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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi Pasteur	**Study Identifiers:** U1111-1120-1300, IND 4518, NCT01427309
Drug substance(s): High-dose trivalent inactivated influenza vaccine	**Study code:** FIM12
Title of the study: Efficacy Study of Fluzone® High-Dose Vaccine Compared With Fluzone® Vaccine In Elderly Adults	
Study center(s): This was a multi-center trial conducted at 126 sites in the United States and Canada.	
Study period: Date first subjects enrolled: 06/Sep/2011 Date last subjects completed: 31/May/2013	
Phase of development: Phase IIIb/IV	

Objectives:

Primary Objectives:

Efficacy Objective

To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to laboratory-confirmed influenza, caused by any influenza viral types/subtypes, associated with the occurrence of a protocol-defined Influenza-like Illness (ILI).

Secondary Objectives:

Efficacy Objectives

1) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to culture-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a protocol-defined ILI
2) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to culture-confirmed influenza, caused by any influenza viral types/subtypes, associated with the occurrence of a protocol-defined ILI
3) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to culture-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a modified Centers for Disease Control and Prevention (CDC)-defined ILI
4) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to culture-confirmed influenza caused by any influenza viral types/subtypes, associated with the occurrence of a modified CDC-defined ILI
5) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to culture-confirmed influenza caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a respiratory illness
6) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to culture-confirmed influenza caused by any influenza viral types/subtypes, associated with the occurrence of a respiratory illness
7) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to laboratory-confirmed influenza caused by viral types/subtypes similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a protocol-defined ILI

8) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to laboratory-confirmed influenza caused by viral types/subtypes similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a respiratory illness

9) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to laboratory-confirmed influenza caused by any influenza viral types/subtypes, associated with the occurrence of a respiratory illness.

10) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to laboratory-confirmed influenza caused by viral types/subtypes similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a modified CDC-defined ILI

11) To compare the clinical efficacy of Fluzone High-Dose to that of Fluzone in elderly adults, with respect to laboratory-confirmed influenza caused by any influenza viral types/subtypes, associated with the occurrence of a modified CDC-defined ILI

Observational Objectives:

Effectiveness Objectives

1) To describe in each vaccine group the following events that are associated with cases of laboratory-confirmed influenza caused by any viral types/subtypes, associated with the occurrence of a protocol-defined ILI:
   - Rates of pneumonia
   - Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
   - Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

2) To describe in each vaccine group the following events that are associated with cases of culture-confirmed influenza caused by viruses antigenically similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a protocol-defined ILI:
   - Rates of pneumonia
   - Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
   - Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

3) To describe in each vaccine group the following events that are associated with cases of culture-confirmed influenza caused by any viral types/subtypes, associated with the occurrence of a protocol-defined ILI:
   - Rates of pneumonia
   - Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
   - Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

4) To describe in each vaccine group the following events that are associated with cases of culture-confirmed influenza caused by viruses antigenically similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a modified CDC-defined ILI:
   - Rates of pneumonia
   - Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
   - Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

5) To describe in each vaccine group the following events that are associated with cases of culture-confirmed influenza caused by any viral types/subtypes, associated with the occurrence of a modified CDC-defined ILI
   - Rates of pneumonia
   - Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
   - Rates of health care utilization (hospitalizations, emergency room visits, or non- routine medical office visits [including urgent care visits]) and medication use

6) To describe in each vaccine group the following events that are associated with cases of culture-confirmed influenza caused by viruses antigenically similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a respiratory illness:

- Rates of pneumonia
- Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
- Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

7) To describe in each vaccine group the following events that are associated with cases of culture-confirmed influenza caused by any viral types/subtypes, associated with the occurrence of a respiratory illness:

- Rates of pneumonia
- Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
- Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

8) To describe in each vaccine group the following events that are associated with cases of laboratory-confirmed influenza caused by viruses similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a protocol-defined ILI:

- Rates of pneumonia
- Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
- Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

9) To describe in each vaccine group the following events that are associated with cases of laboratory-confirmed influenza caused by viruses similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a respiratory illness:

- Rates of pneumonia
- Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
- Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

10) To describe in each vaccine group the following events that are associated with cases of laboratory-confirmed influenza caused by any viral types/subtypes associated with the occurrence of a respiratory illness:

- Rates of pneumonia
- Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
- Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

11) To describe in each vaccine group the following events that are associated with cases of laboratory-confirmed influenza caused by viruses similar to those contained in the respective annual vaccine formulations, associated with the occurrence of a modified CDC-defined ILI:

- Rates of pneumonia
- Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
- Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

12) To describe in each vaccine group the following events that are associated with all cases of laboratory-confirmed influenza caused by any viral types/subtypes, associated with the occurrence of a modified CDC-defined ILI:
    - Rates of pneumonia
    - Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
    - Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use
13) To describe in each vaccine group the following events that are associated with all cases of protocol-defined ILI (with or without laboratory confirmation):
    - Rates of pneumonia
    - Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
    - Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use
14) To describe in each vaccine group the following events that are associated with all cases of respiratory illness (with or without laboratory confirmation):
    - Rates of pneumonia
    - Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
    - Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

