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Sponsor: Protein Sciences Corporation	**Study Identifiers:** NCT00539981
Drug substances: Trivalent Recombinant influenza Vaccine	**Study code:** PSC04

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

Study centers: 24 centers in United States.

Study period:

Date first subject enrolled: 15/Sep/2007

Date last subject completed: 28/May/2008

Phase of development: III

Objectives:

Primary Objectives:

Safety: To determine the safety relative to placebo of a single dose of FluBlok containing 135µg of total rHA as determined by the rates of adverse events (AEs) and the observation of systemic and local reactions.

Lot consistency: To demonstrate clinical consistency among three different lots of FluBlok administered during the study. The primary immunogenicity hypothesis is that for each strain contained within FluBlok, the 2-sided 95% confidence interval (CI) for the ratio of post-vaccination geometric mean titers (GMTs) of HI antibody for Lot A vs. B, Lot A vs. C and Lot B vs. C will all fall within 0.67 to 1.5.

Efficacy: To determine the efficacy, relative to Placebo, of a single dose of FluBlok containing 135µg of total recombinant hemagglutinin (rHA) (45µg per strain) in the prevention of culture-confirmed symptomatic influenza meeting the case definition of CDC-ILI due to strains represented in the vaccine in a population of healthy adults aged 18-49 years.

Secondary Objectives:

Seroconversion rate: Post-vaccination titer of ≥1:40 in subjects with undetectable baseline antibody (HI titer <1:10) or a >4-fold rise in antibody in subjects with a baseline titer of ≥1:10, with the achievement of post-vaccination titer of at least 1:40. For adults <65 years of age, the lower bound of the 2-sided 95% CI should meet or exceed 40%.

Seroprotection rate: Post-vaccination titer of ≥1:40. For adults <65 years of age, the lower bound of the 2-sided 95% CI should meet or exceed 70%.

Efficacy: To determine the efficacy, relative to Placebo, of a single dose of FluBlok containing 135µg of total rHA in the prevention of culture-confirmed respiratory illness (regardless of CDC-ILI) due to strains represented in the vaccine.

Methodology:

This was a randomized, prospective, modified double-blinded trial. A total of 4648 eligible subjects were randomized at a 1:1 ratio into one of two groups:

- FluBlok total 135µg rHA; FluBlok assignment was further stratified into three lots, A, B and C
- Placebo (normal saline for injection, USP)

Number of subjects:

Randomized: 4648

Evaluated:

Immunogenicity (FluBlok): 391

Safety: 4648

Diagnosis and criteria for inclusion:

The study population was comprised of healthy, medically stable adult males and females, aged 18-49 years who met the Study Entry Criteria, agreed to comply with all of the study procedures and be available for follow-up for the duration of the influenza season for a total of approximately 6 months. Women of child-bearing potential had to have a negative urine pregnancy test results at the time of randomization and had to be willing to use an adequate form of contraception during the course of the study.

Study treatments

Investigational product: FluBlok

Formulation: FluBlok was formulated with 0.005% Tween®–20 in 10 mM sodium phosphate buffer, pH 7.0±0.4. Each 0.5 mL dose of FluBlok contained 135µg [as measured by the single radial immunodiffusion (SRID) assay] of rHA, consisting of 45µg each of rHA derived from the respective influenza viruses for the 2007-2008 formulation: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004.

Route of administration and dose regimen: A single dose of FluBlok was injected in a total volume of 0.5 mL into the non-dominant deltoid muscle.

Control Product:

Formulation: Placebo consisted of normal saline for injection, USP.

Route of administration and dose regimen: A single dose of Placebo was administered in a total volume of 0.5 mL by intramuscular injection into the non-dominant deltoid muscle.

Duration of treatment: Study Subjects required to participate for a total of approximately 6 months (until the end of influenza season).

Criteria for Evaluation

Safety endpoints:

- 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.
- 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 the end of the study when the database was locked for final analysis.

Primary 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.

Primary efficacy endpoint:

- Proportion of subjects in the FluBlok-treatment group, relative to Placebo, who experience cell-culture-confirmed CDC-ILI associated with isolation of an influenza virus antigenically resembling the vaccine strain from a nasal/throat swab (NS/TS) specimen collected during the acute illness.

Secondary immunogenicity endpoints:

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

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

Secondary efficacy endpoint:

- Proportion of subjects in the FluBlok-treatment group, relative to Placebo, who experience cell-culture-confirmed respiratory illness (not necessarily CDC-ILI) associated with isolation of an influenza virus antigenically resembling the vaccine strain from a NS/TS collected during the acute illness.

