Vaccine 31 (2013) 861–866

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: Safety, immunogenicity and relative efficacy during the 2009–2010 season

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ARTICLE INFO

Article history:
Received 29 October 2012
Received in revised form 3 December 2012
Accepted 6 December 2012
Available online 20 December 2012

Keywords:
Influenza vaccines, human
Vaccines, inactivated
Clinical trial, phase III
Aged
Aged, 80 and over

ABSTRACT

Background: High-dose trivalent influenza vaccine was developed to improve antibody responses to influenza vaccine in the elderly and hence potentially impact favorably on influenza-associated morbidity and mortality in this population.
Methods: A phase IIIb, multicenter, randomized, double-blind, controlled trial was conducted to compare High-Dose (HD) trivalent inactivated influenza vaccine (60 μg of hemagglutinin [HA] per strain) to standard dose (SD) vaccine (15 μg of HA per strain) in adults ≥65 years of age. Assessments of safety (serious adverse events [SAE]), immunogenicity (hemagglutination inhibition [HAI] titers) and relative efficacy were performed during the 2009–2010 influenza season, which coincided with the H1N1 pandemic.
Results: A total of 9172 participants were enrolled in 99 research centers in the US (6117 and 3055 randomized to the HD and SD groups, respectively). Within 180 days after vaccination, 6.7% and 6.5% of participants in the HD and SD vaccine groups, respectively, experienced at least one SAE, of which 0.4% and 0.3% had a fatal outcome. A total of 0.5% of participants in both groups discontinued the study due to a SAE. Post-vaccination HAI titers and rate of post-vaccination HAI titer ≥1:40 were significantly higher in the HD group. No cases of influenza caused by viral types/subtypes similar to those in the vaccines were observed. All cases genetically or antigenically characterized were classified as similar to influenza A/California/7/2009 (H1N1), the pandemic strain. The vaccine efficacy of HD vaccine relative to SD vaccine against any influenza viral type/subtype was 12.6% (95% CI −140.5; 65.8) in the intent-to-treat analysis.
Conclusion: High-dose trivalent inactivated influenza vaccine is safe and well tolerated and provides superior immune responses compared to standard dose vaccine. Demonstration of a superior vaccine efficacy requires a separate large randomized, controlled trial.

1. Background

Between 1990 and 1999, seasonal influenza caused an average of 36,000 deaths and 226,000 hospitalizations per year in the United States (US) [1–3]. Adults 65 years of age and older are particularly vulnerable to influenza complications, accounting for 60% of seasonal influenza-related hospitalizations and 90% of influenza-related deaths in the US. Vaccination currently represents the most effective medical intervention against influenza and its complications [3,4]. Although vaccination rates in the elderly have increased in the US to 65% and above [5], antibody response and protection elicited by the vaccine are lower in elderly than in younger adults [6–8]. Hence, strategies to improve antibody responses to influenza vaccine in the elderly may have a favorable impact on influenza-associated morbidity and mortality [9]. One strategy to improve vaccine responses is to increase the amount of antigen contained in the vaccine. Fluzone® High-Dose (HD) vaccine has four times the amount of hemagglutinin contained in the standard dose (SD) Fluzone vaccine. Based on superior immune responses compared to SD [10], HD was approved under "accelerated approval" by the FDA for use in the United States on 23 December 2009, with a post-marketing commitment to demonstrate clinical benefit in an efficacy study.

The primary objective of this Phase IIIb study (FIM07, NCT00976027) was therefore to demonstrate the superior efficacy of HD vaccine compared to SD vaccine for the prevention

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0264-410X/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2012.12.013

of laboratory-confirmed influenza caused by influenza types/subtypes similar to those contained in the vaccine formulation. Although the study was originally planned as a 3-year study, the first year of the trial coincided with the first influenza pandemic of the 21st century which resulted in the lack of ascertainment of cases meeting the primary study endpoint (the occurrence of laboratory-confirmed influenza caused by influenza types/subtypes similar to those contained in the vaccine formulation). The study was therefore terminated early and replaced by a different clinical trial aimed at demonstrating superior efficacy (Study FIM12, NCT01427309). The present study (FIM07) however, provided valuable information about the safety and immunogenicity of HD vaccine, and allowed for exploratory assessments of efficacy against strains (A/California/7/2009-like) antigenically distant to the vaccine formulation.

