

OBE/DE REVIEW MEMO

Date: December 14, 2009

FDA STN: 125285

Sponsor: Protein Sciences Corporation (PSC)

Product: FluBlok®
Trivalent Recombinant Hemagglutinin Influenza Virus (rTIV);
Spodoptera frugiperda cell line
Each 0.5 mL dose contains 135 ug protein, 45ug of rHA antigen from each strain

<u>2008-2009 vaccine</u>	<u>2008-2007 vaccine</u>
A/Brisbane/59/2007 (H1N1)	A/Solomon Islands/03/06 (H1N1)
A/Brisbane/10/2007 (H3N2)	A/Wisconsin/67/05 (H3N2)
B/Florida/04/2006 (B strain)	B/Malaysia/2506/04(B strain)

Excipients
Sodium phosphate, 10-20 mM
Sodium chloride, 150 mM
Polysorbate 20 (Tween-20) 0.005%
----(b)(4)-----

Supplied in single dose glass vials with rubber stoppers

Indication: For active immunization of adults 18 years of age and older against influenza disease caused by influenza virus subtypes A and type B represented in the vaccine

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CC: HFM-220/Chronological File

Materials Reviewed:

STN	125285/0	Clinical Study Reports (PSC01, PSC03) Interim Clinical Study Reports (PSC04, PSC06) ISS, Pharmacovigilance Plan
	125285/0/12	Responses to Clinical Comments 29-AUG-2008 CR letter Final Clinical Study Reports (PSC04 and PSC06) Appendices (safety data)
	125285/0/18	Pediatric development plan

1 Background

Influenza

Influenza is a highly transmissible viral infection responsible for 17,000-51,000 deaths and 55,000-431,000 hospitalizations in the US, and 250,000-500,000 deaths worldwide each year. The highest rates of illness are seen in children 5-14 years of age and more severe and fatal outcomes are seen in children < years of age, older adults ≥ 65 years of age and those with chronic medical conditions. In the U.S., over 90% of deaths occur in those ≥ 65 years of age.

Influenza viruses circulate throughout the world in a seasonal pattern and disease is notably affected by antigenic drift (point mutations in the viral genome) and antigenic shifts (recombinant and reassortment based changes in hemagglutinin due to co-circulation of multiple influenza A strains in humans or animals). Individuals with immunity to a particular strain may be susceptible to infection with the resulting new viral type or subtype, and influenza vaccines are necessarily re-formulated annually to best match the anticipated circulating viruses based upon the recommendations of The World Health Organization.

Two approaches are available to deal with influenza infections - treatment and prevention. Antiviral drugs are licensed to both prevent and treat influenza, but are limited by development of drug resistant virus, adverse drug reactions, by actual level of effectiveness and by the need for dose adjustment in those with renal insufficiency, notably in the elderly. Vaccination is the principal method of influenza disease control and is currently recommended by the U.S. Center for Disease Control's (CDC's) Advisory Committee on Immunization Practices (ACIP) annually for children 6 months -18 years of age, pregnant women, those 50 years of age and older and those with certain chronic medical conditions and those in close contact with persons at higher risk of influenza-related complications. There are six currently licensed trivalent influenza vaccines in the U.S. – Afluria (CSL), Fluarix (GSK), FluLaval (GSK, formerly ID Biomedical), Fluvirin (Novartis), Fluzone (sanofi pasteur) and FluMist (MedImmune). All of these products are manufactured in hen eggs.

Neutralizing antibodies against hemagglutinin (HA) are considered protective against infection, and vaccine studies employ HA antibody titers as a surrogate, albeit an inexact one, to predict efficacy as the relationship between antibody levels or titers and protection appears to vary among subpopulations, most notably the elderly.

FluBlok®

FluBlok® utilizes a novel baculovirus / Lepidopteran (*Spodoptera frugiperda*) insect cell line expression system (expresSF+®) to produce recombinant influenza virus hemagglutinin (HA). Evaluation of this cell line has included adventitious agents testing, clearance of known and/or model adventitious agents, and residual host cell protein and/or DNA and other process impurities. .

Influenza HA antigens are cloned from selected influenza A and B viruses and the full length, uncleaved, recombinant HA0 glycoproteins with molecular weights of approximately 65 kilodaltons are produced using a baculovirus expression vectors in an insect cell line. This approach avoids the need to produce potentially pathogenic, live influenza viruses, and the attendant biocontainment issues that would be a particular concern for generation of pandemic vaccines. In addition, currently licensed influenza vaccines are produced using chicken eggs, and are contraindicated in individuals with known hypersensitivity to eggs or egg protein due to possible risk of a hypersensitivity reaction, a concern that does not apply to FluBlok.

The use of recombinant DNA techniques to express proteins in cell culture has been a successful approach for generation of vaccines for the prevention of hepatitis B and Human Papilloma Virus (HPV).

Influenza HA antigens generated in insect cells by recombinant baculoviruses have been evaluated in Phase 1-3 studies in healthy adults, in elderly community dwelling adults over the age of 65, and in B cell lymphoma patients.

1.1. Relevant regulatory history

The BLA was originally received by FDA 18-APR-2008, and reviewed under accelerated approval. A Complete Response was issued 29-AUG-2008. The sponsor has subsequently submitted a response under amendment 12, received 07-APR-2009.

Studies submitted to this BLA in support of FluBlok® were conducted in the U.S. under IND 11951.

CBER has judged that sufficient human safety data had been established with earlier formulations of FluBlok studied under INDs filed by the National Institute of Allergy and Infectious Diseases (NIAID)/NIH, such that no additional animal safety studies were required by CBER for continued clinical evaluation.

This product has not been licensed in any country to date.

2. Safety Specifications

2.1. Non-clinical safety

FluBlok has not been evaluated for carcinogenic or mutagenic potential, or for impairment of male fertility in animals.

A GLP reproductive and developmental toxicity study was performed in female rats with administration of three intramuscular injections of either FluBlok, 135 mcg per dose, or a saline placebo (approximately 300-fold excess relative to the proposed human dose). Two doses were administered prior to mating and one dose was given during the period of organogenesis (gestation day 6). No adverse effects were reported to have been observed with respect to mating, female fertility, implantation, early embryonic development, parturition, lactation of the dams, survival, or growth and development of the first generation until weaning. The effect of FluBlok on male fertility was not studied. On the basis of this study, PSC has requested a Pregnancy Category B in the draft product label.

Non-clinical studies including evaluation of immunogenicity (in mice, chickens and ferrets) and efficacy (influenza H5N1 challenge study in chickens immunized with a monovalent recombinant hemagglutinin [rHA] H5N1 vaccine).

Genotoxicity and carcinogenicity studies are not ordinarily considered to be applicable to vaccines, and FDA has not indicated that this type of testing is expected for FluBlok.

In addition, to address theoretical concerns regarding the use of a product manufactured in an insect cell line (*expresSF+*®), PSC has conducted risk assessment including (1) adventitious agents testing; (2) the robustness of the process in clearing known and/or model adventitious agents; and (3) the presence of residual host cell protein and/or DNA and other process impurities.

2.2. Clinical Study Data and Reports

2.2.1. Pivotal and Supporting Studies – Overview

FluBlok® has been evaluated in 5 clinical studies, four of which have been submitted to this BLA. The 5th study, PSC02, is a pediatric study intended to support expansion of the indication to a pediatric population and will be submitted in a future supplement.

Table 1: Summary of Clinical Trials

Study Age	Status	Design Follow-Up	Outcomes	Flu Season (Years)	Strain and Dose rHA	FluBlok® Recipients (N)	Control Product (No. of Recipients)
PSC01 18-49 yrs.	Complete	Phase 2 RDB Placebo control 6-months	Immunogenicity Safety Influenza-like illness	2004-2005	A/New Caldonia/20/1999 (H1N1) A/Wyoming/3/03 (H3N2) B/Hiangsu/10/03 (Also H1 & B, H3)	153**	Saline (154)
PSC03 ≥ 65	Complete	Phase 3 RDB Active control 9-months	Immunogenicity Safety Influenza-like illness	2006-2007	A/New Caldonia/20/1999 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Ohio/1/2005	436	Fluzone (433)
PSC04* 18-49 yrs.	Complete	Phase 3 RDB Placebo control 6-month	Immunogenicity Safety Influenza-like illness Lot consistency	2007-2008	A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004	2344***	Saline (2304)
PSC06 50-64 yrs.	Complete	Phase 3 RDB Active control 6-month	Safety Immunogenicity ILI	2007-2008	A/Solomon Islands/3/2006 (H1N1) A/Wisconsin/67/2005 (H3N2) B/Malaysia/2506/2004	300	Fluzone (302)
Total Safety Database for adults 18-65 years of age						3233	Total (3139) Saline (2458) Fluzone (735)
<p>*Pivotal Study ** An additional 151 subjects received 75 ug dose (15 ug H1, 15 ug B and 45 ug H3) ***Imbalance in 1:1 randomization due to error at Site 13 NOTE: PSC02 (children 6-59 months) was submitted with request for deferral of studies in support of a pediatric indication STN 125285/0 Clinical Study Report Synopses for PSC01, PSC03, PSC04 and PSC06</p>							

Integrated Summary of Safety (ISS)

The demographic characteristics of the overall safety database are described in Table 2. Individuals exposed to FluBlok were predominantly Caucasian (73%), with a higher proportion of females (59%). The mean and median age of FluBlok recipients was 39.7 years and 37 years, respectively, with a range of 18-92 years. In comparison, while the gender distribution is relatively comparable to FluBlok, the mean age of those receiving the FLUZONE (TIV) comparator was much older (65.9 years) and included an even higher proportion of Caucasians (85.9%). Those receiving the saline placebo had a gender distribution comparable to FluBlok but were slightly younger (mean age 32.5 years). Comparison by treatment or by study is likely confounded by the notable differences in age among vaccine groups, limiting the usefulness of the database. In addition, the ISS contains only preliminary data for several of the studies further limiting its usefulness.

Table 2: ISS Demographics

		Placebo N=2458		FLUZONE (TIV) N=735		FluBlok					
						75 µg N=151		135 µg N=3233		Overall N=3384	
		N	%	N	%	N	%	N	%	N	%
Race	White/Caucasian	1669	67.9%	631	85.9%	126	83.4%	2350	72.7%	2476	73.2%
	Black/African-American	456	18.6%	16	2.2%	12	7.9%	453	14.0%	465	13.7%
	Latino/Hispanic	240	9.8%	29	3.9%	2	1.3%	279	8.6%	281	8.3%
	Asian	56	2.3%	39	5.3%	10	6.6%	101	3.1%	111	3.3%
	American Indian/ Alaska Native	9	<1%	3	<1%	0	8	<1%	8	<1%	
	Native Hawaiian/ Pacific Islander	8	<1%	2	<1%	1	0.7%	8	<1%	9	<1%
	Other	20	0.8%	15	2.0%	0	0%	34	1.1%	34	1.0%
Gender	Male	1020	41.5%	309	42.0%	48	31.8%	1331	41.2%	1379	40.8%
	Female	1438	58.5%	426	58.0%	103	68.2%	1902	58.8%	2005	59.2%
Age (yrs.)	N	2458		735		151		3233		3384	
	Mean	32.4		65.9		32.0		40.0		39.7	
	S.D	9.19		10.00		9.79		16.99		16.82	
	Median	32.0		67.0		32.0		37.0		37.0	
	Min, Max	18, 50		50, 91		18, 49		18, 92		18, 92	
Age Group	18 - 49 Years	2455	99.9%	0	0	151	100%	2496	77.2%	2647	78.2%
	50 - 64 Years	3	<1%	302	41.1%	0	0	301	9.3%	301	8.9%
	65+ Years	0	0	433	58.9%	0	0	436	13.5%	436	12.9%

STN 125285 ISS Table 1

2.2.2 Study PSC01

Title: Evaluation of the Immunogenicity and Safety of Two Preparations of Trivalent Recombinant Baculovirus-Expressed Hemagglutinin Influenza Vaccine Administered Intramuscularly in Healthy Adults Aged 18-49 Years

Design: Phase 2, randomized, prospective, double-blinded trial
Population: 460 healthy adults 18-49 years of age

Randomization / Stratification/ Randomized at a 1:1:1 ratio into one of three groups, each vaccine 0.5 mL administered intramuscularly:

Dose:

- A: FluBlok total 75µg rHA total (15 ug of H1N1, 45 ug of H3N2, 15 ug of B)
- B: FluBlok total 135µg rHA total (45 ug of each strain)
- C: Placebo (normal saline for injection, USP)

Study Period: 17-November-2004 through 26-May-2005
Date of Report: 7-March-2008

Product: FluBlok seasonal influenza vaccine containing: A/New Caledonia/20/99 (H1N1), A/Wyoming/3/03 (H3N2), and B/Jiangsu/10/03
WHO recommended seasonal influenza strains for the 2004-2005 season in U.S.