Safety Objectives

1) To describe the rates in each vaccine group of all SAEs (including AESIs) that occurred during the surveillance period
2) To describe the rates in each vaccine group of all deaths that occurred during the surveillance period

Exploratory Objectives:

Effectiveness Objective

To describe in each vaccine group the following events that were associated with all cases of modified CDC-defined ILI:

- Rates of pneumonia
- Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions
- Rates of health care utilization (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]) and medication use

Immunogenicity Objectives

1) To estimate an HAI correlate of protection against culture-confirmed influenza associated with protocol-defined ILI caused by each viral type/subtype antigenically similar to those contained in the vaccine formulations
2) To estimate an HAI correlate of protection against laboratory-confirmed influenza associated with protocol-defined ILI caused by each viral type/subtype similar to those contained in the vaccine formulations

Methodology:

General Design

This was a Phase IIIb/IV, randomized, modified double-blind, active-controlled, multi-center trial in elderly adults (≥ 65 years of age). The trial compared the efficacy of Fluzone High-Dose to that of Fluzone in preventing laboratory-confirmed (culture or polymerase chain reaction [PCR]) influenza illness in elderly adults.

The trial spanned 2 influenza seasons. Each study year, participants were randomized to 1 of 2 trial groups in a 1:1 ratio to receive, prior to the start of the influenza season, 1 dose of either:

- Fluzone High-Dose vaccine (60 µg of hemagglutinin [HA] for each viral strain)
- Fluzone vaccine (15 µg of HA for each viral strain)

Enrollment was to be continued until each year's enrollment goals were reached or until approximately 15 November. Subjects who had participated in the first year and met the eligibility criteria could have been re-enrolled and re-randomized in the second year, and individuals who had not participated in the first year of the study could have been assessed for eligibility and participated in the second year. A total of 14,500 subjects were to be enrolled in the first year. The sample size in the second year was adjusted to maintain the likelihood of achieving the overall expected number of cases for the primary endpoint. The sample size for the second year was 17,500, for a total of 32,000 subject-seasons of influenza surveillance. Participants were followed until the end of each season.

Each year, a subset of approximately one-third of subjects randomly selected across participating sites was to provide a serum sample for immunogenicity testing 28 days post-vaccination.

Definitions

Respiratory Illness: occurrence of a new onset (or exacerbation of a pre-existing condition/symptom) of one or more of the following symptoms (that persist for or reoccur after a period of at least 12 hours): sneezing, stuffy or runny nose (nasal congestion), sore throat, cough, sputum production, wheezing, difficulty breathing.

Protocol-defined Influenza-like Illness (ILI): occurrence of at least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: fever (defined as temperature > 99.0°F [> 37.2°C]), chills (shivering), tiredness (fatigue), headache, or myalgia (muscle aches).

Modified Centers for Disease Control and Prevention (CDC)-defined ILI: occurrence of fever (defined as temperature > 99.0°F [> 37.2°C]) with cough or sore throat.

Laboratory-confirmed Influenza: a positive influenza result on either PCR and/or viral culture of a nasopharyngeal (NP) swab sample.

Culture-confirmed Influenza: a positive influenza result on viral culture.

Similarity to Vaccine Components: laboratory-confirmed isolate was deemed similar to one of the vaccine components according to genomic sequence or antigenicity testing (hemagglutination inhibition [HAI] against a panel of known standard ferret reference antisera).

Antigenic Similarity to Vaccine Components: culture-confirmed isolate was deemed similar to one of the vaccine components according to antigenicity testing (HAI against a panel of known standard ferret reference antisera).

Surveillance for Respiratory Illness

Following vaccination, subjects were instructed to contact the site (passive surveillance) if they experienced symptoms of a respiratory illness during the annual surveillance periods, from Day 14 after vaccination until 30 April of the following year.

In addition, during a period from 2 weeks post-vaccination until approximately 31 December and from 01 March until 30 April, subjects were contacted by a call center (active surveillance) once a week; between approximately 01 January and the end of February of the respective influenza season, they were contacted by the call center twice a week.

Collection of NP Swabs

During the period from Day 14 after vaccination until 30 April of the following year, the site arranged for a NP swab to be taken if the subject experienced a new onset (or exacerbation of a pre-existing condition/symptom) of one or more of the above-mentioned symptoms of respiratory illness (that persisted for or reoccurred after a period of at least 12 hours).

The NP swab was to be taken as soon as possible and no later than 5 days (between Day 0 and Day 4) of the first occurrence of qualifying respiratory symptom(s) for laboratory confirmation of influenza.

Reporting of Events Temporally Associated With a Respiratory Illness

In addition to obtaining an NP swab, the site collected detailed information about the respiratory illness, including the presence or not of concurrent systemic symptoms as well as information on occurrence of pneumonia, new onset or exacerbations of pre-existing cardio-respiratory conditions, health care utilization events (hospitalizations, emergency room [ER] visits, and non-routine office visits [including urgent care visits]) and medication use within 30 days of illness start date.