2. Methods

2.1. Study design

This was a phase IIIb, multicenter, randomized, double-blind, controlled trial comparing HD vaccine and SD vaccine in elderly adults (≥65 years of age). It was performed at 99 centers in the US between September 22, 2009 and May 28, 2010. The study was approved by one central and six local institutional review boards and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and International Conference on Harmonization guidelines. All participants gave written informed consent before being included in the trial. Enrollment took place between September 22 and November 7, 2009.

2.2. Study participants

The study included medically stable elderly adults. Participants were excluded if they: were bedridden; were deprived from freedom; had personal history of Guillain–Barré syndrome; had known systemic hypersensitivity or history of life-threatening reaction to Fluzone or any vaccine components; had known or suspected human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection or seropositivity; abused alcohol or had drug addition that could interfere with compliance; had dementia or any cognitive condition at a stage that could interfere with compliance; had participated or were participating in another interventional study in the 4 weeks preceding the trial vaccination; had received vaccination against influenza in the 6 months prior to enrollment; had received any vaccination within the 4 weeks preceding the trial; or had thrombocytopenia, bleeding disorder or had received anticoagulants contraindicating intramuscular vaccination. Baseline demographics, medical history and vaccination history were collected on enrollment. Receipt of influenza vaccination (including pandemic influenza vaccination) outside of the study was collected during the follow up period.

2.3. Vaccines

The vaccines were formulated for the 2009/2010 influenza season according to the recommendations of the US Food & Drug Administration's Vaccines and Related Biological Products Advisory Committee. The SD vaccine (Fluzone vaccine, Sanofi Pasteur, Swiftwater, PA, USA; lot number UD12321) contained 15 μg of HA per strain. The HD vaccine (Fluzone High-Dose vaccine, Sanofi Pasteur, Swiftwater, PA, USA; lot numbers UD12307 and UD12314) contained 60 μg of HA per strain. Both vaccines are produced in embryonated chicken eggs, inactivated with formaldehyde, and split with a non-ionic detergent. Both vaccines contained A/Brisbane/59/07 (H1N1), A/Uruguay/716/2007 X-175C (H3N2), and B/Brisbane/60/2008 strains. The SD and HD vaccines were provided in ready-to-use 0.5-mL syringes with identical external appearance, and were administered by intramuscular injection into the deltoid area of the upper arm.

2.4. Treatment allocation and assignment

Participants were randomized 2:1 to receive one dose of the HD vaccine, or one dose of the SD vaccine. The study used concealed allocation through an interactive voice response system (IVRS) that centrally assigned participants to one of the two vaccine arms based on a computer-generated block randomization approach. Approximately 1/3 of study participants were also selected randomly to the immunogenicity subset by the IVRS. Study participants and investigators were blinded to treatment assignments.

2.5. Safety assessments

Participants were followed up for safety between vaccination and approximately May 15, 2010. Given that the safety of the HD vaccine was demonstrated in a previous large-scale pivotal study [10], this trial limited the collection of safety data to serious adverse events (SAEs) and adverse events of special interest (AESIs). AESIs for the study included new onset of Guillain–Barré Syndrome (GBS), Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens–Johnson Syndrome, and toxic epidermal necrolysis. AESIs were captured and reported as SAEs.

2.6. Immunogenicity

Blood samples were collected for measurement of hemagglutination inhibition (HAI) titers at a visit approximately 28 days post-vaccination in a randomly selected subset of 1/3 of study participants. Testing was performed by a single laboratory (Focus Diagnostics, Inc., Cypress, CA, USA). HAI titers against each vaccine strain were measured using a standard assay [11]. Each serum sample was titrated in independent duplicates. The Geometric Mean Titer (GMT) between the two values was calculated for each participant included in the immunogenicity subset. Seroprotection was considered as a post-vaccination HAI titer ≥1:40.