Placebo: normal saline for injection

Schedule: Single dose

- Changes to protocol:
1. Enrollment decreased from 900 to 460 subjects prior to study initiation due to financial constraints
 2. A secondary endpoint listed in the Statistical Analysis Plan (SAP) as "Proportion of subjects in the vaccine and placebo groups with symptomatic influenza as defined above associated without laboratory evidence of influenza infection (positive culture) with any influenza virus strain that FluBlok is formulated to protect against." The intended meaning of this endpoint was clarified and revised according to the actual analysis to read: "Proportion of subjects in the vaccine and placebo groups with CDC-ILI, regardless of influenza culture results".
 3. Collection of nasopharyngeal cultures was prospectively changed to include subjects with flu symptom scores of 2 or greater who did not necessarily meet the illness definition of CDC-ILI at the time the culture sample was collected. Seroconversion and seroprotection levels were later calculated and summarized according to the conventions described previously, based on best approximation to the May 2007 CBER Guidance Document.

Primary Endpoints

- Safety:
1. Frequency of solicited local and systemic reactions in the 7 days following vaccination assessed via diary card
 2. Frequency of adverse events and severe adverse events in the 28-day period following vaccination as assessed on the Day 28 visit, along with any events spontaneously reported by the subject throughout the study period (including events reported during the interval medical history on Day 180).
 3. Serious adverse events through the end of the study (~Day 180).
- Immunogenicity:
- Frequency of ≥ 4 -fold increases in serum HAI antibody titers from pre- to 28-day post-vaccination

Secondary Endpoint

- Efficacy/Effectiveness:
1. Proportion of subjects in the FluBlok and Placebo groups who experienced laboratory documented (culture-confirmed) symptomatic influenza as defined by the presence of CDC-ILI.
 2. Proportion of subjects in the FluBlok and Placebo groups with CDC-ILI, regardless of influenza culture results.
 3. Proportion of subjects in the FluBlok and Placebo groups with laboratory evidence of influenza infection (as assessed by sero-response comparing pre-season and post-season sera by HAI against one or more of the strains represented in the vaccine), regardless of history of symptoms.

Exploratory Endpoints

- Efficacy/effectiveness:
1. Proportion of subjects with culture-confirmed CDC-ILI due to influenza A/H3N2
 2. Proportion of subjects in the FluBlok and Placebo groups with a positive influenza culture regardless of whether the subjects meet the case definition for CDC-ILI.
- Immunogenicity:
- Seroconversion: LL of 2-sided 95% CI for percent achieving seroconversion $\geq 40\%$ for HI antibody for all 3 strains.

Seroprotection: LL of 2-sided 95% CI for percent achieving HI antibody titer >1:40 is ≥70% for all three strains.

Sample Size: To ensure sufficient power for the test of changes in proportion of subjects with ≥4-fold change in pre-vaccination to 28-day post-vaccination titers in FluBlok versus Placebo recipients, a sample size of approximately 150 subjects per treatment (total of 450 subjects) was originally chosen, assuming 60-80% of subjects would experience ≥4-fold change in titer to at least one of the three strains of influenza, using alpha=0.05, and power of 80%.

Safety Monitoring

Diary cards: Solicited local events (pain, bruising, redness, soft swelling, hard swelling (induration) and solicited systemic events (fever (>99.6°F), fatigue/lack of energy, shivering (chills), joint pain, muscle pain, fatigue, headache, sweating, nausea) Days 0-7 post-vaccination

Clinic visits: Solicited events, axillary adenopathy, oculorespiratory syndrome on Day 2
Diary Card review, solicited events, axillary adenopathy at Day 8
AEs, medical visits, changes in health status at Day 28
Nasopharyngeal culture, illness evaluations for flu symptom score ≥2 (symptom card) or if advised at phone follow-up Day 0 – 180
Physical examination, review of all medical events, HAI antibody testing, urine pregnancy testing at Day 180

Phone calls: Signs/symptoms of influenza infection (recorded at home on flu symptom card, unsolicited AEs, weekly Days 35-180)

Protocol PSC01 Demographic and Safety Results

Subject Accounting

Data from 458 (99%) of 460 enrolled subjects were included in safety analyses and overall 98% of subjects were reported to have completed the study.

Table 3: Subject Accounting (PSC01)

Disposition	Treatment			
	FluBlok 75ig N=153	FluBlok 135ig N=153	Placebo N=154	Overall N=460
Randomized	153 (100)	153 (100)	154 (100)	460 (100)
Vaccinated	151 (99)	153 (100)	154 (100)	458 (99)
Completed	148 (97)	151 (99)	152 (99)	451 (98)
Discontinued	5 (3)	2 (1)	2 (1)	9 (2)
Due to AE	0 (0)	0 (0)	0 (0)	0 (0)
Lost to Follow-up	1 (1)	1 (1)	2 (1)	4 (<1)
Withdrew consent	0 (0)	1 (1)	0 (0)	1 (<1)
Died	0 (0)	0 (0)	0 (0)	0 (0)
Randomized, not vaccinated	2 (1)	0 (0)	0 (0)	2 (<1)
Other	2 (1)	0 (0)	0 (0)	2 (<1)
Incarcerated during the study	1 (1)	NA	NA	1 (<1)
Unable to contact during flu surveillance period	1 (1)	NA	NA	1 (<1)

STN 125285 PSC01 CSR Table 6

Demographics

Race/ethnicity was predominantly Caucasian in all groups, although the placebo group enrolled slightly higher proportion of Caucasians (90%) as compared to the two FluBlok groups (83% and 85%); there

was a slightly higher proportion of males (42%) in the placebo group as compared to the proportion of males in the FluBlok groups (32% and 37%); age distributions were similar among the three treatment groups. These data are summarized in Table 4, below.

Table 4: Demographics (PSC01)

Characteristic	Study Treatment			
	FluBlok 75ug N=151	FluBlok 135ug N=153	Placebo N=154	Overall N=458
Race/Ethnicity [n (%)]				
White/Caucasian	126 (83)	130 (85)	139 (90)	395 (86)
Black/African-American	12 (8)	9 (6)	9 (6)	30 (7)
Latino/Hispanic	2 (1)	5 (3)	1 (1)	8 (2)
Asian	10 (7)	4 (3)	4 (3)	18 (4)
American Indian/Alaska Native	0	1 (1)	0	1 (<1)
Native Hawaiian/Pacific Islander	1 (1)	1 (1)	0	2 (<1)
Other	0	3 (2)	1 (1)	4 (1)
Gender [n(%)]				
Male	48 (32)	57 (37)	65 (42)	170 (37)
Female	103 (68)	96 (63)	89 (58)	288 (63)
Age (years)				
Mean (SD)	32.0 (9.79)	31.3 (9.83)	31.9 (9.51)	31.7 (9.70)
Median	32	30	32	31
Minimum-Maximum	18-49	18-49	18-49	18-49
Females of Childbearing Potential [n (% of females)]	99 (96)	92 (96)	86 (97)	277 (96)

STN 125285 PSC01 CSR Table 7

Safety Results

1. Solicited Adverse Events

Solicited adverse events were reported by 72%, 79% and 65% of FluBlok 75µg, FluBlok 135µg and Placebo recipients, respectively. The most commonly reported solicited injection site reaction was injection site pain, headache, muscle pain and fatigue. Two severe solicited events were reported: fatigue and induration at the injection site reported by one subject each in the FluBlok 135ug group. Pain at the injection site was reported by more FluBlok recipients 44% and 38%) compared to Placebo (16%), but other solicited AEs occurred at fairly similar rates among the treatment groups. Grading of severity was similar. The solicited AEs are summarized in Table 5.

Table 5: Solicited Adverse Events Days 0-7, Overall and Grade 3 (Maximal) Severity per Diary Card (PSC01)

Type of Reaction	Number (%) of Subjects					
	FluBlok 75ug N=151		FluBlok 135ug N=153		Placebo N=154	
	Grade 3	All	Grade 3	All	Grade 3	All
With ≥1 solicited AE	0 (0)	109 (72)	2 (1)	123 (80)	0 (0)	99 (64)
Systemic AEs						
Fever (>99.6°F)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)
Fatigue, Lack of Energy	0 (0)	45 (30)	1 (1)	40 (26)	0 (0)	51 (33)
Shivering (chills)	0 (0)	4 (30)	0 (0)	4 (3)	0 (0)	3 (2)
Joint pain	0 (0)	9 (6)	0 (0)	8 (5)	0 (0)	8 (5)
Muscle pain	0 (0)	26 (17)	0 (0)	31 (20)	0 (0)	19 (12)
Fatigue	0 (0)	28 (18)	0 (0)	25 (16)	0 (0)	28 (18)
Headache	0 (0)	52 (34)	0 (0)	65 (42)	0 (0)	63 (41)
Sweating	0 (0)	7 (5)	1 (1)	5 (3)	0 (0)	7 (5)
Nausea	0 (0)	7 (5)	0 (0)	13 (8)	0 (0)	10 (6)
Local (Injection Site) AEs						
Pain	0 (0)	67 (44)	0 (0)	93 (61)	0 (0)	25 (16)
Bruising	0 (0)	2 (1)	0 (0)	10 (6)	0 (0)	6 (4)
Redness	0 (0)	6 (4)	0 (0)	8 (5)	0 (0)	3 (2)
Soft swelling	0 (0)	6 (4)	1 (1)	8 (5)	0 (0)	4 (3)
Hard swelling (Induration)	0 (0)	0 (0)	0 (0)	7 (5)	0 (0)	1 (1)

STN 125285 PSC01 CSR Table 18

PSC01 also evaluated 3 groups of physical exam parameters: ear, nose and throat; lymph nodes and skin at Day 28, and found few abnormalities occurring in those subjects with no abnormalities at baseline prior to vaccination. These shifts from normal to abnormal occurred at similar rates among the treatment groups and were highest for skin (5-8%) and lower for lymph nodes (2-3%) and for ear, nose and throat (1-3%).

3. Unsolicited Adverse Events

The most frequently reported AEs overall were headache (34 subjects, 7%); pharyngolaryngeal pain (22 subjects, 5%); upper respiratory tract infection (21 subjects, 5%); cough (15 subjects, 3%); and nasal congestion (14 subjects, 3%).

Three subjects had unsolicited AEs that were considered to be severe: infected vaginal mole (infected naevus) in FluBlok 75µg treatment group; convulsion in FluBlok 135µg treatment group, and injury to right knee in FluBlok 135µg treatment group. All three events resolved without sequelae

The most commonly reported unsolicited AEs are summarized in Table 6, below.