In the event that an NP swab could not be collected, the research site was still to obtain the above information. For respiratory illnesses that started after 15 April, it was acceptable to follow up for less than 30 days, with information collected up to the time of the last telephone call (15 May [+7 days]).

Laboratory Testing for the Confirmation of Influenza and Determination of Similarity to Vaccine Components

All NP specimens were submitted for analysis by both culture and PCR, and a positive result on either test was considered a laboratory-confirmed case of influenza.

Positive cultures or positive PCR samples underwent additional testing (typing, subtyping, and strain identification, utilizing genetic sequencing and antigenic analysis using HAI against a panel of known standard ferret reference antisera to different viral strains) to determine if the virus detected was similar to any of those contained in the vaccine formulation for the respective season.

Safety Surveillance

All serious adverse events (SAEs) were collected from Day 0 until the last telephone call of the study year.

Adverse events of special interest (AESIs) were captured as SAEs. These included new onset of Guillain-Barré Syndrome (GBS), Bell's Palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.

Number of subjects/patients:	Planned: 32000
	Randomized: 31989
	Treated: 31983
Evaluated:	Efficacy: 31803
	Effectiveness: 31803
	Immunogenicity: 31803
	Safety: 31983

Diagnosis and criteria for inclusion:

A potential subject had to meet all of the following criteria to be considered for trial enrollment:

1) Aged ≥ 65 years on the day of vaccination
2) Informed consent form signed and dated
3) Able to attend all scheduled visits and to comply with all trial procedures

Study treatments

Investigational Product: Fluzone High-Dose is a licensed (in the US) injectable sterile suspension with trivalent inactivated Type A and B influenza split virus antigens, provided in a pre-filled single-dose syringe.

Form: Liquid; essentially clear and opalescent in color

Composition: Each 0.5 mL dose of vaccine contains the following 3 influenza virus strains:

Year 1: Fluzone High-Dose (Influenza Virus Vaccine, 2011–2012 Strains)

- A/California/7/2009 (H1N1) 60 µg
- A/Victoria/210/2009 (H3N2) 60 µg
- B/Brisbane/60/2008 60 µg

Year 2: Fluzone High-Dose (Influenza Virus Vaccine, 2012–2013 Strains)

- A/California/7/2009 (H1N1) 60 µg
- A/Victoria/361/2011 (H3N2) 60 µg
- B/Texas/6/2011 (a B/Wisconsin/1/2010-like virus) 60 µg

Route of administration: Intramuscular (IM), injected into the deltoid area

Control Product: Fluzone is a licensed (in the US and Canada) injectable sterile suspension with trivalent inactivated Type A and B influenza split virus antigens, provided in a pre-filled single-dose syringe.

Form: Liquid; essentially clear and opalescent in color

Composition: Each 0.5 mL dose of vaccine contains the following 3 influenza virus strains:

Year 1: Fluzone (Influenza Virus Vaccine, 2011–2012 Strains)

- A/California/7/2009 (H1N1) 15 µg
- A/Victoria/210/2009 (H3N2) 15 µg
- B/Brisbane/60/2008 15 µg

Year 2: Fluzone (Influenza Virus Vaccine, 2012–2013 Strains)

- A/California/7/2009 (H1N1) 15 µg
- A/Victoria/361/2011 (H3N2) 15 µg
- B/Texas/6/2011 (a B/Wisconsin/1/2010-like virus) 15 µg

Route of administration: IM, injected into the deltoid area

Duration of participation: The duration of each subject's participation in the respective study year was to be 6 to 8 months, depending on the time of enrollment.

Criteria for evaluation:

Primary Endpoints:

Efficacy Endpoint

Occurrences of culture- or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a protocol-defined ILI.

Secondary Endpoints:

Efficacy Endpoints

1) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are antigenically similar to those contained in the vaccine formulations, in association with a protocol-defined ILI
2) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a protocol-defined ILI
3) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are antigenically similar to those contained in the vaccine formulations, in association with a modified CDC-defined ILI
4) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a modified CDC-defined ILI
5) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are antigenically similar to those contained in the vaccine formulations, in association with a respiratory illness
6) Occurrences of culture-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a respiratory illness
7) Occurrences of culture- and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are similar to those contained in the vaccine formulations, in association with a protocol-defined ILI
8) Occurrences of culture- and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are similar to those contained in the vaccine formulations, in association with a respiratory illness
9) Occurrences of culture- and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a respiratory illness

10) Occurrences of culture-and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are similar to those contained in the vaccine formulations, in association with a modified CDC-defined ILI

11) Occurrences of culture- and/or PCR-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a modified CDC-defined ILI

Observational Endpoints:

Effectiveness Endpoints

1) *In association with cases of laboratory-confirmed influenza, caused by any viral types/subtypes that occurred in the context of a protocol-defined ILI*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