2.7. Illness surveillance and influenza case ascertainment

Participants were instructed to contact their study site (passive surveillance) if they experienced symptoms of influenza-like illness (ILI) during the surveillance period. In addition, they were contacted weekly by a call center representative (active surveillance). Both passive and active surveillance ended on April 30, 2010. An ILI was defined as a new onset (or exacerbation of a pre-existing condition) of at least one of the following systemic symptoms: temperature >37.2 °C (>99.0 °F), feverishness (feeling of warmth), chills, tiredness, headaches or myalgia; and at least one of the following respiratory symptoms: nasal congestion or rhinorhea, sore throat, cough, sputum production, wheezing, chest tightness, shortness of breath, or chest pain with breathing. If a participant met the criteria for ILI, the study site was to arrange for a nasopharyngeal (NP) swab to be taken within 5 days of ILI episode onset. NP samples underwent tissue culture and molecular testing (Polymerase-Chain-Reaction [PCR]-based assays) for laboratory confirmation of influenza.

Tissue culture was performed using susceptible tissue culture cell lines (i.e., R-Mix™ [A549: Human Lung Carcinoma and Mv1Lu: Mink Lung cells], MDCK [Madin Darby Canine Kidney] and Rhesus Monkey Kidney [RhMK] cells). Positive cultures were confirmed as influenza using immunofluorescence.

The molecular detection methodology for either Influenza A or B strains was based on a real-time reverse transcriptase-mediated PCR-based assay. The test utilized was the validated ProFlu+™ assay by Prodesse, Inc., Waukesha, WI, USA.

Tissue cultures and PCR were performed at two central laboratories: BARC USA, Inc (Lake Success, NY, USA) and Focus Diagnostics, Inc (Cypress, CA, USA).

A positive result on either the tissue culture or the PCR test was considered a confirmed case of influenza.

Culture-positive samples were antigenically characterized (University of Rochester, Rochester, NY, USA) using the HAI assay method against a panel of known standard ferret reference antisera to different viral strains.

Any positive sample by tissue culture or PCR underwent further testing by genetic sequencing to identify the specific strain causing the ILI and its relationship to the vaccine components. Genetic sequencing was performed by Quest Diagnostics, San Juan Capistrano, CA, USA.

All assays were performed under the direction of Sanofi Pasteur Global Clinical Immunology (GCI), Swiftwater, PA, USA.

2.8. Statistical analysis

A sample size of 27,000 was originally targeted for the 3-year trial based on 80% power to demonstrate the superior efficacy of HD vaccine. However, because the trial was terminated early, the analysis presented here accounts for the participants recruited during the first year of the originally planned study (approximately 1/3 of the initially targeted sample size).

For safety assessments, rates of SAEs (including AESI and deaths) occurring during the 180 days post-vaccination period are presented as frequency counts and percentages in each treatment group.

For immunogenicity assessments, post-vaccination antibody responses are presented as HAI antibody GMTs and seroprotection rates for each treatment group and vaccine strain, together with corresponding 95% Confidence intervals (CIs). CIs for GMTs were calculated based on the *t* distribution and the assumption that log(HAI titer) follows a normal distribution. CIs for seroprotection rates were calculated based on the Clopper–Pearson exact method [12]. In addition, the point estimates and 95% CIs for the GMT ratios (HD to SD) and differences in seroprotection rates for each strain were estimated. CIs for GMT ratios were calculated based on the two-sample *t* distribution and the assumption that log(HAI titer) follows a normal distribution. CIs for the difference in seroprotection proportions were calculated by the Newcombe–Wilson score method [13].

The efficacy of HD vaccine relative to SD vaccine was estimated as (1 − Relative Risk) × 100. The CI for each estimate of efficacy was calculated using the Clopper–Pearson exact method for binomial proportions, conditional on the total number of cases observed [12].

Two analysis sets were used: the Per-Protocol Analysis Set (PPAS) and the Full Analysis Set (FAS). The PPAS was comprised of those participants: (1) who met all study inclusion and exclusion criteria; (2) who received the study vaccine to which they were randomized; (3) for whom successful surveillance contact was achieved at least once post day 28; (4) who did not receive another seasonal influenza vaccine between vaccination and the end of illness surveillance; and (5) who did not have any other protocol deviation identified in the course of study monitoring which, in the opinion of the Sponsor's Responsible Medical Officers based on blinded review, was likely to impact the validity of the data. The FAS was comprised of those participants who received study vaccine. The safety assessments (SAEs, AESI and deaths) were performed in the FAS according to the vaccine actually received (as treated). The immunogenicity assessments were carried out as intent-to-treat (as randomized) in participants included in the FAS who were also in the immunogenicity subset and had a valid serology result. Relative efficacy was evaluated in both the PPAS and the FAS; in the FAS, participants were analyzed according to their randomized treatment (intent-to-treat analysis).

