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Sponsor: Sanofi Pasteur **Drug substance(s):** High-dose trivalent inactivated influenza vaccine	**Study Identifiers:** **Study code:** FIM01 (NIH Study 04-100)
Title of the study: Comparisons of the Reactogenicity and Immunogenicity in Ambulatory Elderly Subjects of Standard-Dose Fluzone (15 µg HA/virus strain) and a High-Dose (60 µg HA/virus strain) of a Trivalent Inactivated Influenza Virus Vaccine	
Study center(s): There were 5 centers in the United States.	
Study period: Date first subjects enrolled: 11/Apr/2005 Date last subjects completed: 28/Nov/2005	
Phase of development: Phase II	

Objectives:

Primary Objectives:

The primary objective of this study was to compare the immunogenicity of a new high-dose trivalent influenza virus vaccine containing 60-µg hemagglutinin (HA) of each virus strain to a standard-dose trivalent influenza virus vaccine containing 15-µg HA of each virus strain in ambulatory elderly adults by hemagglutination inhibition assay (HAI) approximately 1 month after vaccination.

Secondary Objectives:

The secondary objective was to assess reactogenicity according to frequencies and severity of solicited local and systemic adverse events (AEs). The frequency of reports of individual AEs listed of any severity that were reported by the subjects, the number of subjects in each group experiencing any injection site or systemic events, and the proportions of subjects who experienced moderate-to-severe events were determined for each vaccine.

Methodology:

This was a prospective, multicenter, double-blind, parallel, randomized, active-controlled study to compare the reactogenicity and immunogenicity of a new high-dose trivalent influenza vaccine to the standard-dose trivalent vaccine. Vaccines were the standard-dose sanofi pasteur 2004-2005 inactivated influenza vaccine containing 15-µg HA of each virus strain and an investigational high-dose inactivated influenza vaccine containing 60-µg HA of each virus strain recommended for the 2004-2005 influenza season. Subjects who met the entry criteria for this study were placed into 1 of 2 previous vaccination strata (previously vaccinated or not previously vaccinated) based on self-reporting of receipt of influenza vaccine for the 2004-2005 influenza season. Randomization to vaccine dose group was conducted within stratum in order to obtain similar proportions of recently vaccinated subjects in each dose group. Subjects were randomized in a 1:1 ratio to receive a single intramuscular injection of either the high-dose or standard-dose trivalent vaccine (approximately 200 per group). Subjects were observed in the clinic for at least 20 minutes after immunization and maintained a memory aid to record oral temperature and systemic and local events for 7 days after immunization. Subjects were contacted by telephone between 8 and 12 days after immunization to review their recorded daily oral temperature and assess for the occurrence and severity of any local or systemic events or other AEs. Serum for immunogenicity evaluations were obtained prior to the first vaccination and approximately 1 month later. Subjects either returned to the study site or were contacted by telephone, depending upon the subject's preference, approximately 6 months after immunization to assess the occurrence of serious AEs. Serious adverse events were collected from Day 0 through study termination (6 months after the last vaccination). Following completion of the study, former subjects were offered a dose of the 2005-2006 Fluzone vaccine at no charge.

Number of subjects/patients:	Planned: 400 Randomized: 415 Treated: 414
Evaluated:	Immunogenicity: 414 Safety: 414

Diagnosis and criteria for inclusion:

Subjects must have met all of the following inclusion criteria to be eligible for study participation:

- Ambulatory medically stable persons 65 years and older on the date of vaccination
- Provided written informed consent and were available for all study visits
- Able to understand and comply with planned study procedures

Subjects were considered ambulatory if they were not institutionalized, bedridden, or homebound. Medically stable subjects may have had underlying illnesses such as hypertension, diabetes, ischemic heart disease, or hypothyroidism, but their symptoms must have been controlled with medical therapy. Subjects with acute febrile illnesses (oral temperature equal to or exceeding 99.5°F [37.5°C]) were deferred until 3 days after illness resolution.

Study treatments

Investigational Product: High-dose 2004-2005 (60-µg HA/virus) of a trivalent inactivated influenza virus vaccine.

Form: Ten 0.5-mL prefilled syringes/box

Reference Therapy: Standard-dose 2004-2005 (15-µg HA/virus) of a trivalent inactivated influenza virus vaccine

Form: Ten 0.5-mL prefilled syringes/box

Duration of participation: Each subject's participation lasted approximately 8 to 12 days with a follow-up visit at Day 28 and an additional follow-up visit or phone call at 6 months. The total duration of subject participation was approximately 7 months.