Summary:

Primary Pre-specified Endpoints

Immunogenicity results based on the protocol-specified analysis:

Lot Consistency: Immunogenicity was assessed on samples from 391 subjects at 5 study sites. 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 all fall within 0.67 to 1.5. The Drug Product Lots meet the pre-defined criteria for A/Solomon Islands and B/Malaysia, but not for A/Wisconsin. Confidence intervals range from 0.67 to 1.31 for A/Solomon Islands, and from 0.64 to 1.25 for B/Malaysia. While the B/Malaysia lower bound CI is slightly below the CI from the May 2007 Center for Biologics Evaluation and Research (CBER) Seasonal Influenza Guidance document, the three lots can still be considered equivalent based on the methodology proposed by Lachenbruch et al. The CIs for A/Wisconsin range from 0.56 to 2.91 resulting in a failure of lot consistency for this strain. The analysis did not materially change when immunogenicity was assessed on samples from 448 subjects (after data from 57 missing subjects not included in the locked database was added and all immunogenicity analyses were repeated).

To further define the potential clinical impact of the results for A/Wisconsin, an exploratory analysis was undertaken to calculate seroconversion and seroprotection rates for Clinical Lots A, B, and C, based on the "placebo controlled" criteria listed in CBER's May 2007 Guidance. The lower bound of the 2-sided 95% CI of the seroconversion rate and seroprotection rate exceeded the criterion of ≥40% and ≥70%, respectively, for all three lots for all three strains. More specifically, the A/Wisconsin (H3) antigen, which failed to meet the clinical lot consistency criteria as described above, exceeded the ≥40% threshold for seroconversion (lower bound of the 2-sided 95% CI = 80% for Lot A, 66% for Lot B and 72% for Lot C), as well as the threshold of ≥70% for seroprotection (lower bound of the 2-sided 95% CI = 95% for Lot A, 89% for Lot B, and 91% for Lot C).

An investigation was undertaken to attempt to identify the underlying cause for the lot consistency failure for the A/Wisconsin strain. The most important difference observed for the A/Wisconsin Drug Substance lots was the variation in SRID/BCA ratio, e.g. 0.65 for batch 45-07011-1 versus 1.28 for batch 45-07013 and 1.32 for batch 45-07023A. Also, the purity of these lots varied from 85% (batch 45-07023A) to 94% (45-07013). The Drug Product Lot 50-07010 contained approximately 61µg of A/Wisconsin rHA on a protein mass basis corrected for product purity, whereas Lots 50-07011 and 50-07014 contained 29 and 33 µg, respectively. The observed GMT's appear to be better correlated with the total mass of protein included than the amount of antigen measured by the SRID assay.

Efficacy results:

A total of five subjects (one FluBlok and four Placebo) experienced culture-confirmed CDC-ILI with a strain antigenically resembling the vaccine strain. In all cases, the strain was identified as A/Wisconsin/67/2005 (H3N2). The protective efficacy of FluBlok, relative to Placebo, was determined to be 75.4%, with a 95% confidence interval (CI) of -148 to 99.5.

Secondary Pre-specified Endpoints

Immunogenicity results (CBER criteria):

Seroconversion

"Seroconversion" is defined as a post-vaccination titer of ≥1:40 in subjects with undetectable baseline antibody (HI titer = <1:10) or a ≥4-fold rise in antibody in subjects with a baseline titer of ≥1:10, with the achievement of post-vaccination titer of at least 1:40. The May 2007 CBER Seasonal Influenza Guidance document specifies, for adults <65 years of age, that the lower bound of the 2-sided 95% CI should meet or exceed 40%.

All Evaluable subjects vaccinated with FluBlok met the per-protocol, pre-specified analysis as described in the CBER Guidance document. The seroconversion rate to A/Solomon Islands (H1) was 78%, for A/Wisconsin 81% and for B/Malaysia 53%. The lower limit of the 2-sided 95% CI of each of these rates exceeded 40% for all three strains, including 73.8% for A/Solomon Islands, 76.3% for A/Wisconsin, and 48.1% for B/Malaysia.

Seroprotection.

"Seroprotection" is defined as a post-vaccination HAI antibody titer of ≥ 1:40. The Guidance Document specifies, for adults <65 years of age, that the lower bound of the 2-sided 95% CI should meet or exceed 70%.

All Evaluable subjects vaccinated with FluBlok met the per-protocol, pre-specified analysis as described in the CBER Guidance document. The seroprotection rate for A/Solomon Islands (H1) was 98%, for A/Wisconsin (H3) 96% and for B/Malaysia 96%. The lower limit of the 2-sided 95% CI of each of these rates exceeded 40% for all three strains, including 96.7% for A/Solomon Islands, 94.1% for A/Wisconsin, and 93.4% for B/Malaysia.

