in the IIV4 group), 13 reports of “rash” (5 in the Flublok Quadrivalent group and 8 in the IIV4 group) and one report of “allergic pruritus” in the Flublok Quadrivalent group. None of these incidences were significantly different.

Serious Adverse Events (SAEs):

Serious Adverse Events were reported by 145 (3.4%) and 132 (3.0%) of Flublok Quadrivalent and IIV4 recipients, respectively (p=0.43) over the ~6 months of follow-up. Eight of the SAEs were fatal in the Flublok Quadrivalent group and 11 fatalities occurred in the IIV4 group. None of these events was considered related to study vaccine. No SAE term was reported by 1% or more of subjects in either treatment group and most were reported by only one or two individuals.

Issue date: 22-Feb-2021