2) *In association with cases of culture-confirmed influenza, antigenically similar to those contained in the respective annual vaccine formulations that occurred in the context of a protocol-defined ILI*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

3) *In association with cases of culture-confirmed influenza, caused by any viral types/subtypes that occurred in the context of a protocol-defined ILI*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

4) *In association with cases of culture-confirmed influenza, antigenically similar to those contained in the respective annual vaccine formulations that occurred in the context of a modified CDC-defined ILI*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

5) *In association with cases of culture-confirmed influenza, caused by any viral types/subtypes that occurred in the context of a modified CDC-defined ILI*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

6) *In association with cases of culture-confirmed influenza, antigenically similar to those contained in the respective annual vaccine formulations that occurred in the context of a respiratory illness*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

7) *In association with cases of culture-confirmed influenza, caused by any viral types/subtypes that occurred in the context of a respiratory illness*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

8) *In association with cases of laboratory-confirmed influenza, similar to those contained in the respective annual vaccine formulations that occurred in the context of a protocol-defined ILI*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

9) *In association with cases of laboratory-confirmed influenza, similar to those contained in the respective annual vaccine formulations that occurred in the context of a respiratory illness*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

10) *In association with cases of laboratory-confirmed influenza, caused by any viral types/subtypes that occurred in the context of a respiratory illness*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

11) *In association with cases of laboratory-confirmed influenza, similar to those contained in the respective annual vaccine formulations that occurred in the context of a modified CDC-defined ILI*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

12) *In association with cases of laboratory-confirmed influenza, caused by any viral types/subtypes that occurred in the context of a modified CDC-defined ILL*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

13) *In association with all cases of protocol-defined ILI*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

14) *In association with all cases of respiratory illness*: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), instances of medication use, from 14 days post-vaccination until the end of each respective influenza season

Safety Endpoints

1) SAEs (including AESIs) from Day 0 until end of surveillance period

2) Deaths from all causes, from Day 0 until end of surveillance period

Exploratory Endpoints:

Effectiveness Endpoint

In association with all cases of modified CDC-defined ILI: episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as occurrences of health care utilization events (hospitalizations, emergency room visits, or non-routine medical office visits [including urgent care visits]), and instances of medication use, from 14 days post-vaccination until the end of each respective influenza season.

Immunogenicity Endpoints

1) HAI titer 28 days post-vaccination (measured in a randomly selected subset of approximately one-third of the subjects across all sites each year) for the influenza types/subtypes contained in the vaccines, together with occurrences of culture-confirmed influenza illness caused by isolates antigenically similar to the vaccine components associated with a protocol-defined ILI as described for Secondary Endpoint 1

2) HAI titer 28 days post-vaccination (measured in a randomly selected subset of approximately one-third of the subjects across all sites each year) for the influenza types/subtypes contained in the vaccines, together with occurrences of culture- or PCR-confirmed influenza caused by isolates similar to the vaccine components associated with a protocol-defined ILI as described for Secondary Endpoint 7

Statistical methods:

Primary Objectives:

Efficacy Objectives:

The vaccine efficacy (VE) of Fluzone High-Dose relative to Fluzone was estimated for the primary endpoint by:

$$\text{Relative VE} = 1 - [\ (C_{HD} / N_{HD}) / (C_{FL} / N_{FL})\ ]$$

where:

- Relative VE is the efficacy of Fluzone High-Dose vaccine relative to that of Fluzone vaccine
- C_{HD} is the number of cases in the Fluzone High-Dose Group
- N_{HD} is the number of subjects in the Fluzone High-Dose Group
- C_{FL} is the number of cases in the Fluzone Group
- N_{FL} is the number of subjects in the Fluzone Group

Confidence intervals (CIs) for relative VE were calculated by an exact method conditional on the total number of cases in both groups.

Fluzone High-Dose was considered superior to Fluzone if the lower bound of the 95% two-sided CI for relative VE was > 9.1% for the primary objective.

Secondary Objectives:

Efficacy Objectives:

Estimation of relative VE for the secondary objectives was as described for the primary objective; for each estimate of relative VE, a 95% CI was calculated.

Observational Objectives

Effectiveness Objectives:

For each observational effectiveness objective, rates of the specified conditions and events in each vaccine group were presented and the relative risk calculated, together with 95% CIs for the relative risks.

Safety Objectives:

For each observational safety objective, percentages of subjects in each vaccine group reporting the specified conditions and events were presented, together with 95% CIs. For aggregate numbers of SAEs and deaths, the relative risk was calculated, together with a 95% CI.

Exploratory Objectives

Effectiveness Objective:

For the effectiveness exploratory objective, the statistical methods were as for the observational effectiveness objectives above.

Immunogenicity Objectives:

For the immunogenicity exploratory objectives, a threshold value of HAI predictive of the efficacy observed was found, based on the methods used for invasive pneumococcal disease following vaccination with 7-valent pneumococcal conjugate vaccine and for meningococcal C infection.