Geometric Mean Titers

At baseline (Day 0), antibody responses as assessed by the geometric mean of the HAI antibody titers (GMTs) was 31.26 for A/Solomon Islands, 49.75 for B/Malaysia, and 22.36 for A/Wisconsin. By Day 28, GMTs increased 11.5-fold for both A/Solomon Islands and A/Wisconsin and 3.9-fold for B/Malaysia.

Efficacy results:

A total of eight subjects (two FluBlok and six Placebo) experienced culture-confirmed influenza illness with a strain antigenically resembling the vaccine strain. In all cases, the strain was identified as A/Wisconsin/67/2005 (H3N2). The protective efficacy of FluBlok, relative to Placebo, was determined to be 67.2%, with a 95% confidence interval (CI) of -83.2 to 96.8.

Safety:

A total of 4648 subjects were included in the Safety Population, including 2344 in the FluBlok group, and 2304 in the Placebo group. The final analysis includes all events up through the end of study visit or contact.

Solicited Adverse Events (AEs)

Reactogenicity events occurring on Days 0-7 (as solicited from the subjects by means of a memory aid) were reported frequently: 1198 (53%) FluBlok recipients and 727 (32%) Placebo recipients reported at least one systemic or local (injection site-related) AE. The most frequent AE reported was pain at the injection site (37% and 8% for FluBlok and Placebo, respectively), followed by headache (15% for each treatment group) and fatigue (14% for each treatment group). Most AEs were mild and had resolved completely by Day 7. Severe fever (≥102.2ºF) was reported in 4 FluBlok recipients and 1 Placebo recipient. Moderate (≥101.2ºF through <102.2ºF) was reported in 5 FluBlok and 6 Placebo recipients. There was no difference in reactogenicity in pair-wise comparisons among the three FluBlok lots (Lots A, B and C).

Unsolicited and/or Treatment-Emergent AEs

Unsolicited and/or treatment-emergent AEs collected and assessed via questions about interval health status during the Day 8 and Day 28 clinic visit or telephone call. Continuation (or initial onset) of local and systemic events that were listed in the memory aid were also captured as treatment-emergent AEs. The most frequently reported unsolicited and/or treatment-emergent AE overall (both groups combined) were pharyngolaryngeal pain (91 subjects, 2%); cough (85 subjects, 2%); and headache (78 subjects, 2%).

Cough was the most frequently reported unsolicited and/or treatment-emergent AE in FluBlok recipient (48 [2%] subjects versus 37 [2%] in placebo), whereas pharyngolaryngeal pain was the most frequently reported unsolicited and/or treatment-related 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 (36 subjects, 2%) and rhinorrhea (30 subjects, 1%);

For the Placebo group: headache (42 subjects, 2%) nasal congestion (31 subjects, 1%) and rhinorrhea (27 subjects, 1%).

A total of 132 subjects (3%) had unsolicited AEs that were considered as possibly or definitely related to the Study Treatment: 62 (3%) in the FluBlok 135µg group, and 70 (3%) in the Placebo group. The most frequently reported Study Treatment-related AEs overall, i.e., for both treatment groups, were fatigue (12 subjects, <1%), cough (16 subjects, <1%), nasal congestion (12 subjects, <1%), pharyngolaryngeal pain (16 subjects, <1%), rhinorrhea (15 subjects, <1%) and headache reported in 22 subjects (<1%) each.

The most frequently reported Study Treatment-related AEs, by treatment group were:

For the FluBlok group: nasal congestion (8 subjects, <1%), headache reported in 11 subjects (<1%), and cough (8 subjects, <1%), pharyngolaryngeal pain (6 subjects, <1%).

For the Placebo group: pharyngolaryngeal pain (10 subjects, <1%), headache reported in 10 subjects (<1%), rhinorrhea (9 subjects, <1%), fatigue (8 subjects, <1%), and cough (8 subjects, <1%).

Serious Adverse Events (SAEs):

There were 85 SAEs reported overall for 64 subjects. A total of 41 SAEs were reported for 30 subjects in the FluBlok-treatment group, and 44 events were reported for 34 subjects in the placebo-treatment group. Two deaths occurred, both of which were unrelated. All but two SAEs (liposarcoma in a FluBlok recipient and breast cancer in a placebo recipient) had resolved by the end of the study period. Of the 85 SAEs, none were considered to be related, and only one, “pericardial effusion”, in a FluBlok recipient, was judged to be “possibly related”.

Other Adverse Events (AE) of Interest:

One case of mild Bell’s palsy was reported in the FluBlok group. The event was initially classified as a treatment-related SAE, but was reclassified as “not-related” treatment-emergent event upon subsequent investigation.

Five female subjects became pregnant during this Study. One of these subjects received FluBlok, whereas four received placebo.

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