All statistical analyses were performed using SAS® software version 9.1 (SAS Institute, Cary, NC, USA).

Table 1
Baseline demographic and clinical characteristics, by vaccine received.

	Fluzone HD (*N* = 6108)	Fluzone (*N* = 3050)
Sex *n* (%)		
Male	2840 (46.5)	1403 (46.0)
Female	3268 (53.5)	1647 (54.0)
Age (years)		
Mean	72.8	72.8
Median	71.4	71.5
SD	6.0	5.9
Minimum	64.3	65.0
Maximum	99.8	99.9
Race *n* (%)		
Asian	46 (0.8)	19 (0.6)
Black	286 (4.7)	164 (5.4)
Caucasian	5198 (85.1)	2590 (84.9)
Hispanic	540 (8.8)	256 (8.4)
American Indian or Alaska native	25 (0.4)	5 (0.2)
Native Hawaiian or other Pacific Islander	3 (0.0)	3 (0.1)
Other	10 (0.2)	13 (0.4)
Significant medical history *n* (%)		
Blood and Lymphatic Disorders	387 (6.3)	220 (7.2)
Cardiac disorders	1468 (24.0)	732 (24.0)
Ear and labyrinth disorders	1193 (19.5)	602 (19.7)
Endocrine disorders	1165 (19.1)	618 (20.3)
Eye disorders	3084 (50.5)	1524 (50.0)
Gastrointestinal disorders	1072 (17.6)	536 (17.6)
Hepatobiliary disorders	522 (8.5)	257 (8.4)
Immune system disorders	2714 (44.4)	1342 (44.0)
Chronic infections	71 (1.2)	49 (1.6)
Metabolic disorders	3878 (63.5)	1847 (60.6)
Musculoskeletal disorders	3348 (54.8)	1674 (54.9)
Neoplasms	1305 (21.4)	649 (21.3)
Nervous system disorders	1064 (17.4)	537 (17.6)
Psychiatric disorders	1473 (24.1)	740 (24.3)
Renal and urinary disorders	805 (13.2)	389 (12.8)
Reproductive system disorders	779 (12.8)	411 (13.5)
Respiratory disorders	998 (16.3)	467 (15.3)
Vascular disorders	3990 (65.3)	1970 (64.6)
Previous influenza vaccination *n* (%)	5427 (88.9)	2692 (88.3)

3. Results

3.1. Participants

A total of 9172 participants were enrolled in 99 centers in the US, with 6117 randomized to the HD vaccine group and 3055 randomized to the SD vaccine group (Fig. 1).

Of the 9172 participants randomized, 9158 received study vaccine and were included in the FAS. There were a total of 9021 (98.4%) participants in the PPAS. The most frequent reason for exclusion from the PPAS was no successful surveillance contact after 28 days post-vaccination (0.7% of participants). A total of 626 (6.8%) of the vaccinated participants discontinued the trial before the end of the study year: 411 (6.7%) in the HD vaccine group and 215 (7.0%) in the SD vaccine group. The most common reason for discontinuation from the study was lost to follow-up (3.4% of participants), followed by voluntary withdrawal not due to an adverse event (1.9% of participants).

Baseline demographic and clinical characteristics were similar between HD and SD vaccine recipients (Table 1). Overall, 88.7% of