Summary:

Population Characteristics:

Study Subjects

A total of 31,989 subjects were enrolled (15,991 in the Fluzone High-Dose Group and 15,998 in the Fluzone Group). The first subject in this trial was enrolled on 06 September 2011 (FVFS). The trial was completed (defined as the date of the LCLS) on 31 May 2013. A total of 14,500 and 17,489 subjects were enrolled in Year 1 and Year 2, respectively. There were 7645 subjects who were enrolled and randomized in both years.

Out of the 31,989 randomized subjects, 31,983 subjects received a study vaccine (1 subject in the Fluzone High-Dose Group and 2 subjects in the Fluzone Group did not receive a study vaccine during Year 1; 3 subjects in the Fluzone Group did not receive a study vaccine during Year 2). A total of 5 subjects in the Fluzone High-Dose Group and 7 subjects in the Fluzone Group during Year 1, and 4 subjects in the Fluzone High-Dose Group and 8 subjects in the Fluzone Group during Year 2 did not receive the vaccine they were randomized to.

A total of 1522 (4.76%) of the randomized subjects discontinued the study before the end of the study year: 373 (5.14%) subjects in the Fluzone High-Dose Group and 409 (5.64%) subjects in the Fluzone Group discontinued before the end of Year 1; 361 (4.13%) subjects in the Fluzone High-Dose Group and 379 (4.33%) subjects in the Fluzone Group discontinued before the end of Year 2.

Protocol deviations

A total of 186 subjects were excluded from the Per Protocol Analysis Set (PPAS). The most frequent reason for exclusion from the PPAS was no surveillance contact, reported for 93 (0.29%) subjects (50 [0.34%] subjects during Year 1, and 43 [0.25%] subjects during Year 2).

A total of 16 (0.05%) subjects (1 [0.01%] during Year 1, and 15 [0.09%] during Year 2) were excluded from the PPAS based on protocol deviations identified in the course of study monitoring which, in the opinion of the Sponsor's Responsible Medical Officers (based on blinded review), were likely to impact the validity of the data. These 16 subjects received a vaccine that was deemed unacceptable for use due to temperature excursion during storage.

Efficacy and Effectiveness

Primary Objective

Efficacy Objective:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of laboratory-confirmed influenza caused by any viral types/subtypes associated with the occurrence of a protocol-defined ILI in the PPAS, was 24.24% (95% CI 9.69; 36.52) for Year 1 and Year 2 combined, 45.25% (95% CI 6.86; 68.57) for Year 1, and 20.74% (95% CI 4.39; 34.36) for Year 2. The lower bound of the 95% CI for Year 1 and Year 2 combined exceeded 9.1%, the pre-defined superiority threshold for Fluzone High-Dose compared to Fluzone.

Similar results were shown for the Full Analysis Set (FAS) as randomized (see Section 9, Table 9.61). The lower bound of the 95% CI for Year 1 and Year 2 combined also exceeded 9.1% (VE was 24.24% [95% CI 9.71; 36.50]).

Secondary Objectives

Efficacy Objective #1:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of culture-confirmed influenza caused by influenza viral types/subtypes antigenically similar to those contained in the vaccine associated with the occurrence of a protocol-defined ILI in the PPAS, was 31.44% (95% CI 4.51; 51.05) for Year 1 and Year 2 combined, 71.44% (95% CI -50.02; 97.10) for Year 1, and 28.06% (95% CI -1.14; 49.09) for Year 2.

Efficacy Objective #2:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of culture-confirmed influenza caused by any viral types/subtypes associated with the occurrence of a protocol-defined ILI in the PPAS, was 23.13% (95% CI 7.44; 36.24) for Year 1 and Year 2 combined, 39.41% (95% CI -8.76; 67.05) for Year 1, and 20.75% (95% CI 3.48; 35.00) for Year 2.

Efficacy Objective #3:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of culture-confirmed influenza caused by influenza viral types/subtypes antigenically similar to those contained in the vaccine associated with the occurrence of a modified CDC-defined ILI in the PPAS was 51.05% (95% CI 16.77; 72.01) for Year 1 and Year 2 combined, 100.00% (95% CI -141.9; 100.00) for Year 1, and 47.49% (95% CI 10.02; 70.15) for Year 2.

Efficacy Objective #4:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of culture-confirmed influenza caused by any influenza viral types/subtypes associated with the occurrence of a modified CDC-defined ILI in the PPAS, was 23.55% (95% CI -2.50; 43.14) for Year 1 and Year 2 combined, 0.03% (95% CI -234.0; 70.08) for Year 1, and 25.06% (95% CI -1.66; 44.96) for Year 2.

Efficacy Objective #5:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of culture-confirmed influenza caused by influenza viral types/subtypes antigenically similar to those contained in the vaccine, associated with the occurrence of a respiratory illness in the PPAS, was 27.88% (95% CI 3.88; 46.08) for Year 1 and Year 2 combined, 22.24% (95% CI -134.6; 75.39) for Year 1, and 28.27% (95% CI 3.19; 47.06) for Year 2.