Table 6: Unsolicited Adverse Events Occurring in ≥1% of Subjects Days 0-180 (PSC01)

Body System and Preferred Term	Number (%) of Subjects			
	FluBlok 75ug N=151	FluBlok 135ug N=153	Placebo N=154	Overall N=458
Gastrointestinal disorders				
Diarrhea	4 (3)	1 (1)	4 (3)	9 (2)
Nausea	2 (1)	3 (2)	0	5 (1)
General disorders/admin. Site conditions				
Fatigue	2 (1)	2 (1)	3 (2)	7 (2)
Infections and infestations				
Nasopharyngitis	2 (1)	4 (3)	4 (3)	10 (2)
Sinusitis	3 (2)	2 (1)	1 (1)	6 (1)
Upper respiratory tract infection	5 (3)	9 (6)	7 (5)	21 (5)
Musculoskeletal and connective tissue disorders				
Arthralgia	3 (2)	2 (1)	3 (2)	8 (2)
Back pain	4 (3)	1 (1)	3 (2)	8 (2)
Myalgia	3 (2)	1 (1)	5 (3)	9 (2)
Nervous system disorders				
Headache	9 (6)	12 (8)	13 (8)	34 (7)
Psychiatric disorders				
Insomnia	3 (2)	2 (1)	1 (1)	6 (1)
Respiratory, thoracic and mediastinal disorders				
Cough	6 (4)	6 (4)	3 (2)	15 (3)
Nasal congestion	3 (2)	5 (3)	6 (4)	14 (3)
Pharyngolaryngeal pain	7 (5)	7 (5)	8 (5)	22 (5)
Rhinorrhea	2 (1)	1 (1)	4 (3)	7 (2)
Sinus congestion	1 (1)	2 (1)	2 (1)	5 (1)
Skin and subcutaneous tissue disorders				
Hyperhidrosis	2 (1)	1 (1)	2 (1)	5 (1)

STN 125285 PSC01 CSR Table 22

4. Serious Adverse Events (SAEs)

Two SAEs were reported, both in the FluBlok 135µg group:

- Seizure secondary to hypoglycemia (blood glucose 48mg/dL, normal 74-100), resolved without sequelae in a 20 year-old female with history of bulimia, 2 episodes of syncope in the previous year, skull fracture 2 years prior to the event.
- Lobular carcinoma *in situ* (left breast) in a 47 year-old female detected on routine screening mammogram. This subject also experienced syncope during the course of her chemotherapy and found to be hypokalemic (serum potassium 3.1 mmol/L); no recurrence of carcinoma at last follow-up 6 months post-vaccination.

5. Deaths

No deaths were reported during the study.

6. Withdrawals Due to AEs

There were no discontinuations from the study due to AEs.

7. Pregnancies

Three female subjects became pregnant after vaccination with FluBlok. Two pregnancies ended in elective termination and one proceeded normally to full-term, resulting in the live birth of a normal infant.

8. Influenza-infections based upon various criteria:

a. Culture-confirmed, symptomatic influenza infections:

FluBlok 75ug group: 4 (3%)

FluBlok 135µg group: 1 (1%)

Placebo group: 8 (5%)

NOTE: 10/13 isolates genetically similar to A/California/7/04 (H3N2); 3 isolates similar to Type B.

b. Culture-confirmed, CDC influenza-like-illness (ILI):

FluBlok 75ug group: 2 (1%)

FluBlok 135µg group: 0 (0%)

Placebo group: 7 (5%)

c. Laboratory-confirmed influenza (positive culture or ≥4-fold rise HAI antibody titer Day 28-180):

FluBlok 75ug group: 10 (7%)

FluBlok 135µg group: 18 (12%)

Placebo group: 41 (27%)

d. CDC ILI:

FluBlok 75ug group: 14 (9%)

FluBlok 135µg group: 9 (6%)

Placebo group: 20 (13%)

The sponsor reports no particular relationship between antibody titer and risk of influenza.

2.2.3 PSC03

Title:	Comparison of the Immunogenicity, Safety and Reactogenicity of FluBlok®, Trivalent Recombinant Baculovirus-Expressed Hemagglutinin Influenza Vaccine, To a Licensed Egg-Grown Influenza Vaccine (Fluzone) In Ambulatory Elderly Adults
Design:	Phase 3, randomized, controlled, modified double-blinded trial
Population:	870 healthy, medically stable adults ≥65 years of age
Randomization / Stratification/	Randomized at a 1:1 ration into one of two vaccination groups: <ul style="list-style-type: none">• A: FluBlok• B: TIV (Fluzone)
Dose:	<ul style="list-style-type: none">• FluBlok total 45µg rHA (15 ug of each strain)/0.5mL• Fluzone total 45 ug HA (15ug of each strain)/0.5mL
Study Period:	09-October-2006 through 09-July-2007
Date of Report:	03-April-2008
Product:	FluBlok influenza vaccine containing: A/New Caledonia/20/99 (H1N1)-like A/Wisconsin/67/05 (H3N2)-like B/Ohio/01/05 (NOTE: B strain not matched to licensed vaccine, i.e., WHO recommendation) Fluzone licensed seasonal influenza vaccine containing: A/New Caledonia/20/99 (H1N1)-like A/Wisconsin/67/05 (H3N2)-like B/Malaysia/2506/04 WHO recommended seasonal influenza strains for the 2006-2007 season in U.S.
Schedule:	Single dose
Changes to protocol:	<ol style="list-style-type: none">1. Enrollment decreased from planned 1,350 to 870 subjects due to slow enrollment and the time constraint of vaccinating all subjects in a single influenza season.2. Statistical analyses for seroconversion, seroprotection and GMTs were also carried out for subgroups of subjects that were not pre-specified in the SAP. These subgroups included subjects > 75 years of age; subjects with prevaccination HI titers of <1:40; subjects who did and did not receive a licensed influenza vaccine the previous year (i.e., 2005-2006 influenza season); and subjects according to study site. These endpoints are all considered exploratory, and have been noted as such in this report.3. As previously reported in Amendment 0030 to the IND (submitted on January 31, 2007), several GCP violations occurred at a single study site, Site 5; Passport Health, Baltimore, MD, and were identified during a routine site monitoring. These violations included access by blinded study personnel to the randomization code, and improper disposal of Study Vaccine after administration. Protein Sciences proposed to (1) compare the safety and immunogenicity data from this site versus all other sites to assess the similarities and/or differences with respect to primary and secondary endpoints; and (2) include the entire dataset in the final analysis, assuming that data from these comparisons showed no apparent differences that were considered important by the Sponsor or by CBER. The Sponsor did not receive any feedback from CBER concerning this

proposal. The results of the analyses comparing the two strata are presented in Section 16.1.13 of this study report, and, in the Sponsor's judgment, do not show any clinically meaningful differences in results between Site 5 (n=126) and the remaining sites (n=735). Therefore, the analyses presented in this report reflect the entire safety and Evaluable Population datasets.

Major Endpoints

Safety:

1. Frequencies of adverse events (AEs) and serious adverse events (SAEs) solicited in clinic, via memory aids and telephone and/or clinic follow-up, and targeted physical examination.

1° Immunogenicity:

1. Proportion of subjects who seroconvert (either ≥ 4 -fold rise in HI antibody if seropositive at baseline; or titer $\geq 1:40$ if seronegative at baseline [HI titer $< 1:10$] for each of the 3 antigens at 28 days post-vaccination.
2. Geometric mean titers (GMTs) of serum HI antibody against each of the three antigens represented in the vaccine 28 days after vaccination

2° Immunogenicity/ Efficacy:

1. Proportion of subjects in each vaccine group achieving post-vaccination HI antibody titer (Day 28) of $\geq 1:40$ to each vaccine antigen.
2. GMTs, seroconversion rates, and proportions of subjects in each vaccine group with serum HI antibody titers $\geq 1:40$ at end of influenza season (EOIS) visit.
3. Proportion of subjects in each vaccine group who experience culture-positive CDC-ILI and/or culture-positive medically attended acute respiratory illness during the 2006-2007 influenza season.

Exploratory Immunogenicity Endpoints:

Calculated for each for each of the following subgroups:

- Those ≥ 75 years of age
 - Those who received a licensed influenza vaccine the previous year (2005-2006 season)
 - Those with baseline HI antibody titers $< 1:40$
1. Number and proportion of subjects exhibiting a titer of > 40 or greater ("seroprotection rate") on Day 28 and at EOIS
 2. Ratio of Geometric Mean Titers (GMT TIV/GMT FluBlok) on Day 28 and at EOIS
 3. Seroconversion rates at Day 28 and EOIS (as defined by the proportion of subjects with a > 4 -fold rise in HI titer response from baseline to EOIS).

Sample Size:

Demonstration of non-inferiority for seasonal influenza vaccines requires two co-primary endpoints for each viral strain represented in the vaccine (for a total of six co-primary endpoints). These include (1) GMT and (2) Seroconversion rates, and (1) the upper bound of the two-sided 95% CI on the ratio of the GMTs should not exceed 1.5; and (2) the upper bound of the two-sided 95% CI on the difference between the seroconversion rates in the two study groups should not exceed 10%. This requires α for each constraint be equal to .05 (two tailed). Power, however, must be specified to an overall level. Thus, all six individual comparisons must be constructed at a level of .05 (two tailed), for an overall power of 96.34%. Based on historic seroconversion rates and GMTs for FluBlok and TIV, a minimum of 655 subjects per arm would be required to ensure 80% power for the test of non-inferiority of FluBlok to TIV. The trial ultimately enrolled 870 subjects randomized to two arms of the study.

Safety Monitoring

Memory aid:	Solicited systemic events: fever, fatigue, shivering, joint pain, muscle pain, tiredness/lack of energy, headache, sweating, nausea and solicited local events: pain, bruising, redness, soft swelling and hard swelling (induration), monitored Days 0-7 post-vaccination
Clinic visits:	AEs, SAEs, medications, physical exam (on Day 0, otherwise targeted) at Days 0, 28 and End of Influenza Season (EOIS) visit at ~Day 180
Phone calls:	AEs, SAEs, medication at Day 8 CDC-ILI symptoms, flu symptom card review weekly throughout subsequent influenza season (up to 9 months post-vaccination)
Supplemental follow-up visit:	As needed for evaluation of possible influenza including review of CDC-ILI symptoms, targeted H&P, flu symptom card review, concomitant medications, and nasal or throat swab culture for those meeting CDC-ILI criteria.

Protocol PSC03 Demographic and Safety Results

Subject Accounting

Data from 869 (99%) of 870 enrolled subjects were included in safety analyses. Overall, 98% of subjects were reported to have completed the study.

Table 7: Subject Accounting (PSC03)

Disposition	Treatment Number (%)	
	FluBlok	Fluzone
Randomized	436 (100)	434 (100)
Vaccinated	436 (100)	434 (100)
Completed	428 (98)	426 (98)
Discontinued	8 (2)	8 (2)
Due to AE	0	1 (<1)
Lost to Follow-up	0	1 (<1)
Withdrew consent	1 (<1)	2 (<1)
Died	2 (<1)	2 (<1)
Randomized, not vaccinated	0	1 (<1)
Other	5 (1)	1 (<1)
Overseas travel	1 (<1)	0
Moved out of area	3 (<1)	1 (<1)
Protocol violation	1 (<1)	0

STN 125285 PSC03 CSR Table 4

Demographics

Race/ethnicity was overwhelmingly Caucasian (97%, 99%) in both vaccination groups, there were a slightly higher proportions of females (52%, 54%) in the FluBlok and Fluzone groups, respectively. The age distributions were similar between the treatment groups. These data are summarized in Table 8. below.

Table 8: Demographics (PSC03)

Characteristic	Study Treatment	
	FluBlok N=436	Fluzone N=433
Race/Ethnicity [n (%)]		
White/Caucasian	432 (99)	420 (97)
Black/African-American	2 (<1)	7 (2)
Latino/Hispanic	1 (<1)	0
Asian	0	2 (<1)
American Indian/Alaska Native	0	3 (1)
Native Hawaiian/Pacific Islander	0	0
Other	1 (<1)	1 (<1)
Gender		
Male	208 (48)	199 (46)
Female	228 (52)	234 (54)
Age		
Mean (SD)	72.9 (6.66)	73.0 (6.13)
Median	71.0	72.0
Minimum-Maximum	65-92	65-91
STN 125285 PSC03 CSR Table 5		

Safety Results

1. Solicited Adverse Events

The sponsor reports that 47% of FluBlok recipients and 50% of Fluzone recipients reported at least one reactogenicity event. Occurrence of event by severity grade was similar between the vaccination groups. The solicited AEs are summarized in Table 9 and reveal that pain was the most frequent solicited local AE, and tiredness/lack of energy was the most common solicited systemic AE. Aggregate data, i.e., rate of event regardless of grade, are not provided.