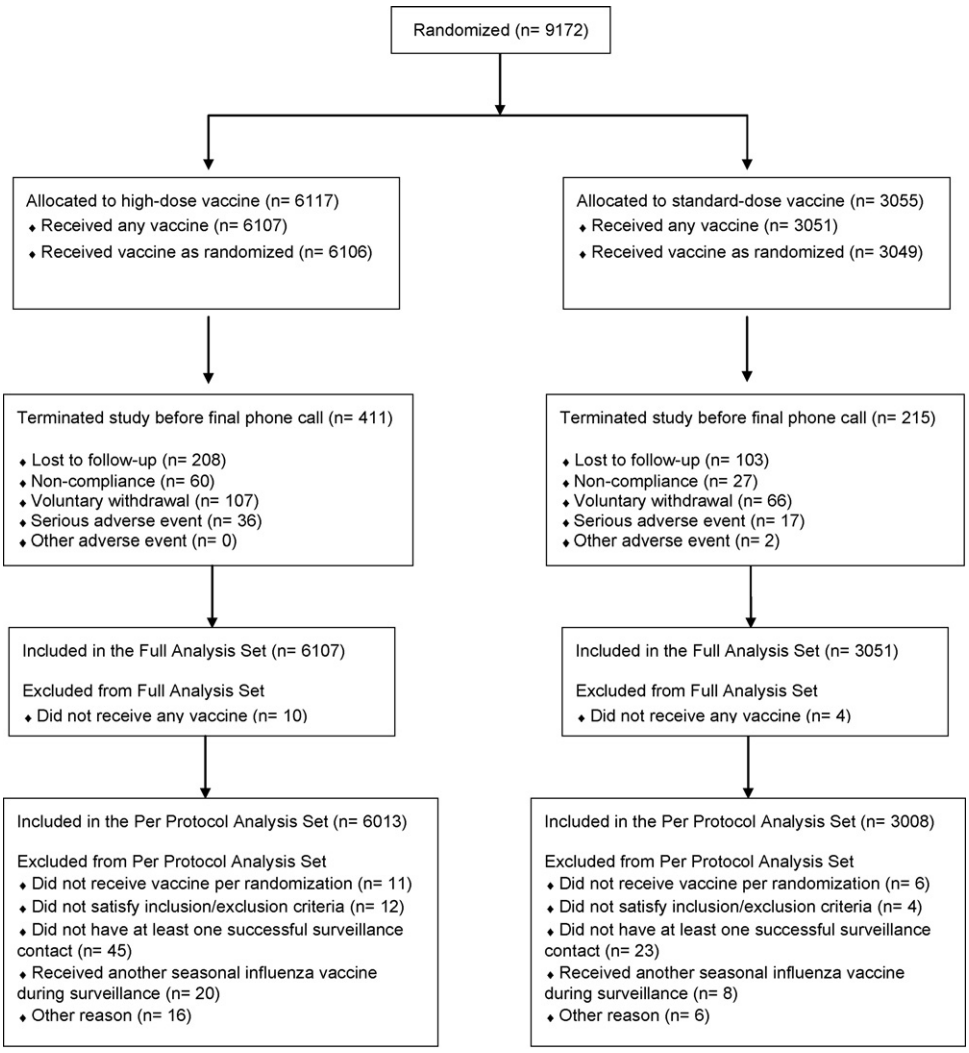

Fig. 1. Flow diagram of study participants' disposition.

participants in the FAS had previous history of seasonal influenza vaccination.

3.2. Safety

Within 180 days after vaccination, 408 (6.7%) and 197 (6.5%) participants in the HD and SD vaccine groups, respectively, experienced at least 1 SAE, with 24 (0.4%) and 10 (0.3%), respectively, having a fatal outcome.

One participant in the HD vaccine group and two participants in the SD vaccine group experienced an SAE that was considered by the Investigator to be related to vaccination: the HD group participant was reported to have cardiac chest pain starting one day after vaccination, and recovering after 2 days; one participant in the SD group was reported to have Bell's palsy 34 days after vaccination and the event was still ongoing at the time of study completion; a second participant in the SD group developed immune thrombocytopenia 13 days after vaccination and recovered after 5 days. One additional SAE occurring in a HD vaccine recipient was reported without causality assessment by the investigator and was considered related for analysis purposes. None of these related SAEs resulted in discontinuation from the study.

The occurrence of AESIs was rare in both study groups. For the HD vaccine group, three participants developed AESIs within 180 days of vaccination; all were instances of Bell's palsy, which developed 116, 126, and 178 days post-vaccination, and all were ongoing at the time of study completion. For the SD vaccine, there were two cases of Bell's palsy reported that developed 34 days (described above) and 176 days post-vaccination.

A total of 30 (0.5%) and 15 (0.5%) of participants in the HD and SD vaccine groups, respectively, discontinued the study due to SAEs; none of these were considered related to study vaccination.