Efficacy Objective #6:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of culture-confirmed influenza caused by any influenza viral types/subtypes associated with the occurrence of a respiratory illness in the PPAS, was 18.25% (95% CI 3.87; 30.52) for Year 1 and Year 2 combined, 13.66% (95% CI -36.38; 45.57) for Year 1, and 18.85% (95% CI 3.40; 31.89) for Year 2.

Efficacy Objective #7:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of laboratory-confirmed influenza caused by influenza viral types/subtypes similar to those contained in the vaccine associated with the occurrence of a protocol-defined ILI in the PPAS, was 35.32% (95% CI 12.42; 52.49) for Year 1 and Year 2 combined, 64.01% (95% CI 20.29; 85.22) for Year 1, and 27.10% (95% CI -1.75; 48.01) for Year 2.

Efficacy Objective #8:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of laboratory-confirmed influenza caused by influenza viral types/subtypes similar to those contained in the vaccine associated with the occurrence of respiratory illness in the PPAS, was 27.31% (95% CI 6.01; 43.94) for Year 1 and Year 2 combined, 27.29% (95% CI -26.81; 58.88) for Year 1, and 27.26% (95% CI 2.48; 45.94) for Year 2.

Efficacy Objective #9:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of laboratory-confirmed influenza caused by any influenza viral types/subtypes associated with the occurrence of a respiratory illness in the PPAS, was 18.30% (95% CI 4.94; 29.82) for Year 1 and Year 2 combined, 17.57% (95% CI -23.46; 45.19) for Year 1, and 18.34% (95% CI 3.76; 30.77) for Year 2.

Efficacy Objective #10:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of laboratory-confirmed influenza caused by influenza viral types/subtypes similar to those contained in the vaccine associated with the occurrence of a modified CDC-defined ILI in the PPAS, was 48.96% (95% CI 16.60; 69.45) for Year 1 and Year 2 combined, 62.51% (95% CI -56.20; 93.59) for Year 1, and 46.38% (95% CI 9.03; 69.16) for Year 2.

Efficacy Objective #11:

The VE of Fluzone High-Dose relative to Fluzone, based on cases of laboratory-confirmed influenza caused by any influenza viral types/subtypes associated with the occurrence of a modified CDC-defined ILI in the PPAS, was 20.57% (95% CI -4.70; 39.88) for Year 1 and Year 2 combined, 9.12% (95% CI -135.7; 65.40) for Year 1, and 21.63% (95% CI -4.87; 41.59) for Year 2.

Observational and Exploratory Objectives (Effectiveness)

For Year 1 and Year 2 combined, the evaluable point estimates of the relative risks for the pneumonia events occurring within 30 days of a study-specified illness were consistently below 1. The comparisons were significant for pneumonia occurring within 30 days of a protocol-defined ILI regardless of laboratory confirmation of influenza (0.65 [95% CI 0.51; 0.84]) and pneumonia occurring within 30 days of a respiratory illness regardless of laboratory confirmation of influenza (0.71 [95% CI 0.58; 0.87]) in the PPAS.

The point estimates of the relative risks for new onset or exacerbation of pre-existing cardio-respiratory conditions occurring within 30 days of a study-specified illness were below 1 for 14 out of 15 comparisons. The comparison was significant for cardio-respiratory conditions occurring within 30 days of a modified CDC-defined ILI regardless of laboratory confirmation of influenza (0.76 [95% CI 0.63; 0.94]) in the PPAS.

The evaluable point estimates of the relative risks for any hospitalization event occurring within 30 days of a study-specified illness were consistently below 1. The comparison was significant for hospitalizations occurring within 30 days of a protocol-defined ILI regardless of laboratory confirmation of influenza (0.69 [95% CI 0.53; 0.90]) in the PPAS.

The comparisons for any ER visit within 30 days of a study-specified illness showed less consistency, with CIs for all comparisons including 1 in the PPAS.

The point estimates of the relative risks for any non-routine medical office visit occurring within 30 days of a study-specified illness were below 1 for 12 out of 15 comparisons. However, several of these point estimates were very close to 1. The comparisons were significant for non-routine medical office visits occurring within 30 days of a culture-confirmed modified CDC-defined ILI caused by strains antigenically similar to the vaccine components (0.50 [95% CI 0.27; 0.93]), and of a laboratory-confirmed modified CDC-defined ILI caused by strains similar to the vaccine components (0.53 [95% CI 0.30; 0.96]) in the PPAS.