Table 9: Solicited Adverse Events Days 0-7, Overall and by Severity Days 0-7 Post-vaccination (PSC03)

	Number (%) of Subjects							
	FluBlok N=436				Fluzone N=433			
Severity Grade*	0	1	2	3	0	1	2	3
No. (%) with ≥ 1 reaction	226(52)	162 (37)	37 (8)	8 (2)	216 (50)	173 (40)	31 (7)	13 (3)
Systemic								
Fever (≥100.4)	1 (<1)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Fatigue	393 (90)	30 (7)	9 (2)	1 (<1)	391 (90)	29 (7)	12 (3)	1 (<1)
Shivering (chills)	417 (96)	13 (3)	2 (<1)	1 (<1)	417 (96)	10 (2)	6 (1)	0 (0)
Joint pain	411 (94)	16 (4)	6 (1)	0 (0)	408 (94)	19 (4)	6 (1)	0 (0)
Muscle pain	401 (92)	26 (6)	5 (1)	1 (<1)	395 (91)	30 (7)	8 (2)	0 (0)
Tiredness, Lack of Energy	368 (84)	54 (12)	10 (2)	1 (<1)	368 (85)	51 (12)	13 (3)	1 (<1)
Headache	387 (89)	42 (10)	4 (1)	0 (0)	392 (91)	33 (8)	8 (2)	0 (0)
Sweating	422 (97)	9 (2)	2 (<1)	0 (0)	426 (98)	6 (1)	1 (<1)	0 (0)
Nausea	414 (95)	15 (3)	4 (1)	0 (0)	418 (97)	11 (3)	3 (1)	1 (<1)
Local (Injection Site)								
Pain	339 (78)	91 (21)	3 (1)	0 (0)	333 (77)	99 (23)	1 (<1)	0 (0)
Bruising	418 (96)	12 (3)	3 (1)	0 (0)	411 (95)	20 (5)	1 (<1)	1 (<1)
Redness	389 (89)	35 (8)	7 (2)	2 (<1)	379 (88)	42 (10)	6 (1)	6 (1)
Soft swelling	400 (92)	21 (5)	10 (2)	2 (<1)	392 (91)	34 (8)	3 (1)	4 (1)
Hard swelling (Induration)	420 (96)	8 (2)	2 (<1)	3 (1)	416 (96)	16 (4)	0 (0)	1 (<1)
NOTE: Sum of numbers within row may not add up to total safety population within respective vaccine group due to missing values. *Fever: 0 = any; 1 = ≥100.4F – 101.1F (≥38C–38.4C); 2 = ≥101.2F–102.1F (≥38.5C–38.9C); 3 = ≥102.2F(≥39C); Injection site: 0 = <1cm; 1 = ≥1cm and <2cm, 2 = ≥2cm and <5cm; 3 = ≥5cm; Systemic AEs: 0 = none; 1 = experienced but didn't interfere with activities; 2 = prevented a part of activities; 3 = prevented most /all activities, or had to see a doctor for prescription medicine								
STN 125285 PSC03 CSR Table 20								

3. Unsolicited Adverse Events

Unsolicited AEs were termed “treatment emergent AEs” and included those ascertained at clinic visits, telephone contacts as well as solicited events that persisted beyond Day 7 or first reported after the Study Days 0-7.

A similar number of subjects reported as least on unsolicited AE (21% of FluBlok recipients; 20% of Fluzone recipients). The most frequently reported MedDRA System Organ Class reported after the immediate 0-7 Day post-vaccination period, i.e., during Days 8-28, was “Infections and infestations (4% FluBlok, 5% Fluzone).

The most commonly reported ($\geq 1\%$ of the overall population) unsolicited AEs are summarized in Table 10, below.

Table 10: Unsolicited Adverse Events Occurring in $\geq 1\%$ of Overall Study Population, Onset Days 0-28 by MedDRA Body System (System Organ Class) and Preferred Term and by Vaccination Group (PSC03)

Timeframe	Number (%) of Subjects							
	Days 0-28		Day of Vaccination		Days 1 to 7		Days 8 to 28	
	TIV	FluBlok	TIV	FluBlok	TIV	FluBlok	TIV	FluBlok
Body System								
Preferred Term								
Number with ≥ 1 AE	85 (20)	90 (21)	6 (1)	14 (3)	36 (8)	43 (10)	54 (12)	47 (11)
Gastrointestinal signs and symptoms	10 (2)	10 (2)	---	---	---	---	5 (1)	8 (2)
Diarrhea	3 (1)	5 (1)	---	---	---	---	2 (<1)	5 (1)
Nausea	3 (1)	1 (<1)	---	---	---	---	---	---
General disorders and administration site conditions	12 (3)	19 (4)	5 (1)	14 (3)	8 (2)	17 (4)	---	---
Injection site erythema/redness	1 (<1)	10 (2)	1 (<1)	9 (2)	1 (<1)	10 (2)	---	---
Injection site hemorrhage	3 (1)	6 (1)	1 (<1)	4 (1)	2 (<1)	6 (1)	---	---
Injection site swelling	1 (<1)	5 (1)	---	---	1 (<1)	5 (1)	---	---
Infections and infestations	25 (6)	28 (6)	---	---	---	---	18 (4)	22 (5)
Nasopharyngitis	8 (2)	4 (1)	---	---	---	---	6 (1)	3 (1)
Sinusitis	1 (<1)	6 (1)	---	---	---	---	0	5 (1)
Tooth abscess	4 (1)	1 (<1)	---	---	---	---	3 (1)	1 (<1)
Upper respiratory tract infections	3 (1)	5 (1)	---	---	---	---	2 (<1)	5 (1)
Musculoskeletal and connective tissue disorders	10 (2)	11 (3)	---	---	5 (1)	9 (2)	---	---
Back pain	3 (1)	1 (<1)	---	---	---	---	---	---
Pain in extremity	2 (<1)	3 (1)	---	---	1 (<1)	3 (1)	---	---
Nervous system disorders	9 (2)	5 (1)	1 (<1)	0	---	---	---	---
Headache	4 (1)	2 (<1)	---	---	---	---	---	---
Respiratory, thoracic and mediastinal disorders	19 (4)	11 (3)	---	---	6 (1)	5 (1)	13 (3)	5 (1)
Cough	8 (2)	3 (1)	---	---	3 (1)	3 (1)	5 (1)	0
Nasal congestion	3 (1)	3 (1)	---	---	---	---	3 (1)	1 (<1)
Pharyngolaryngeal pain (lower level term, not preferred term)	5 (1)	2 (<1)	---	---	---	---	4 (1)	2 (<1)
Rhinorrhoea	3 (1)	2 (<1)	---	---	---	---	---	---

Subject experiencing multiple adverse events were counted once per body system and once per preferred term.
STN 125285 PSC03 CSR Table 22

4. Serious Adverse Events (SAEs)

Serious adverse events were reported in 8% both vaccine groups: 36 of 436 FluBlok recipients and 34 of 433 Fluzone recipients and are summarized in Table 11. Within each vaccine group, two SAEs were reported as fatal and are described in Section 5, below.

Table 11: Serious Adverse Events (SAE) by Body System / Preferred Term – Safety Population (PSC03)

	Fluzone (N= 433)	FluBlok (N=436)
Body System	Number (%)	Number (%)
Preferred Term		
Total Subjects with SAE	34 (8%)	36 (8%)
Blood and lymphatic system disorders	0	1 (<1%)
Coagulopathy	0	1 (<1%)
Cardiac disorders	8 (2)	8 (2%)
Acute myocardial infarction	1 (<1)	0
Angina pectoris	1 (<1)	0
Angina unstable	0	1 (<1%)
Atrial fibrillation	1 (<1)	2 (<1%)
Atrial flutter	1 (<1)	0
Cardiac arrest	1 (<1)	0
Cardiac failure congestive	0	1 (<1)
Coronary artery disease	2 (<1)	2 (<1)
Myocardial infarction	1 (<1)	2 (<1)
Gastrointestinal disorders	3 (1)	5 (1)
Barrett's oesophagus	0	1 (<1)
Diarrhoea	1 (<1)	0
Intestinal perforation	0	1 (<1)
Lower gastrointestinal haemorrhage	0	1 (<1)
Pancreatitis	2 (<1)	1 (<1)
Volvulus of bowel	0	1 (<1)
General disorders and administration site conditions	0	1 (<1)
Adverse drug reaction	0	1 (<1)
Hepatobiliary disorders	2 (<1)	1 (<1)
Cholecystitis	1 (<1)	0
Cholecystitis acute	0	1 (<1)
Cholelithiasis	1 (<1)	0
Infections and infestations	5 (1)	4 (1)
Appendicitis	0	1 (<1)
Bronchitis acute	0	1 (<1)
Cellulitis	1 (<1)	0
Diverticulitis	0	1 (<1)
Gastroenteritis	0	1 (<1)
Gastroenteritis viral	1 (<1)	0
Pneumonia	2 (<1)	0
Septic shock	1 (<1)	0
Injury, poisoning and procedural complications	4 (1)	2 (<1)
Device malfunction	1 (<1)	0
Haemothorax	1 (<1)	0
Meniscus lesion	0	1 (<1)
Pelvic fracture	1 (<1)	0
Radius fracture	1 (<1)	0

	Fluzone (N= 433)	FluBlok (N=436)
Body System	Number (%)	Number (%)
Preferred Term		
Subdural haematoma	1 (<1)	0
Traumatic brain injury	0	1 (<1)
Metabolism and nutrition disorders	3 (1)	0
Dehydration	2 (<1)	0
Hypokalaemia	1 (<1)	0
Musculoskeletal and connective tissue disorders	3 (1)	3 (1)
Lumbar spinal stenosis	0	1 (<1)
Osteoarthritis	3 (1)	2 (<1)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	4 (1)	4 (1)
Adenocarcinoma	0	1 (<1)
Benign laryngeal neoplasm	1 (<1)	0
Breast cancer metastatic	0	1 (<1)
Colon adenoma	0	1 (<1)
Prostate cancer	2 (<1)	0
Prostate cancer stage II	0	1 (<1)
Renal cell carcinoma stage unspecified	1 (<1)	0
Nervous system disorders	5 (1)	7 (2)
Brain stem haemorrhage	0	1 (<1)
Carotid artery stenosis	2 (<1)	0
Cerebral haemorrhage	1 (<1)	0
Convulsion	0	2 (<1)
Dizziness	0	1 (<1)
Global amnesia	1 (<1)	0
Syncope	0	1 (<1)
Syncope vasovagal	0	1 (<1)
Transient ischaemic attack	1 (<1)	1 (<1)
Psychiatric disorders	1 (<1)	1 (<1)
Alcohol withdrawal syndrome	1 (<1)	0
Anxiety	0	1 (<1)
Renal and urinary disorders	0	2 (<1)
Renal failure acute	0	2 (<1)
Reproductive system and breast disorders	0	1 (<1)
Benign prostatic hyperplasia	0	1 (<1)
Respiratory, thoracic and mediastinal disorders	2 (<1)	2 (<1)
Dyspnoea	1 (<1)	0
Pulmonary embolism	1 (<1)	2 (<1)
Surgical and medical procedures	1 (<1)	0
Wound drainage	1 (<1)	0
Vascular disorders	0	3 (1)
Aortic aneurysm	0	1 (<1)
Peripheral artery aneurysm	0	2 (<1)
Subjects experiencing multiple SAEs were counted once per body system and once per preferred term		
STN 125285 PSC03 CSR Table 25		

5. Deaths

Four deaths were reported among study participant, two in the FluBlok group and two in the Fluzone group are summarized in Table 12, below. The narrative summaries provided by the sponsor are included in Appendix I at the end of this review.

Table 12: Summary of Deaths Reported in PSC0

Vaccine Group	Adverse Event Leading to Death	Demographics	Time from Vaccination to Onset of Adverse Event
FluBlok	Pontine hemorrhage	89-year old Caucasian female	92 days
FluBlok	Perforated viscus with secondary peritonitis	80-year old Caucasian female	4 days
Fluzone	Cardiac Arrest	73-year old Caucasian male	177 days
Fluzone	Coronary Artery Disease	69-year old Caucasian male	4 days

STN 125285 PSC03 CSR

6. Withdrawals Due to Adverse Events

One Fluzone recipient who suffered a cerebral hemorrhage is reported to have withdrawn from the study due to an AE and no FluBlok recipients were reported to have withdrawn from the study due to an AE. (STN 125285 PSC03 CSR Table 14.3.1.18)

7. Pregnancies

No pregnancies occurred in this study of older adults.