Table 2 presents SAEs within 180 days after vaccination according to MedDRA System Organ Classes (SOC).

3.3. Immunogenicity

HAI antibody titers (GMTs), and seroprotection rates at day 28 post-vaccination were higher following vaccination with the HD vaccine than with the SD vaccine for all three vaccine strains (Table 3). Both GMT ratios and seroprotection rate differences met criteria for standard statistical superiority (95% CIs exclude null value).

3.4. Efficacy

A total of 1320 (21.6%) participants in the HD group and 662 (21.7%) in the SD group reported at least one protocol-defined ILI, with 973 (73.7%) and 486 (73.4%) providing at least one NP swab, respectively.

Table 2
Serious Adverse Events within 180 days post-vaccination according to MedDRA System Organ Class, by vaccine received (Full Analysis Set).

Participants experiencing at least one event of:	Fluzone HD (*N* = 6108)			Fluzone (*N* = 3050)		
	n	%	(95% CI)	*n*	%	(95% CI)
Blood and lymphatic system disorders	7	0.1	(0.0; 0.2)	2	0.1	(0.0; 0.2)
Cardiac disorders	69	1.1	(0.9; 1.4)	46	1.5	(1.1; 2.0)
Congenital, familial and genetic disorders	1	0.0	(0.0; 0.1)	1	0.0	(0.0; 0.2)
Ear and labyrinth disorders	0	0.0	(0.0; 0.1)	2	0.1	(0.0; 0.2)
Eye disorders	0	0.0	(0.0; 0.1)	1	0.0	(0.0; 0.2)
Gastrointestinal disorders	47	0.8	(0.6; 1.0)	20	0.7	(0.4; 1.0)
General disorders and administration site conditions	21	0.3	(0.2; 0.5)	14	0.5	(0.3; 0.8)
Hepatobiliary disorders	6	0.1	(0.0; 0.2)	5	0.2	(0.1; 0.4)
Immune system disorders	2	0.0	(0.0; 0.1)	0	0.0	(0.0; 0.1)
Infections and infestations	69	1.1	(0.9; 1.4)	24	0.8	(0.5; 1.2)
Injury, poisoning and procedural complications	33	0.5	(0.4; 0.8)	17	0.6	(0.3; 0.9)
Investigations	2	0.0	(0.0; 0.1)	0	0.0	(0.0; 0.1)
Metabolism and nutrition disorders	8	0.1	(0.1; 0.3)	8	0.3	(0.1; 0.5)
Musculoskeletal and connective tissue disorders	45	0.7	(0.5; 1.0)	10	0.3	(0.2; 0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	39	0.6	(0.5; 0.9)	17	0.6	(0.3; 0.9)
Nervous system disorders	40	0.7	(0.5; 0.9)	22	0.7	(0.5; 1.1)
Psychiatric disorders	7	0.1	(0.0; 0.2)	4	0.1	(0.0; 0.3)
Renal and urinary disorders	22	0.4	(0.2; 0.5)	6	0.2	(0.1; 0.4)
Reproductive system and breast disorders	3	0.0	(0.0; 0.1)	3	0.1	(0.0; 0.3)
Respiratory, thoracic and mediastinal disorders	41	0.7	(0.5; 0.9)	18	0.6	(0.4; 0.9)
Skin and subcutaneous tissue disorders	2	0.0	(0.0; 0.1)	0	0.0	(0.0; 0.1)
Surgical and medical procedures	1	0.0	(0.0; 0.1)	2	0.1	(0.0; 0.2)
Vascular disorders	18	0.3	(0.2; 0.5)	8	0.3	(0.1; 0.5)

Table 3
Immunogenicity analysis (intent-to-treat) of Fluzone High-Dose compared to Fluzone in the immunogenicity subset.