Criteria for evaluation:

Immunogenicity was assessed via assay for the titer of HAI antibodies against vaccine antigens in 2 laboratories (Baylor College of Medicine [primary data set] and sanofi pasteur) to determine the following endpoints:

- The proportion of subjects in each group who achieved a serum HAI antibody titer of at least 1:32 in the Baylor HAI assay for each of the 3 vaccine antigens approximately 1 month after vaccination
- The geometric mean titer (GMT) of serum HAI antibody against each of the 3 vaccine antigens
- The proportion of subjects in each group who achieved at least 4-fold increases in serum HAI antibody titer between preimmunization and postimmunization serum samples
- The proportion of subjects who achieved serum HAI antibody titers of 1:64 and 1:128 in the Baylor HAI assay for each of the 3 vaccine antigens approximately 1 month after vaccination

Safety was based on reactogenicity and AEs. Reactogenicity was assessed according to solicited events experienced after vaccination on Days 0 through 7 and included local events (injection site pain, injection site erythema, and injection site swelling) and systemic events (fever, headache, malaise, and myalgia). Adverse events were assessed according to unsolicited events collected for 28 days after vaccination and included any other events (including reactogenicity events reported after Day 7). The number and proportions of subjects in each group who experienced any injection site or systemic events, and the proportions of subjects who experienced moderate-to-severe events for each vaccine was also assessed.

Statistical methods:

Key enrollment and retention milestones and demographic information were summarized.

Immunogenicity

The immunogenicity outcomes for this trial were obtained from both Baylor and sanofi pasteur laboratories; however, the results obtained from the Baylor laboratory were used for the primary analysis. All results are presented on a strain-specific basis for each of the 3 strains contained in the vaccines. Estimates and 95% confidence intervals were produced for the proportions of subjects with titers of 1:32, 1:64, and 1:128, and for the GMT of each of the 3 antigens following vaccination. Confidence limits for proportions were computed using either asymptotic or exact methods if the observed rates were extreme. Confidence intervals for geometric means were expected to be based on assumptions of approximate normality for log transformed titers, but the data were reviewed to assess the appropriateness of this assumption. Prevaccination and postvaccination HAI titer levels were cross tabulated by dose levels for all subjects with paired responses (first for all subjects, then separately for the 2 previous trivalent inactivated influenza vaccination strata). The HAI results are also presented graphically using reverse cumulative distributions. The GMTs and confidence intervals were produced against each antigen based on the Baylor assay for all subjects, then in 2 subsets based on receipt of 2004-2005 trivalent inactivated influenza vaccine prior to study participation. These data are also presented, but were limited to facilitate comparisons of GMTs for all antigens tested. The tabulations present ratios of GMTs for postvaccination titers divided by prevaccination and for high-dose vaccine divided by standard-dose. Both tables compare all subjects and then subsets based on receipt of 2004-2005 trivalent inactivated influenza vaccine. Using the same format, the response to vaccination was examined first for all subjects and then by subgroup. The numbers and percentages of subjects achieving Baylor HAI titers of at least 32, 64, and 128 against each strain were calculated. Results were summarized for 2-fold and 4-fold increases in anti-HA antibodies by strain as assessed by the Baylor assay. The intent-to-treat response to vaccination by GMT, percentage of subjects achieving a 4-fold increases in titer, and percentages achieving a titer of at least 32 at 1 month postvaccination were summarized.

Safety

Safety analyses were based on reactogenicity (solicited events) collected at 20 minutes and daily for 7 days after vaccination, and AEs (all unsolicited events plus reactogenicity events reported after Day 7) collected for 28 days after vaccination. Measurements for fever, injection site erythema, and injection site swelling were reported in the case report form. Other AEs were reported according to the grading system in the protocol. Reactogenicity was analyzed using the grading system presented in Table 3 in Section 9.7.1.3.1. Reactogenicity was tabulated by time (days) following vaccination for vaccine group and within vaccine group for systemic events and local events. Individual subject responses were further summarized across all 7 days for each reactogenicity parameter to a single binary outcome (0=no reports of moderate or severe responses, 1=one or more reports of moderate or severe events). These parameters were further summarized into 3 binary variables (local, systemic, or any reactogenicity), and the binary outcomes were used to compute event rates and 95% confidence intervals. They were also used as dependent variables in logistic regression models to test for treatment/dose effects with the primary models controlled for the stratification variable, previous trivalent inactivated influenza vaccination. Reactogenicity data are also graphically presented, summarizing maximum systemic and local reactogenicity by dose group.

Adverse events were coded by Medical Dictionary for Regulatory Activities (MedDRA) coded preferred term and system organ class. Serious adverse events were listed by vaccine dose with their attribute. This analysis was repeated for AEs, regardless of association to vaccine. All AEs deemed associated to vaccination were tabulated separately, and the event rates were compared by treatment groups.