2.2.4 PSC04

NOTE: PSC04 is the major study supporting licensure of FluBlok®, enrolling 2344 subjects receiving FluBlok® and 2304 subjects receiving saline placebo to evaluate safety and immunogenicity. The original BLA includes an interim study report including data through 28 days post-vaccination, submitted for Accelerated Approval. The final study report including clinical endpoints and 6-month safety follow-up was proposed to be submitted as a post-marketing commitment, following licensure.

Title: Evaluation of the Immunogenicity, Safety, Reactogenicity, Efficacy, Effectiveness and Consistency of FluBlok® Trivalent Recombinant Baculovirus-Expressed Hemagglutinin Influenza Vaccine in Healthy Adults Age 18 to 49 Years

Design: Phase 3, randomized, prospective, modified double-blinded
Population: 4648 healthy adults 18-49 years of age

Randomization / Stratification/ Randomized at a 1:1 ratio into one of two groups:

- FluBlok (further stratified 1:1:1 to one of three lots, A, B, C)
- Placebo (normal saline for injection (USP))

Dose: • FluBlok 135µg rHA total (45 ug of each of three strains)/0.5 mL intramuscularly
• Placebo (normal saline for injection, USP)/0.5 mL intramuscularly

Study Period: 15-September-2007 through 21-November-2007 (Interim Report through Day 28)
15-September-2007 through 28-MAY-2009 (Final Study Report)

Date of Report: 04-April-2008 Interim Study Report
06-April-2009 Final Study Report

Product: FluBlok seasonal influenza vaccine containing: A/Solomon Islands/3/2006 (H1N1); A/Wisconsin/67/2005 (H3N2) and B/Malaysia/2506/2004 (B)

WHO recommended seasonal influenza strains for the 2007-2008 season in U.S.

Placebo: normal saline for injection (USP)

Schedule: Single dose

Changes to protocol: 1. Site 13, Los Angeles, CA [Investigator = Hazan], one of five sites chosen to participate in the immunogenicity subset began vaccinating individuals (N=37) before receiving the study randomization scheme and instead used a plan initiated by the investigator, allocating subjects into four equal groups (Lot A, Lot B, Lot C and Placebo) rather than two Groups (FluBlok and Placebo [to be followed by sub-randomization of the FluBlok group into the three Lot subgroups]). This is why, within the overall Safety and Evaluable populations, the FluBlok group has ~40 more subjects than the Placebo group (see Section 10 of Clinical Study Report). The Sponsor has argued that the difference in randomization procedure has no impact, because subjects were randomly allocated to the treatment arms, such that comparison of lots and treatment groups will remain unbiased within the site. Appendix 16.1.13, provides a post-hoc immunogenicity analysis which revealed very similar results at Site 13 in comparison to the other four sites. NOTE: The above is not a change to the protocol but an intentional protocol violation on the part of the clinical investigator.

2. Because of the failed lot-to-lot consistency comparison for the H3 antigen (see Section 11.1 below), seroconversion rates, seroprotection rates and adverse events were calculated individually for each of the three lots (A, B and C) and then compared. Also, exploratory analyses were conducted in which seroconversion and seroprotection rates (with 95% CI) were calculated for the following subpopulations: (1) subjects with baseline (Day 0) HAI titers of <1:40; and (2) subjects who were and who were not vaccinated with TIV the previous year (2006-2007 influenza season), and additional exploratory efficacy analyses were conducted over various time periods within the study.

Safety endpoints: 1. Frequency of solicited local and systemic reactions (reactogenicity events) in the 7 days following vaccination, as noted on the subject memory aid and collected by telephone interview 8-10 days postvaccination.

2. Frequency of adverse events that occurred in the 28-day period following vaccination as assessed on the Day 28 visit or phone call. Serious adverse events were data collected through December 14, 2007 when the database was locked for the interim analysis.

1^o immunogenicity endpoint:

The 2-sided 95% CI for each strain contained within FluBlok for the ratio of post-vaccination GMTs for Lot A vs. B, Lot A vs. C and Lot B vs. C should entirely be within 0.67 to 1.5.

2^o immunogenicity endpoints:

For each strain contained within FluBlok, the immune response will meet or exceed the following criteria:

1. By Day 28, a post-vaccination HAI antibody titer of $\geq 1:40$ in subjects with undetectable baseline antibody or a ≥ 4 -fold rise in antibody in subjects with a baseline titer of $\geq 1:10$, with the achievement of post-vaccination titer of $\geq 1:40$. The lower bound of the 2-sided 95% CI of the seroconversion rate must meet or exceed 40%.

2. By Day 28, a post-vaccination HAI antibody titer of $>1:40$ (seroprotection level). The lower bound of the 2-sided 95% CI of the seroprotection level must meet or exceed 70%.

1^o efficacy
endpoint:

Cell-culture confirmed CDC-ILI antigenically resembling a vaccine strain

2^o efficacy
endpoint:

Cell-culture confirmed respiratory illness, not necessarily CDC-ILI

Exploratory efficacy
endpoints:

1. Cell-culture confirmed CDC-ILI with any influenza virus
2. CDC-ILI, regardless of culture confirmation

Sample Size:

A sample size of 150 subjects per lot was calculated to be sufficient to establish clinical lot consistency using an overall $\alpha = .05$ and individual test power of 97.55% and thus overall power of at least 80%. No justification is provided for the overall study sample size.

Safety Monitoring

Memory Aid:

Solicited local events (pain, bruising, measured redness, measured swelling) and solicited systemic events (fever ($>100.4^{\circ}\text{F}$), fatigue/lack of energy, shivering (chills), joint pain, muscle pain, headache, nausea) Days 0-7 post-vaccination

Clinic visits:

Day 0: History, targeted physical and vaccination Day 0
Immunogenicity subset returned for blood samples, history and if indicated, a targeted physical exam at Day 28
Day 0 – 180: Nasopharyngeal culture, illness evaluations for flu symptom score ≥ 2 (symptom card) or if advised at phone follow-up Day 0 - 180

Phone calls:

Day 8-10: Follow-up for solicited AEs (as recorded in Memory Aid)

Day 28: Follow-up for AEs, change in health status, concomitant medications (if not in immunogenicity subset who were seen in clinic)

Weekly: Surveillance for influenza during influenza season, SAEs, significant changes in health status. Signs/symptoms of influenza infection (recorded at home on flu symptom card) through approximately Day 180

End of influenza season (EOIS): Follow-up for SAEs, concomitant medications and review of Flu Symptom Card

Flu Symptom
Card:

Subjects to call study site for influenza symptoms score ≥ 2 . At the time of such a call and return to the clinic within 24-72 hours for further evaluation including history, physical examination, Nasal swab/throat culture samples will be collected for testing. Any SAEs and changes in health status will be recorded and followed to resolution or stabilization and changes in health status recorded. If the subject is too ill to travel the site may send a traveling nurse to the subject's home to obtain a culture sample.

Protocol PSC04 Study Results

Subject Accounting

Only 88% of study subjects completed through Day 28 and the final clinical study report (CRS) makes no mention of how many subjects completed the entire study. Subject accounting for this study is summarized in Table 13.

Table 13: Subject Accounting (PSC04)

Disposition	Treatment		
	FluBlok N=2344*	Placebo N=2304	Overall N = 4648
	n (%)	n (%)	n (%)
Randomized and vaccinated	2344 (100)	2304 (100)	4648 (100)
Immunogenicity subset	391 (17)	0 (0)	391 (8)
Completed through Day 28	2249 (96) ¹ 2049 (87) ²	2211 (96) ¹ 2022 (88) ²	4460 (96) ¹ page 52 sect 10.1 4272 (92) ¹ page 8, synopsis 4071 (88) ²
Discontinued as of Day 28	95 (4) ¹ 295 (13) ²	93 (4) ¹ 282 (12) ²	188 (4) ¹ 577 (12) ²
Due to AE	0 (0) ¹ 3 (<1) ²	0 (0) ¹ 3 (<1) ²	0 (0) ¹ 6 (<1) ²
Lost to Follow-up	88 (4) ¹ 260 (11)	85 (4) ¹ 251 (11) ²	175 (4) ¹ 511 (11) ²
Withdrew consent	7 (<1) ¹ 22 (1)	2 (<1) ¹ 14 (1) ²	9 (<1) ¹ 36 (1) ²
Died	0 (0) ¹ 1 (<1) ²	0 (0) ¹ 1 (<1) ²	0 (0) ¹ 2 (<1) ²
Other Reasons (e.g., move, exclusion criteria, noncompliance, discontinuation per investigator)	9 (<1) ²	13 (1) ²	22 (<1) ²
Moved	0 (0) ¹	2 (<1) ¹	2 (<1) ¹
Received another dose of influenza elsewhere	0 (0) ¹	1 (<1) ¹	1 (<1) ¹
Previously undisclosed exclusion criteria	0 (0) ¹	1 (<1) ¹	1 (<1) ¹
Noncompliance with protocol	0 (0) ¹	1 (<1) ¹	1 (<1) ¹
Discontinued at discretion of investigator	0 (0) ¹	1 (<1) ¹	1 (<1) ¹
*See description of intentional protocol violation contained in changes to protocol section of the review of this study. 1 = reported in interim study report, original BLA 2 = reported in final study report, BLA amendment 12 STN 125285 PSC04 Interim CSR Table 4 and Section 10.1 Disposition of Subjects; Final CSR Table 4			

Demographics

Race/ethnicity was predominantly Caucasian in all groups, and racial/ethnic representation was similar between vaccine groups. Slightly higher proportions of females were enrolled in both vaccine groups (59% in FluBlok and 55% in Placebo). Demographic data are summarized in Table 14, below.

Table 14: Demographics (PSC04)

Characteristic	Study Treatment		
	FluBlok N=2344	Placebo N=2304	Overall N=4648
Race/Ethnicity [n (%)]			
White/Caucasian	1570 (67)	256 (65)	1530 (66)
Black/African-American	430 (18)	73 (19)	447 (19)
Latino/Hispanic	250 (11)	36 (9)	239 (10)
Asian	62 (3)	21 (5)	52 (2)
American Indian/Alaska Native	7 (<1)	1 (<1)	9 (<1)
Native Hawaiian/Pacific Islander	6 (<1)	1 (<1)	8 (<1)
Other	19 (1)	3 (1)	19 (1)
Gender [n(%)]			
Male	953 (41)	176 (45)	955 (41)
Female	1391 (59)	215 (55)	1349 (59)
Age (years)			
Mean (SD)	32.5 (9.3)	32.9 (9.98)	32.5 (9.17)
Median	32	31	32
Minimum-Maximum	18-55	18-49	18-50
STN 125285 PSC01 Interim CSR Table 5, final CSR Table 6			

Safety Results

1. Solicited Adverse Events

At least 1 systemic or local AE was reported by 1198 (53%) FluBlok recipients and by 726 (32%) Placebo recipients. The most frequent AE reported was injection site pain (37% and 8%, FluBlok and Placebo, respectively), headache (15% in each group) and fatigue (14% in each group). Severe fever ($\geq 102.2^{\circ}\text{F}$) was reported in 4 FluBlok recipients and 1 Placebo recipient, moderate fever ($\geq 101.2^{\circ}\text{F}$ through $< 102.2^{\circ}\text{F}$) in 5 FluBlok and 6 Placebo recipients. Adverse events were collected using a Memory Aid (Day 0 through Day 8) and phone call (at Days 8-10). Solicited AEs are summarized in Table 15.