	Fluzone High-Dose (*N* = 2000[a])	Fluzone (*N* = 991[b])	
GMT (95% CI)			GMT ratio (95% CI)
H1N1	176.3 (168.0; 185.0)	112.2 (104.5; 120.5)	1.57 (1.44; 1.71)
H3N2	503.4 (473.5; 535.1)	289.0 (264.7; 315.6)	1.74 (1.57; 1.94)
B	159.0 (151.6; 166.7)	98.9 (92.3; 105.9)	1.61 (1.48; 1.75)
Seroprotection, % (95% CI)			Seroprotection difference, % (95% CI)
H1N1	94.9 (93.9; 95.9)	87.4 (85.2; 89.4)	7.6 (5.4; 9.9)
H3N2	97.3 (96.5; 98.0)	94.8 (93.2; 96.1)	2.5 (1.1; 4.2)
B	93.4 (92.2; 94.4)	84.5 (82.1; 86.7)	8.9 (6.4; 11.5)

[a] Of the total *N* in this group, 1 participant had a valid serology test for influenza B but not for influenza A.
[b] Of the total *N* in this group, 2 participants had a valid serology test for influenza A but not for influenza B.

No cases meeting the primary endpoint of laboratory-confirmed influenza caused by viral types/subtypes similar to those in the vaccine were observed. Only 22 cases of laboratory-confirmed influenza caused by any viral types/subtypes were ascertained, with all samples further characterized (21 out of 22) being classified as A/California/7/2009-like by genetic sequencing and/or standard ferret HAI testing. The efficacy of HD vaccine relative to SD vaccine, based on cases of laboratory-confirmed ILI caused by any viral types/subtypes was 12.5% and 12.6% in the PPAS and FAS (intent-to-treat), respectively (Table 4). CIs for these estimates were wide and did not allow the demonstration of superior efficacy for the HD vaccine. Among participants in the FAS, 1500 (24.56%) of HD participants and 737 (24.16%) of SD participants reported having received H1N1 monovalent pandemic influenza vaccine at any time during the season.

4. Discussion

The study did not meet its primary objective because no cases of laboratory-confirmed influenza illness caused by viral types/subtypes antigenically similar to the vaccine formulation were documented. However, the study allowed for evaluation of the safety and immunogenicity of Fluzone High-Dose compared to Fluzone.

Table 4
Efficacy of Fluzone High-Dose relative to Fluzone.

	Fluzone HD *n*/*N* (per 1000 participants)	Fluzone *n*/*N* (per 1000 participants)	Relative efficacy % (95% CI)
Per-Protocol Analysis Set			
Laboratory-confirmed influenza-like illness caused by any viral types/subtypes	14/6013 (2.33)	8/3008 (2.66)	12.5 (−140.9; 65.7)
Culture-confirmed influenza-like illness caused by any viral types/subtypes	13/6013 (2.16)	7/3008 (2.33)	7.1 (−175.0; 65.6)
PCR-confirmed influenza-like illness caused by any viral types/subtypes	14/6013 (2.33)	8/3008 (2.66)	12.5 (−140.9; 65.7)
Full Analysis Set (intent-to-treat)			
Laboratory-confirmed influenza-like illness caused by any viral types/subtypes	14/6107 (2.29)	8/3051 (2.62)	12.6 (−140.5; 65.8)
Culture-confirmed influenza-like illness caused by any viral types/subtypes	13/6107 (2.13)	7/3051 (2.29)	7.2 (−174.6; 65.6)
PCR-confirmed influenza-like illness caused by any viral types/subtypes	14/6107 (2.29)	8/3051 (2.62)	12.6 (−140.5; 65.8)

n: participants with laboratory-confirmed influenza
N: vaccinated participants randomized to the respective vaccine in the Full Analysis Set and randomized and administered the respective vaccine in the Per-Protocol Analysis Set.

The study provided further reassurance regarding the safety of Fluzone High-Dose. The rates of SAEs and deaths were similar between groups and also similar to those reported for the pivotal study FIM05 [10]. Very few study participants discontinued the study due to SAEs, and the proportion was identical for both vaccine groups. Three SAEs were classified as related to the vaccines according to the investigators' judgment, one in the Fluzone High-Dose group and two in the Fluzone group. None of the related SAEs led to study discontinuation.

This study demonstrated that in elderly adults, the HD vaccine induces significantly higher antibody responses to all three influenza strains compared to the SD vaccine, extending the results of the previous pivotal study [10].

Acknowledging the questionable value of any efficacy estimates due to the limited number of laboratory-confirmed influenza cases ascertained, the study allowed for the exploratory assessments of vaccine efficacy against a major variant influenza strain. Efficacy results derived from this study need to be interpreted with caution given the lack of precision of the study efficacy estimates.