The point estimates of the relative risks for medication use (antipyretics/analgesics/NSAIDs, antivirals or antibiotics) within 30 days of a study-specified illness were consistently lower than 1 in the PPAS. The comparisons were significant for medication use within 30 days of: a culture-confirmed protocol-defined ILI caused by strains antigenically similar to the vaccine components (0.71 [95% CI 0.52; 0.99]); a culture-confirmed modified CDC-defined ILI caused by strains antigenically similar to the vaccine components (0.44 [95% CI 0.27; 0.72]); a culture-confirmed respiratory illness caused by strains antigenically similar to the vaccine components (0.69 [95% CI 0.51; 0.94]); a laboratory-confirmed respiratory illness caused by strains similar to the vaccine components (0.75 [95% CI 0.57; 0.98]); a laboratory-confirmed modified CDC-defined ILI caused by strains similar to the vaccine components (0.54 [95% CI 0.34; 0.84]); and a modified CDC-defined ILI regardless of laboratory confirmation of influenza (0.90 [95% CI 0.83; 0.99]).

Immunogenicity

For the estimation of an HAI correlate of protection against culture-confirmed influenza caused by viral types/subtypes antigenically similar to the vaccine components, the number of cases was insufficient to obtain a reliable estimate for the influenza H1N1 subtype (in both years and overall), the influenza H3N2 subtype in Year 1, and the influenza B type in Year 1. The HAI correlate of protection estimated by the method used in the study for the A/Victoria/361/2011 strain (Year 2 H3N2 vaccine component) was 538.58; the estimate for the B/Texas/6/2011 strain (Year 2 B vaccine component) was 44.89. However, for both strains the 95% CIs were wide: (139.50, 3550.40) for the A/Victoria/361/2011 strain and (7.47, 287.54) for the B/Texas/6/2011 strain.

For the estimation of an HAI correlate of protection against laboratory-confirmed influenza caused by viral types/subtypes similar to the vaccine components, the number of cases was insufficient to obtain a reliable estimate for the influenza H1N1 subtype (in both years and overall) and for the influenza B type in Year 1. The HAI correlate of protection estimated by the method used in the study for the A/Victoria/210/2009 strain (Year 1 H3N2 vaccine component) was 46.41; the estimate for the A/Victoria/361/2011 strain (Year 2 H3N2 vaccine component) was 614.45; the estimate for the B/Texas/6/2011 strain (Year 2 B vaccine component) was 44.89. However, for the 3 strains the 95% CIs were wide: (8.24, 511.27) for the A/Victoria/210/2009 strain, (164.32, 4123.35) for the A/Victoria/361/2011 strain, and (7.47, 287.54) for the B/Texas/6/2011 strain.

Safety

Overview of Safety Findings

There were 1323 (8.27%) and 1442 (9.02%) subjects in the Fluzone High-Dose and Fluzone Groups, respectively, who experienced at least one SAE throughout the entire study period. A total of 99 (0.62%) subjects in the Fluzone High-Dose Group, and 103 (0.64%) subjects in the Fluzone Group experienced at least one SAE leading to study discontinuation. There were 3 subjects, all in the Fluzone High-Dose Group, who experienced at least one SAE considered as related to vaccination.

Deaths, Other SAEs, and Other Significant AEs

Deaths:

Throughout the study, there were a total of 83 (0.52%) and 84 (0.53%) deaths in the Fluzone High-Dose and Fluzone Groups, respectively. Of these deaths, 6 occurred within 30 days after vaccination, all in the Fluzone High-Dose Group. None of these 6 deaths were considered by the Investigator to be related to vaccination.

SAEs other than Deaths:

For both study groups, SAEs were most frequently reported in the SOC of Cardiac disorders (257 [1.61%] subjects in the Fluzone High-Dose Group and 287 [1.79%] subjects in the Fluzone Group), with the most frequently reported events within this SOC being atrial fibrillation (51 [0.32%] subjects in the Fluzone High-Dose Group and 67 [0.42%] subjects in the Fluzone Group), cardiac failure congestive (34 [0.21%] subjects in the Fluzone High-Dose Group and 51 [0.32%] subjects in the Fluzone Group), and myocardial infarction (35 [0.22%] subjects in the Fluzone High-Dose Group and 31 [0.19%] subjects in the Fluzone Group).

Most subjects with non-fatal SAEs recovered completely (1135 and 1258 subjects in the Fluzone High-Dose and Fluzone Groups, respectively). A minority of subjects reporting an SAE recovered with sequelae (75 and 73 subjects in the Fluzone High-Dose and Fluzone Groups, respectively) or had the event still ongoing at the time of final contact (103 and 111 subjects in the Fluzone High-Dose and Fluzone Groups, respectively).

Three subjects in the Fluzone High-Dose Group experienced at least 1 SAE that was considered by the Investigator to be related to the vaccination. Two of these related SAEs occurred within 30 days after vaccination. None of these related SAEs resulted in discontinuation from the study and all 3 subjects recovered completely.

AEs considered as Significant:

AESIs

The occurrence of AESIs was rare in both study groups, with 3 (0.02%) and 6 (0.04%) subjects reporting AESIs in the Fluzone High-Dose and Fluzone Groups, respectively, throughout the study. One of these AESIs occurred within 30 days after vaccination. None of these AESIs led to study termination.