Table 15: Solicited Adverse Events Days 0-7, Overall and Grade 3 (Maximal) Severity (PSC04)

Type of Reaction	Number (%) of Subjects			
	FluBlok 135ug N=2344		Placebo (normal saline) N=2304	
	Grade 3	Grades 1-3	Grade 3	Grades 1-3
With ≥ 1 solicited AE	34 (1)	1198 (51)	30 (1)	726 (32)
Systemic AEs				
Fever ($> 100.4^{\circ}\text{F}$)	4 (<1)	17 (1)	1 (<1)	12 (1)
Fatigue, Lack of Energy	12 (<1)	340 (15)	11 (<1)	333 (14)
Shivering (chills)	6 (<1)	70 (3)	4 (<1)	71 (3)
Joint pain	6 (<1)	89 (4)	4 (<1)	83 (4)
Muscle pain	6 (<1)	239 (10)	8 (<1)	154 (7)
Headache	15 (<1)	349 (15)	13 (<1)	354 (15)
Nausea	6 (<1)	129 (6)	10 (<1)	109 (5)
Local (Injection Site) AEs				
Pain	2 (<1)	851 (36)	1 (<1)	181 (8)
Bruising	1 (<1)	75 (3)	1 (<1)	58 (3)
Measured Redness	4 (<1)	91 (4)	1 (<1)	47 (2)
Measured Swelling	6 (<1)	77 (3)	2 (<1)	42 (1.8)
Note: Table does not include missing values - number in each row may not add up to total number of subjects. Redness or swelling: Grade 0: < 10 mm, Grade 1: ≥ 10 mm - < 20 mm, Grade 2: ≥ 20 mm - < 50 mm, Grade 3: ≥ 50 mm. Symptoms: Grade 0: not at all; Grade 1: Didn't interfere with activities; Grade 2: Prevent part of activities; Grade 3: Prevented most/all activities, or had to see a doctor for prescription medicine. Fever: 1=Mild ($\geq 100.4^{\circ}$ to $< 101.1^{\circ}\text{F}$); 2=Moderate ($\geq 101.2^{\circ}\text{F}$ to $< 102.2^{\circ}\text{F}$); 3=Severe ($\geq 102.2^{\circ}\text{F}$) Subjects with multiple symptoms in the same category were counted once per category using the symptom with the maximum grade STN 125285 PSC04 interim CSR Table 21, final CSR Table 27				

3. Unsolicited Adverse Events

At the Preferred Term level, cough was the most frequently reported unsolicited AE in FluBlok recipient (48 [2%] subjects versus 37 [2%] in placebo), whereas pharyngolaryngeal pain was the most frequently reported unsolicited AE in the placebo group (49 [2%] subjects versus 42 [2%] in FluBlok recipients). Other frequently reported AEs, by treatment group, were as follows: For the FluBlok group: nasal congestion (37 subjects, 2%), headache (35 subjects, 2%) and rhinorrhea (30 subjects, 1%); and for the Placebo group: headache (43 subjects, 2%) nasal congestion (31 subjects, 1%) and rhinorrhea (27 subjects, 1%). The most commonly reported unsolicited AEs are summarized in Table 16, below.

Table 16: Unsolicited Adverse Events Occurring in $\geq 1\%$ of Subjects Days 0-28 (PSC04)

	Number (%) of Subjects	
	FluBlok N=2344	Placebo N=2304
Number of Subjects With At Least One Adverse Event	396 (17)	382 (17)
Body System		
Preferred Term		
Gastrointestinal disorders	48 (2)	47 (2)
Diarrhea	13 (1)	14 (1)
Nausea	13 (1)	13 (1)
General disorders and administration site conditions	45 (2)	47 (2)
Fatigue	13 (1)	22 (1)
Pyrexia	16 (1)	9 (<1)
Infections and infestations	101 (4)	103 (4)
Nasopharyngitis	15 (1)	23 (1)
Sinusitis	12 (1)	13 (1)
Upper respiratory tract infection	18 (1)	24 (1)
Injury, poisoning & procedural complications	30 (1)	18 (1)
Musculoskeletal and connective tissue disorders	30 (1)	36 (2)
Nervous system disorders	58 (2)	57 (2)
Headache	35 (1)	43 (2)
Pregnancy, puerperium and perinatal conditions	18 (1)	17 (1)
Pregnancy	18 (1)	16 (1)
Psychiatric disorders	13 (1)	11 (<1)
Respiratory, thoracic and mediastinal disorders	130 (6)	116 (5)
Cough	48 (2)	37 (2)
Nasal congestion	37 (2)	31 (1)
Pharyngolaryngeal pain	42 (2)	49 (2)
Rhinorrhea	30 (1)	27 (1)
Skin and subcutaneous tissue disorder	16 (1)	16 (1)
Subject experiencing multiple adverse events were counted once per body system and once per preferred term.		
STN 125285 PSC04 final CSR Table 30		

4. Serious Adverse Events (SAEs)

Forty-one SAEs were reported in 30 FluBlok recipients and forty-four SAEs were reported in thirty-four placebo recipients and are summarized in Table 17. Two deaths were reported (see section #10, below). Only two SAEs, liposarcoma in a FluBlok recipient and breast cancer in a placebo recipient were ongoing at the end of the study, the remaining SAEs were reported as resolved. Adverse events related to pregnancy are further described in Section 8, below.

Table 17: Serious Adverse Events Reported (PSC04)

FluBlok Group	Placebo Group
Pericardial effusion	SAE
Pulmonary embolism (death)	Death due to MVA
Liposarcoma	Breast Cancer
Appendicitis	Non-ST elevation myocardial infarction
Viral hepatitis	Depression (2 episodes)
Symptomatic cholelithiasis	Infectious mononucleosis; strep. pharyngitis; dehydration
Attempted suicide, angina, persistent sinus tachycardia	Abscess left tonsil
Tonsillitis	Inflammatory bowel disease
Herniated cervical disc	Crohn's disease
Small bowel obstruction	Supraventricular tachycardia
Suicide attempt	Abdominal pain of unknown etiology
Worsening uterine fibroids	Worsening depression; suicide attempt by overdose
Worsening chronic low back pain	Rathke's cleft cyst; head trauma
Bilateral acetabular & bilateral open femur fractures	Head trauma
Chest pain, non-cardiac origin	Kidney infection; kidney stone
Right first metacarpal fracture	Swelling right lymph node inguinal
Uterine fibroids, adnexal mass	Perianal abscess
Left knee, torn ACL	Herniated nucleus pulposus L-4-5, L5-S1 w/ radiculopathy
Abdominal pain; right thigh numbness	Appendicitis
Assault injury	Atypical chest pain
Recurrent iron-deficiency anemia	Pneumonia
Hyperemesis	Suicidal ideation
Right tibial pylon [plateau?] fracture, right fibular fraction	Post-op infection
Adjustment disorder/bipolar disease	Dysmenorrhea; dyspareunia; metrorrhagia
Avascular necrosis, left femoral head	Appendicitis
Abnormal uterine bleeding	Herniated disk
Ovarian cysts; dysmenorrhea; menorrhagia, bladder prolapse	Ectopic pregnancy
Dyssynchronous endometrium	Cellulitis right groin/left knee
Right side acute pyelonephritis	Pyelonephritis infection
Dysfunctional uterine bleed	Biliary colic
	Recurrent abscesses w/ Staph. aureus, not methacillin resistant
	Pregnancy-induced hypertension
	Hyperosmolar non-ketotic hyperglycemia
	Subhyaloid hemorrhage
	Left facial cellulitis
	Headache, dehydration
	Depression

STN 125285 PSC04 Final CSR Table 33

6. Deaths

Two deaths were reported during the study: one FluBlok recipient due to a pulmonary embolism and one placebo recipient due to injuries sustained in a motor vehicle accident.

7. Withdrawals Due to AEs

Nine subjects discontinued due to an AE, not including the two deaths that occurred during the study. The AE's associated with the discontinuations included a subject with a pericardial effusion and four subjects with pregnancy in the FluBlok group, and one subject with multiple fracture and 3 subjects with pregnancy in the placebo group.

8. Pregnancies

Thirty-seven pregnancies were reported in the 2740 female subjects (1%). There were 20 pregnancies in the FluBlok group, 15 with complete follow-up. A summary of these events and associated complications are summarized in Table 18.

Table 18: Pregnancies Reported Through End of Study (PSC04)

Age	Live Birth?	Complications or AEs
FluBlok Recipients		
25	Y	None
35	Y	None
25	Y	None
21	Y	None
29	Y	None
24	Y	None
18	Y	Hyperemesis (SAE)
19	Y	None
35	Y	None
23	Y	None
23	Y	Pulmonary embolism
23	Y	None
24	N	Miscarriage
33	N	Staph. infection
18	N	None
25	Unknown	None
20	Unknown	None
23	Unknown	Unknown
33	Unknown	Unknown
20	Unknown	Unknown
Placebo Recipients		
30	Y	None
30	Y	None
26	Y	Kidney stones/infection (SAE)
18	Y	None
24	Y	None
25	Y	Appendicitis (SAE)
26	Y	None
25	Y	None
30	Y	Pregnancy-induced hypertension
22	Y	None
24	Y	None
36	N	Miscarriage
27	N	Ectopic pregnancy (SAE)
27	Termination	None
23	Termination	None
23	Unknown	None
26	Unknown	None

STN 125285 PSC04 Final CSR Table 33

2.2.5 Study PSC06

Title: Evaluation of the Safety and Reactogenicity of FluBlok®, Trivalent Recombinant Baculovirus-Expressed Hemagglutinin Influenza Vaccine, and Comparison of the Immunogenicity, Efficacy and Effectiveness of FluBlok® to a Licensed Egg-Grown Influenza Vaccine in Adults Aged 50 to 64

Design: Modified double-blind, randomized, active-controlled, Phase III multi-center clinical trial.

Population: Healthy, medically stable adults 50 to 64 years of age

Randomization/

Stratification: 602 subjects were randomized at a 1:1 ratio to FluBlok or Fluzone.

Study Period: 25-SEP-2007 through 19-DEC-2007

Report Date: 01-Apr-2008 (interim report)

Vaccines: FluBlok (total 135µg rHA, 45ug rHA/strain) or Fluzone® (total 45µg HA, 15 ug HA/strain)
2007-2008 seasonal influenza strains: A/Solomon Islands/03/06 (H1N1)
A/Wisconsin/67/05 (H3N2)
B/Malaysia/2506/04

Schedule: Single 0.5 mL dose

Changes to the protocol: None

Primary Safety Endpoint:

Frequency of solicited AEs, unsolicited AEs and SAEs

Primary Immunogenicity Endpoints:

1. Seroprotection rate: Proportion of subjects with HI antibody titer ≥ 40 for each to the three vaccine antigens at Day 28 postvaccination (CBER 2007 Guidance)
2. Seroconversion rate: Proportion of subjects with four-fold rise if seropositive at baseline (HI titer ≥ 110) or attainment of a titer ≥ 140 if seronegative at baseline (HI titer < 110) against each of the three vaccine antigens at Day 28 postvaccination (CBER 2007 Guidance)

Secondary Efficacy/Effectiveness Endpoints:

1. The upper bound of the two-sided 95% CI on the GMT ratio (US licensed vaccine/FluBlok) should not exceed 1.5 (CBER Guidance)
2. The upper bound of the two-sided 95% CI on the differences in seroconversion rates (CBER Guidance)
3. (Seroconversion US licensed vaccine – Seroconversion FluBlok) should not exceed 10%
4. Proportion of subjects with cell-culture-confirmed CDC-ILI (vaccine strain)
5. Proportion of subjects with cell-culture-confirmed respiratory illness with isolation of vaccine strain

Exploratory Endpoints:

1. CDC-ILI with positive culture for any influenza virus strain
2. CDC-ILI regardless of culture results

Sample Size:

Chosen to provide adequate power to demonstrate immunogenicity (CBER's May 2007 Seasonal Influenza Guidance recommendations) using Farrington Manning Likelihood Score Test for proportions.

Safety Monitoring:

- Solicited AEs captured via a phone call between Day 8 -10.
- Unsolicited AEs and SAEs captured at 2nd clinic visit at Day 28.
- ILI monitored by symptom card at bi-weekly phone follow-up for 6 months postvaccination, during the influenza season.
- Possible influenza monitored by culture of nasal swabs/throat swabs in those with a Flu Symptom score ≥ 2 , including those who met CDC-ILI definition (fever and sore throat/cough, a respiratory and systemic symptom or fever and a systemic symptom)
- Final safety follow-up by telephone call at end of influenza season to review Flu Symptom Card and to record SAEs, concomitant medications and any changes in the subject's health status.
- SAEs identified from Day 0 through end of influenza season were to be followed to resolution or stabilization.

Protocol 006 Study Results

Subject Accounting

All randomized subjects are included in the safety analysis cohort as shown in Table 19.

Table 19: Subject Accounting (PSC06)

	FluBlok	Fluzone Group
Enrolled	300	302
Safety Cohort	300	302
Completed Active Phase	299	302

STN125285/OS: PSC06 Interim Report, Section 10.1 Disposition of Subjects

Demographics

Demographic data are summarized in Table 20, below. There were no notable differences in demographic characteristics between the two treatment groups. The majority of subjects were white (71%) and female (63%). The mean age of all subjects was 55.8 years (range: 50 to 64 years). Ten percent of the women were of child-bearing potential based on current menstrual history.