Summary:

Immunogenicity:

There was a significant increase in proportion of subjects given the 60 µg high-dose influenza vaccine who achieved a serum HAI titer of 1:32 for the H1 antigen compared to those for the 15 µg standard dose vaccine. For the high-dose vaccine, the rates for all subjects, those **not** previously vaccinated and those previously vaccinated were 62.3%, 74.5% and 58.8%, respectively; comparable rates for standard vaccine were 48.3%, 54.3%, and 46.6%. The increase in rates achieving titers of 1:32 to the H3 antigen for all subjects and those who had not or had been previously vaccinated were 94.7%, 100%, and 93.1%, respectively, compared to 91.8%, 89.1% and 92.5% for standard vaccine. The comparable high dose rates for influenza B were 62.3%, 68.1%

and 60.6% and 57%, 65.2% and 54.7% for standard vaccine. None of these H3 or B antigen differences were statistically significant. When those who achieved titers of 1:64 were compared, a statistically significant increase for the high dose vaccine was noted for the H3 antigen for all subjects (84.5% versus 71.5%), those **not** previously vaccinated (93.6% versus 67.4%), and those previously vaccinated (81.9% versus 72.7%). For influenza B, the increase was statistically significant for all subjects (36.2% versus 23.7%) and those previously vaccinated (32.5% versus 21.7%) but not for those **not** previously vaccinated (48.9% versus 30.4%; p = 0.699). Rates for those who achieved titers of 1:128 were statistically significant for the H3 antigen among those **not** previously vaccinated (74.5% versus 47.8%). Although the rates for achieving 1:128 for the H3 and B antigens were increased for the high dose vaccine in all remaining analysis categories, none were statistically significant.

The postvaccination GMTs were significantly higher in the high-dose group than in the standard-dose group for all antigens: 35.50 and 21.34, respectively for the H1 antigen, 137.79 and 96.94, respectively for the H3 antigen, and 31.26 and 25.40, respectively for the B antigen. In the not previously vaccinated subjects, the high-dose group had significantly higher postvaccination GMTs for the H1 and H3 antigens (54.42 and 248.56, respectively) than the standard-dose group (24.03 and 87.82, respectively). There was no difference between groups for the B antigen. In previously vaccinated subjects, the high-dose group had a significantly higher postvaccination GMT for the H1 antigen (31.31) than the standard-dose group (20.63). There were no differences between groups for the H3 or B antigens.

Safety:

Solicited Reactogenicity: The incidence of any local reactogenicity event in the high-dose group was 117 (57%) subjects: 91 (44%) were mild, 14 (7%) were moderate, and 12 (16%) were severe. The incidence of any local reactogenicity event in the standard-dose group was 91 (44%) subjects: 74 (36%) were mild, 12 (6%) were moderate, and 5 (2%) were severe. Local reactogenicity events were similarly distributed between vaccine groups, with the exception of pain, which was higher in the high-dose group (83 subjects) than the standard-dose group (41 subjects). The majority of local reactogenicity events were mild or moderate. Severe events included redness and swelling [6 (3%) subjects each in the high-dose group and 2 (1%) and 3 (1%) subjects, respectively in the standard-dose group]. The incidence of subjects with any systemic reactogenicity event in the high-dose group was 85 (41%) subjects, 62 (30%) were mild, 22 (11%) were moderate, and 1 was severe. The incidence of any systemic reactogenicity event in the standard-dose group was 61 (29%): 50 (24%) were mild, 11 (5%) were moderate, and none were severe. Nine subjects given the high-dose vaccine developed a fever versus 1 subject given standard vaccine. Most reactogenicity events occurred between Day 0 and 3 after vaccination.

Unsolicited AEs: The incidence and frequency of AEs was 84 subjects with 152 events, respectively, in the high-dose group and 60 subjects with 97 events, respectively, in the standard-dose group. AEs considered related to the study drug were 38 subjects with 73 related events in the high-dose group and 27 subjects with 36 related events in the standard-dose group. In addition, the high-dose group had 14 and 15 subjects with serious and severe AEs, respectively, compared with 9 and 6 subjects, respectively, in the standard-dose group. One subject in the high-dose group died during the study due to a myocardial infarction (day 169 after vaccination), which was considered not related to study vaccine. No SAE was considered related to the study vaccine.

Most unsolicited AEs were respiratory symptoms or continuation of local or systemic reactions. One subject developed oculorespiratory syndrome. Subject 13FBA047 was a 72-year-old female who received a dose of study product on 14 April 2005. On the evening of vaccination, the subject reported experiencing Grade 3 chills and labored breathing and Grade 2 flushed face, cramps, increased pulse, lightheadedness, and nausea, all of which were considered associated with study vaccine and resolved without sequelae on 15 April 2005. On 15 April 2005, the subject reported Grade 3 heavy fluid in the right eye and Grade 1 runny nose and sneezing, all of which were considered associated with study vaccine and resolved without sequelae on 16 April 2006. The subject was counseled by the PI at the Day 28 visit.

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