The point estimates for efficacy assessments suggest that Fluzone High-Dose may confer some clinical benefit over Fluzone for strains that are quite distant antigenically from the vaccine formulations. The observed relative vaccine efficacy against laboratory-confirmed ILI caused by "any" influenza viral type/subtype (irrespective of matching to the vaccine) was 12.6% in the intent-to-treat analysis. All of the strains that could be antigenically characterized were proven to be similar to the pandemic strain A/California/7/2009, considered extremely distant antigenically from the actual H1N1 strain formulation contained in the control and investigational study vaccines [14]. Since the frequency of vaccination with monovalent pandemic influenza vaccine was essentially the same for both groups, this observation is not confounded by misbalanced between-group exposure to the pandemic vaccine. Although it remains to be proven, it is reasonable to hypothesize that the level of relative efficacy observed for strains that are closer to the vaccine formulation will likely be higher. Multiple studies have indicated that the level of similarity between circulating strains and the vaccine formulation has a significant impact on the observed absolute vaccine efficacy [15], and the same is expected for relative vaccine efficacy assessments. Moreover, one earlier study suggests that Fluzone High-Dose may confer increased cross-protection against antigenically different strains compared to Fluzone, based on observed antibody responses [16].

In conclusion, the study confirms that Fluzone High-Dose is safe and well tolerated, and that it provides superior immune responses than standard dose Fluzone. Although a modest positive efficacy was suggested against a strain highly distant from the vaccine components, demonstration of the clinical benefit of Fluzone High-Dose over Fluzone requires a separate large randomized, controlled trial.

Acknowledgments

The authors would like to thank the investigators from the 99 participating research sites and the FIM07 Study Team for their contributions to the trial, and the subjects for their participation.

Conflict of interest statement: The study was sponsored by Sanofi Pasteur. C.A.D., A.J.D., E.J., V.L. and M.D. are employees of Sanofi Pasteur. H.K.T. has received research funding from Sanofi Pasteur and MedImmune/Astrazeneca.

References

[1] Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003;289(2):179–86.
[2] Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, et al. Influenza-associated hospitalizations in the United States. JAMA 2004;292(11):1333–40.
[3] Fiore AE, Uyeki TM, Broder K, Finelli L, Euler GL, Singleton JA, et al. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep 2010;59(RR-8):1–62.
[4] Palache A. Seasonal influenza vaccine provision in 157 countries (2004–2009) and the potential influence of national public health policies. Vaccine 2011;29(51):9459–66.
[5] Takayama M, Wetmore CM, Mokdad AH. Characteristics associated with the uptake of influenza vaccination among adults in the United States. Prev Med 2012;54(5):358–62.
[6] Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. Adv Intern Med 1995;123:518–27.
[7] Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. JAMA 1994;272(21):661–5.
[8] Praditsuwan R, Assantachai P, Wasi C, Puthavatana P, Kositanont U. The efficacy and effectiveness of influenza vaccination among Thai elderly persons living in the community. J Med Assoc Thai 2005;88(2):256–64.
[9] Couch RB, Keitel WA, Cate TR. Improvement of inactivated influenza virus vaccines. J Infect Dis 1997;176(Suppl. 1):S38–44.
[10] Falsey A, Treanor JJ, Tornieporth N, Capellan J. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis 2009;200:172–80.
[11] Wood JM, Gaines-Das RE, Taylor J, Chakraverty P. Comparison of influenza serological techniques by international collaborative study. Vaccine 1994;12(2):167–74.
[12] Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17:857–72.
[13] Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873–90.
[14] Garten RJ, Davis CT, Russell CA, Shu B, Lindstrom S, Balish A, et al. Antigenic and genetic characteristics of swine origin 2009 A(H1N1) influenza viruses circulating in humans. Science 2009;325(5937):197–201.
[15] Jefferson T, Di Pietrantonj C, Rivetti A, Bawazeer GA, Al-Ansary LA, Ferroni E. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev 2010;7:CD001269.
[16] Keitel WA, Atmar RL, Nino D, Cate TR, Couch RB. Increasing doses of an inactivated influenza A/H1N1 induce increasing levels of cross-reacting antibody to subsequent, antigenically different, variants. J Infect Dis 2008;198:1016–8.