Table 20: Subject Demographics and Baseline Characteristics – Safety Population (PSC06)

		FluBlok (n=300)	FLUZONE (n=302)	Overall (n=602)
Race/Ethnicity (%)	White/Caucasian	218 (73)	211 (70)	429 (71)
	Black/African-American	12 (4)	9 (3)	21 (3)
	Latino/Hispanic	23 (8)	29 (10)	52 (9)
	Asian	35 (12)	37 (12)	72 (12)
	Native Hawaiian/Pacific Islander	1 (<1)	2 (<1)	3 (<1)
	Other	11 (4)	14 (5)	25 (4)
Gender (%)	Male	113 (38)	110 (36)	223 (37)
	Female	187 (62)	192 (64)	379 (63)
Age in years	Mean (SD)	55.9 (3.71)	55.7 (3.64)	55.8 (3.67)
	Median	56	55	56
	Minimum-Maximum	50-64	50-64	50-64

125285/OS PSC06 InterimRpt2008 Table 3

Safety Results for PSC006

Safety Population: All randomized subjects who received any dose of study medication.
The Safety Population was used for all safety analyses.

Solicited Adverse Events (AEs)

Reactogenicity events during Days 0-7 were reported at similar rates, 68% of FluBlok recipients and 72% of FLUZONE (TIV) recipients. The most frequently reported reactogenicity event was injection site pain (51% for FluBlok vs. 55% for FLUZONE (TIV)) followed by headache (20% for FluBlok vs. 21% for FLUZONE (TIV)). A single case of mild fever was noted in the FluBlok group. These events are summarized in Table 21. Only 3% in each group reported solicited AEs with Grade 3 severity.

Table 21: Incidence of Solicited Adverse Events Days 0 - 7 Postvaccination (PSC06)

		FluBlok N=300	Fluzone N=302	Overall N=602
		N (%)	N (%)	N (%)
≥ 1 solicited adverse event		203 (68%)	217 (72%)	420 (70%)
Fever	Mild (≥100.4 - 101.1°F)	1 (<1)	0	1 (<1)
	Moderate (≥101.2 - 102.1°F)	0	0	0
	Severe (≥102.2)	0	0	0
Local AE	Pain	154 (51%)	165 (55%)	319 (53%)
	Bruising	16 (5%)	14 (5%)	30 (5%)
	Redness	24 (8%)	25 (8%)	49 (8%)
	Swelling	25 (8%)	30 (10%)	55 (9%)
Systemic AE	Fatigue	40 (13%)	62 (21%)	102 (17%)
	Shivering	12 (4%)	15 (5%)	27 (4%)
	Joint pain	15 (5%)	19 (6%)	34 (6%)
	Muscle pain	40 (13%)	41 (14%)	81 (13%)
	Headache	59 (20%)	63 (21%)	122 (20%)
	Nausea	13 (4%)	15 (5%)	28 (5%)
STN 125285 PSC06 CSR Table 16 and section 12.1.1 Reactogenicity Events				

Unsolicited AEs

Unsolicited AEs were occurring during Day 0 – 28 were ascertained via query on interval health status during the Day 28 clinic visit. Continuation (or initial onset) of local and systemic events that were listed in the Memory Aid were also captured as AEs. The most frequently reported AEs overall were pharyngolaryngeal pain (13 subjects, 2%), rhinorrhea (9 subjects, 1%), and cough (7 subjects, 1%). The majority of all AEs overall were mild and included 36 subjects (12%) in the FluBlok group and 33 subjects (11%) in the FLUZONE (TIV) group. Moderate AEs were reported by 24 subjects (4%) overall and included 6 subjects (2%) in the FluBlok group and 18 subjects (6%) in the FLUZONE (TIV) group. The most frequently reported AEs by treatment group are summarized in the table below:

Table 22: Unsolicited Adverse Events Occurring in ≥ 2 Subjects (PSC06)

	FluBlok N=300	Fluzone N=302	Overall N=602
Subjects With At Least One Adverse Event	43 (14)	53 (18)	96 (16)
Preferred Term			
Pharyngolaryngeal pain	4 (1)	9 (3)	13 (2)
Rhinorrhea	4 (1)	5 (2)	9 (1)
Cough	5 (2)	2 (<1)	7 (1)
Nasal congestion	3 (1)	3 (<1)	6 (<1)
Injection site erythema	5 (2)	1 (<1)	6 (<1)
Upper respiratory tract infection	3 (1)	3 (<1)	6 (<1)
Back pain	2 (<1)	4 (1)	6 (<1)
Diarrhea	4 (1)	0	4 (<1)
Nasopharyngitis	1 (<1)	3 (<1)	4 (<1)
Arthralgia	2 (<1)	1 (<1)	3 (<1)
Sinus headache	2 (<1)	1 (<1)	3 (<1)
Fatigue	0	2 (<1)	2 (<1)
Injection site pruritis	1 (<1)	1 (<1)	2 (<1)
Shoulder pain	1 (<1)	1 (<1)	2 (<1)
Headache	1 (<1)	1 (<1)	2 (<1)
STN 125285/0 PSC06 Interim CSR Tables 17-18; amendment 13?, PSC06 Final CSR Tables 19 & 20			

Serious Adverse Events (SAEs)

Four SAEs was reported during the study and summarized by treatment group in the table below.

Table 23: Serious Adverse Events (PSC06)

FluBlok Group	Fluzone Group
Vasovagal syncope	Prostate cancer
Acute pancreatitis	Cerebrovascular accident
STN125285 CSR06 Section 12.3.2 Serious Adverse Events	

Deaths

No deaths were reported during the study.

3. Planned Studies (Post-licensure)

PSC07/09

A Phase 4 open label multi-center study comparing safety and immunogenicity of FluBlok® to FLUZONE (TIV) over 2 successive influenza seasons in 100,000 adults ≥ 18 years of age, with and without high risk medical conditions within the Northern California Kaiser Permanente clinic system. Approximately half of the individuals will receive either FluBlok® or a U.S.-licensed egg-derived vaccine (TIV), and monitored, via electronic medical record review, for clinically significant AEs. The only subjects excluded for medical reasons will be those with contraindications for receipt of the respective influenza vaccines. An attempt will be made to use the same TIV throughout the study, or at least within a season.

A subset of subjects (10,000) will receive telephone interviews to capture local and systemic post vaccine reactions.

Subjects will be monitored for medically attended events, including clinic or emergency department visits and/or hospitalizations. Using a retrospective cohort design with self-control analytical approach, detection of significant AEs for each cohort will be based on risk windows of 0 to 3 days, 1 to 14 days (primary analysis), 1 to 42 days, and 15 to 42 days after vaccination, and compared with two control periods: one before vaccination (days -56 to -15 for the primary analysis [to exclude "healthy vaccinee"]

effects]) and the second after the risk window (days 15-28 for the primary analysis). All individual ICD-9 codes as well as predefined aggregate codes will be examined. Any diagnoses which appear to occur more frequently in a risk window based on electronic review will be further assessed via medical chart review. The final protocol for this study (including a statistical analysis plan) will be submitted within 12 months following FluBlok approval and will be scheduled shortly thereafter. Data will be analyzed annually, with the final study report to be submitted by December 31, 2013.

Protocol was to have been submitted within 12 months of FluBlok® accelerated approval.

PSC10

Phase 4 extension safety and immunogenicity study in subjects from PSC04 and PSC06 who received FluBlok (FB) or Fluzone (FZ) in 2007-2008. Subjects will be re-randomized to receive either vaccine in successive years. Comparisons: FB-FB, FB-FZ, FZ-FB, FZ-FZ. The protocol is to be submitted within 12 months of FluBlok approval.

Pediatric Development Plan

Study PSC02, the only study of FluBlok in the pediatric age group, was conducted during the 2006-2007 influenza season and enrolled children ages 6-59 months. The clinical study report has not been submitted to CBER; however, the sponsor reports that FluBlok was poorly immunogenic and states "it seems highly probable that an alternative formulation of FluBlok will have to be developed for this age group" speculating the use in children might require an even higher antigen dose (the proposed adult product contains 3-fold higher HI antigen as compared to licensed TIV products), a 3-dose schedule, restriction of use of FluBlok to children who have previously received another influenza vaccine, in alternative route of delivery, e.g., intradermal, or use of an adjuvant or co-stimulatory molecule. Given the uncertainties of these various strategies, the sponsor requests deferral of pediatric studies in the 6-59 month age group.

Table 24: Summary of Pediatric Development Plan

Age	PREA Action	Sample size Products	Major Outcomes
0 to <6 mos.	Waiver request	---	---
6 to 36 mos.	Deferral request	---	---
3 to 8 yrs.	PSC08B RCDB 2011-2012 season	750 subjects FluBlok vs. Fluzone	Unsolicited AEs Days 0-28 SAEs, new medical conditions Days 0-180 Immunogenicity at Day 0 and Day 28
9 to 17 yrs.	PSC08A RCDB 2010-2011 season	720 subjects FluBlok vs. Fluzone	Reactogenicity Days 0-7 Unsolicited AEs Days 0-28 SAEs, new medical conditions Days 0-180 Immunogenicity at Day 0 and Day 28

STN 125285/0/18 Pediatric Development Plan, Appendices 1-2

FDA Pediatric Review Committee

The FDA Pediatric Review Committee on 02-DEC-2009 determined that FluBlok studies in children 0 to < 6 months can be waived, but that study of children from 6 months through 17 years of age is required, but the study of the older pediatric age group can be deferred until after licensure.

4. Limitations of Studies

a. Populations not studied in the pre-approval phase

- i. The sponsor acknowledges that the majority of subjects enrolled in studies to date have been younger (median age 37 years), predominantly Caucasian (73% subjects), and relatively healthy and/or with stable underlying medical conditions.
- ii. A relatively small number of older subjects have been studied: 300 individuals aged 50-64 years, and 436 individuals aged ≥65 years of age, the latter age group in an active comparator (Fluzone) study.
- iii. The only pediatric study, PSC02, a preliminary dose ranging/dose finding study in children 6-59 months of age, is referenced in the BLA for informational purposes and to

support PSC's request for a deferral of additional studies in support of a pediatric indication. The sponsor has requested a deferral for studies in the pediatric age group, noting that immunogenicity responses in children are not adequate and speculating on various approaches to improving immunogenicity, including development of an alternate formulation (Pediatric Development Plan, amendment 18).

- iv. Pregnant/lactating women (other than those who became pregnant during a study), and immunocompromised individuals have not been studied.

b. *Limitations of study design (safety)*

The power to detect a particular AE is based upon the Poisson distribution, but these estimations are also based upon the assumption that the particular AE does not occur in the placebo or comparator group. While not formally calculated, for a given sample size, the power to detect a specific absolute increase in the occurrence of an AE decreases appreciably as the background rate increases. This is of particular concern in the evaluation of safety in older adults and in other populations with relatively high prevalence rates of pre-existing conditions and/or anticipated higher incidence rates of adverse events. Uncontrolled studies, e.g., typical post-marketing safety surveillance studies, are not sufficiently sensitive to detect increases in the rates of relatively common background events.

c. *Limitations in data submitted to date*

- i. It is noted that study PSC01 planned to enroll 900, but actually enrolled only 460 subjects, reportedly due to financial constraints; and study PSC03 planned to enroll 1,350 subjects but actually enrolled only 870 subjects, reportedly due to slow enrollment and time constraints.
- ii. The duration of actual safety follow-up and how a subject was classified as having completed a study is unclear. While there are explicit data indicating rates of participation through Day 28, postvaccination, the CSRs do not appear to provide an indication of the number of enrolled subjects who completed planned safety follow-up at approximately 6 months post-vaccination in either narratives or tables. It appears that, except for those studies with surveillance focused primarily on occurrence of influenza, safety data after Day 28 may have been gathered in a relatively passive manner. If this is so, safety data should be interpreted with great caution.
- iii. Immunogenicity evaluations point to potentially problematic variability in manufacturing, e.g., failure to demonstrate lot consistency, and notable differences in certain immunogenicity responses when directly compared to a licensed influenza vaccine (Fluzone).
- iv. Failure to demonstrate lot to lot consistency in the pivotal trial, PSC04, confounds interpretation of any data from this study, including safety data.
- v. Rates of influenza, particularly strains antigenically similar to the vaccine strains, are so low that the studies to date were underpowered to measure real clinical efficacy.

5. Pharmacovigilance Plan (PVP)

The sponsor proposed routine pharmacovigilance based upon the submitted CMC and clinical data. Please refer to Section 3.0, Planned Studies.

The Pharmacovigilance Plan is intended to comply with:

- Current FDA Guidance including "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" (March 2005) and ICH "E2E Pharmacovigilance Planning" (April 2005)
- 21 CFR 600.80 (c)(2) (and/or analogous sections of 21 CFR 314.80) regarding submission of periodic adverse events

Protein Sciences Corporation (PSC) will utilize a 3rd party contractor (to be identified) to perform the following duties with respect to pharmacovigilance:

- Prepare and submit to FDA case reports and periodic adverse event reports for FluBlok.
- Monitor adverse events reported from clinical studies of FluBlok in collaboration with the CRO (if different than the PV contractor) and with PSC
- Manage and house a safety database pertaining to adverse events as described above. The safety database system will be validated according to FDA (21 CFR Part 11) and international standards.

Protein Sciences Corporation (PSC) will monitor relevant published literature, abstracts and/or other sources of publicly available information pertaining to the safety of FluBlok.

PSC believes that no important definite or potential risks associated with FluBlok have been identified, either from the existing clinical study safety database or from considering the safety of inactivated influenza vaccines from a product class point of view.

Studies Planned Following Licensure (See Section 3, above)

- PSC10: A Phase 4 extension safety and immunogenicity study of vaccination over multiple influenza seasons
- PSC07/09: A Phase 4 open label multi-center study comparing safety and immunogenicity of FluBlok® to FLUZONE (TIV) over 2 successive influenza seasons in 100,000 healthy adults ≥18 years of age

Adverse Events of Potential Interest

PSC will monitor for events that have been reported following the use of currently licensed influenza vaccines including specific events: anaphylaxis, vasculitis, acute disseminated encephalomyelitis (ADEM), Guillain-Barré syndrome, myocarditis/pericarditis, vasculitis, and Bell's palsy. In addition, general safety surveillance will monitor: blood and lymphatic system disorders (e.g., thrombocytopenia); immune system disorders (including anaphylactic shock, serum sickness, and other allergic reactions, such as hives, angioedema, and allergic asthma); nervous system disorders (i.e., encephalopathy, neuritis/neuropathy, partial facial paralysis, transverse myelitis, and neuralgia, paresthesia, and convulsions); skin and subcutaneous tissue disorders (pruritus, urticaria, and rash); general disorders and administration site conditions (influenza-like illness [e.g., pyrexia, chills, headache, malaise, myalgia], injection-site inflammation [e.g., pain, erythema, swelling, warmth], and induration.

Potential for transmission of infectious (adventitious) agents

Adventitious agents might be introduced into FluBlok by one of three sources: (1) the expression vector baculovirus Autographa californica Nuclear Polyhedrosis Virus (AcNPV), the baculovirus expression vector plasmid, into which cDNA influenza HA sequences are inserted by homologous recombination; (2) raw materials, including the cell substrate used for manufacturing (expresSF+ cells, which are derived from Sf9 cells of the fall armyworm *Spodoptera frugiperda*); and (3) contamination via human operators during the manufacturing process. The risk of contamination by adventitious agents has been extensively and rigorously evaluated, as summarized elsewhere in this application (see Module 3), as has the ability of the downstream process to clear any residual agents that may be present. PSC concludes that the results of this extensive assessment indicate an extraordinarily low risk of any agent being present in the final product.

Use in pediatric populations

Off-label use in children will be monitored and efforts including educational programs and "Vaccine Information Statements", will reinforce the fact that FluBlok is not indicated for (and therefore should not be given to) children. Given preliminary data from PSC02 (data not submitted) the sponsor does not feel that there are any particular safety concerns that would warrant more aggressive risk management programs at this time

Pregnancy

The sponsor does not plan to conduct any prospective studies in pregnant women or to establish a pregnancy registry. Spontaneous reports which indicated vaccination while pregnant will trigger follow-up of pregnancy outcome

Risk Minimization Plan

No Risk Minimization Plan or Activities are proposed.

OBE/DE REVIEWER SUMMARY COMMENTS:

1. No particular pattern of adverse events is identified from the submitted clinical study data, but the clinical data as described in this review have numerous limitations.
2. The database is limited by the relatively small size (N = 3233 exposed to FluBlok 135 ug), a predominantly Caucasian population (73% of FluBlok subjects), relatively few data from older adults (median subject age 37 years) and from pregnant women, no final study report for the single study conducted in children, failure of the lot consistency study, and failure to meet immunogenicity endpoints and uncertainty regarding the degree of active safety follow-up after Day 28 in the studies.
3. A final clinical study report for PSC02, the only pediatric study conducted to date, should be submitted for safety review prior to finalizing any pediatric protocols that are intended to support an indication in a pediatric age group.
4. The proposed postmarketing study of 100,000 individuals offers potential to provide data on potential rare or infrequent risks in adults. Details that should be further clarified in future discussions with the sponsor include the specific protocol, feasibility, and timeframe.

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Appendix I: Narratives of Deaths Reported in Study PSC06

Deaths in FluBlok Recipients

Pontine Hemorrhage (Fatal)

Subject 1017, an 89-year-old Caucasian female, received the study vaccination on October 13, 2006.

On ----(b)(4)-----, 92 days after vaccination, the subject presented to the emergency room with an altered level of consciousness, which began just prior to arrival at the hospital. The admission ECG showed sinus bradycardia. The subject was non-verbal and generally unresponsive. She was intubated in the emergency room. A CT scan of the brain performed that day revealed an intraparenchymal pontine hemorrhage with associated pontine edema and mild mass effect on the fourth ventricle without evidence of hydrocephalus. A Neurosurgery consult was obtained and the subject was admitted to the hospital. The family was informed of the nonsurvivability of this type of bleed and Do Not Resuscitate (DNR) status was discussed. The subject was maintained on a morphine drip and her status was made DNR. She was found to have no spontaneous breathing and was pronounced dead at 12:10 AM on ---(b)(6)-----. No autopsy was performed.

The subject's relevant medical history includes hypertension since 2004. Among the concomitant medications taken within two weeks of this event was diclofenac 50 mg QD. The investigator assessed the serious event of Pontine Hemorrhage as not related to the study vaccine. The Medical Monitor commented that even though intracerebral hemorrhage rates have fallen dramatically with improved control of hypertension, they may rise as the population ages due to amyloid angiopathy. Also, diclofenac, one of the subject's concomitant medications, is a weak and reversible inhibitor of thrombocytic aggregation needed for normal coagulation.

Additional AEs were reported for this subject which includes tiredness/lack of energy and fatigue during the week following vaccination.

Perforated Viscus with Secondary Peritonitis (Fatal)

Subject 3027, an 80 year-old, Caucasian female, received the study vaccine on ----(b)(4)-----.

On ----(b)(4)-----, 4 days after vaccination, the subject presented to the emergency room with an acute abdomen and was admitted to the hospital. Upon hospital admission, the subject underwent a CT scan. She was discovered to have a perforated diverticulum and subsequently underwent laparotomy and bowel resection. The subject was tachycardic prior to surgery despite aggressive fluid resuscitation. During surgery, she became hypotensive and tachycardic (blood pressure 74/52, pulse 112 at consultation post-surgery). Final pathology report (recto-sigmoid colon) was diverticulosis, perforation and peritonitis. She was diagnosed as being septic and received piperacillin and tazobactam injection, metronidazole, IV fluids, and phenylephrine. She was also noted to have thrombocytopenia, related to sepsis. Multiple weaning trials were attempted. On ----(b)(4)-----, she was extubated. Later in the day, she developed respiratory distress but declined to be re-intubated. She was made a Do Not Resuscitate/Do Not Intubate (DNR-DNI). On ----(b)(6)-----, the subject expired. Relevant laboratory findings (reference ranges not provided) on ----(b)(4)----- included WBC 2.16 K/cm³, hemoglobin 15.4 gm/dL, hematocrit 46.1%, platelets 141,000, BUN 22 M/cm³, and creatinine 1.1 mg/dL.

The subject's medical history is non-contributory for this event.

Concomitant medications taken within 2 weeks of this event included aspirin 81mg, calcium with vitamin C 600 mcg, multivitamin, lisinopril 20mg, and ibandronate sodium 150 mg. The investigator reported this serious event, Perforated Viscus and Secondary Peritonitis, as not related to the study vaccine. The Medical Monitor commented that the information received confirms the investigator's assessment that this fatal event was unrelated to the study vaccine; the final pathology confirmed acute peritonitis.

Deaths in Fluzone Recipients:

Cardiac Arrest (Fatal)

Subject 1166, a 73-year-old Caucasian male received the study vaccination on ----(b)(4)-----.

On ----(b)(4)-----, the subject had been hospitalized with a complaint of fatigue and had been discharged (date unknown). During hospitalization, he had been found to have hypotension, esophagitis and acute renal failure. Multiple consults were obtained to rule out septic shock and to evaluate renal failure. Probable rhabdomyolysis was noted. An endoscopic procedure had revealed probable candida esophagitis and nonsteroidal anti-inflammatory drug (NSAID) gastroduodenitis. (This prior event was reported as PSC03 SAE #07-042.)

On ----(b)(6)----- days after vaccination, the subject was found in his home by a neighbor, in cardiac arrest. He was taken via ambulance to the emergency room where death was pronounced after attempts at resuscitation and intubation. Asystole was noted. The anesthesiologist also noted that, during intubation, the oropharynx was suctioned for copious amounts of blood during intubation attempts.

The subject's relevant medical history includes hypertension (1998), diabetes (1998), hyperlipidemia (1998), and asthma (2004).

Concomitant medications taken at the time of enrollment included: gemfibrozil (600mg, BID, PO), glipizide (10mg, BID, PO), quinapril (20mg, QD, PO), montelukast sodium (10mg, QD, PO), theophylline (200mg, BID, PO), salmeterol (250/50mg, BID, IH), albuterol sulfate (2 puffs, prn, IH), azelastine HCl (4 sprays, BID, IH), mometasone (4 sprays, QD, IH), ocuvite (1 tablet, QD, PO), omega 3 fish oil (1 tablet, QD, PO), and leutin (1 tablet, QD, PO).

The investigator reported this serious event, Cardiac Arrest, as fatal, and not related to the study vaccine. The Medical Monitor commented that the significance of the finding of blood in the oropharynx was unclear, but medical records, including diagnostic reports and hospital documentation, could not be obtained [no next of kin].

Coronary Artery Disease (Fatal)

Subject 1589, a 69-year-old Caucasian male, received the study vaccine on ----(b)(4)----- On ----(b)(6)----- days after vaccination, the subject died. The record of death from the County Health Department indicated that this subject died from coronary artery disease with valvular heart disease as a contributing condition. The subject did not experience any adverse events in the 15 minutes of monitoring time following vaccination. The subject had received influenza vaccine during the 2005-2006 season.

The subject's medical history included coronary artery disease since 1978, hyperlipidemia since 1975, valvular heart disease diagnosed in 1978, stroke in 1991 with residual upper extremity weakness, hemiplegia, transient ischemic attack in October 2004, melena on October 3, 2006, and squamous cell carcinoma removed on August 7, 2006. Concomitant medications taken within two weeks of this event included Clopidogrel Bisulfate 75 mg QD, diltiazem 180 mg QD, niaspan 2500 mg QD, pravastatin sodium 80 mg QD, ezetimibe 10 mg QD, allopurinol 100 mg QD, aspirin 81 mg QD, colesevelam HCl 1250 mg QD, atenolol 1215 mg QD.

The investigator reported this event, Coronary Artery Disease, as serious due to the fatal outcome. The investigator has assessed this serious event as not related to the study vaccine. Autopsy information is not available.

The Medical Monitor commented: "The subject was unblinded. Per the randomization schedule, this subject was randomized to the licensed TIV treatment arm. The subject had not been exposed to FluBlok™."