AEs Leading to Withdrawal from the Study

SAEs

Throughout the study, 99 (0.62%) subjects and 103 (0.64%) subjects in the Fluzone High-Dose and Fluzone Groups, respectively, discontinued the study due to SAEs, most of which were deaths. None of these SAEs were considered by the Investigator to be related to the study vaccination. Of these discontinued subjects, 12 (0.08%) and 2 (0.01%) subjects in the Fluzone High-Dose and Fluzone Groups, respectively, experienced the SAE within 30 days after vaccine injection.

Other AEs

Three (0.02%) and 1 (0.01%) subjects in the Fluzone High-Dose and Fluzone Groups, respectively discontinued the study due to other AEs.

Issue date: 06-Jul-2020

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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi Pasteur	**Study Identifiers:** U1111-1120-1300, IND 4518, NCT01427309
Drug substance(s): High-dose trivalent inactivated influenza vaccine	**Study code:** FIM12
Title of the study: Efficacy Study of Fluzone® High-Dose Vaccine Compared With Fluzone® Vaccine in Elderly Adults	
Study center(s): Study FIM12 was a multi-center study conducted at 126 sites in the United States and Canada.	
Study period: Date first subjects enrolled: 06/Sep/2011 Date last subjects completed: 31/May/2013	
Phase of development: Phase IIIb/IV	
Objectives: The objective of this addendum is to provide data on the effectiveness of Fluzone High-Dose vaccine compared to Fluzone vaccine in preventing all-cause hospitalization and serious cardiorespiratory events possibly related to influenza infection.	
Methodology: Study FIM12 was a Phase IIIb/IV, randomized, modified double-blind, active-controlled, multi-center study in elderly adults (≥ 65 years of age). The study compared the efficacy of Fluzone High-Dose vaccine to that of Fluzone vaccine in preventing laboratory-confirmed (culture or polymerase chain reaction) influenza illness in elderly adults. The study spanned 2 influenza seasons (2011–2012 [Year 1] and 2012–2013 [Year 2]). Each study year, subjects were randomly assigned in a 1:1 ratio to receive 1 dose of either Fluzone High-Dose (60 µg of hemagglutinin [HA] for each viral strain) or Fluzone vaccine (15 µg of HA for each viral strain) prior to the start of the influenza season. Each season, subjects were followed for 6–8 months post-vaccination for the occurrence of influenza and serious adverse events (SAEs), including adverse events of special interest. Serious adverse events were defined as events that led to death or hospitalization (or its prolongation), were considered life-threatening or medically important, or resulted in disability. Based on available medical information, study investigators reported the diagnoses associated with all SAEs through an electronic data capture system. ***Adjudication of SAEs as "Serious Events Possibly Related to Influenza"*** Two physicians blinded to vaccination group independently reviewed all SAE diagnostic categories that were reported during Study FIM12; these diagnostic categories had been coded as "preferred terms" using the Medical Dictionary for Regulatory Activities versions 14.0 (for Year 1) and 15.0 (for Year 2) before study unblinding. A total of 1347 SAE preferred terms were reviewed. Cardiorespiratory SAE categories considered as possibly related to influenza infection were selected by each reviewer based solely on the medical nature of the reported preferred term for the diagnosis (for example, SAEs with a diagnosis preferred term of "pneumonia" were selected as possibly related to influenza, whereas SAEs with a diagnosis preferred term of "hip fracture" were excluded). The physician-reviewers then compared their respective selections and exclusions to attempt consensus, which was attained for 1335 (99.1%) SAE preferred terms. The 12 remaining discrepant SAE preferred term categorizations were arbitrated by a third blinded physician-reviewer. Final adjudication of SAE categories as "possibly related to influenza" was done before study unblinding, and the selected categories were pre-specified in a supplementary analysis plan. Adjudication was done without regard to influenza confirmation in the study.	

Number of subjects/patients:	Planned: 32000 Randomized: 31989 Treated: 31983
Evaluated:	Effectiveness:31803

Criteria for evaluation:

The endpoints reported in this CSR addendum include all-cause hospitalizations and selected serious cardiorespiratory events. For the supplementary analysis, selected serious cardiorespiratory events reported in Study FIM12 were grouped into 7 pre-specified categories and represented the following endpoints: pneumonia events, asthma/chronic obstructive pulmonary disease (COPD)/bronchial events, influenza events (serious laboratory-confirmed influenza diagnosed outside study procedures by a subject's health-care provider), other respiratory events, coronary artery events, congestive heart failure events, and cerebrovascular events.

Statistical methods:

Rates of all-cause hospitalizations and selected serious cardiorespiratory events were derived for Fluzone High-Dose and Fluzone vaccine groups using the number of hospitalizations or events per 1000 subject-seasons. For this calculation, the assumption of independence of observations was not achieved in case of multiple occurrences of events for the same subject-season. Therefore, a complementary analysis was also performed for confirmation, using the number of subjects with at least 1 episode of a specified event per 1000 subject-seasons. Rate ratios (RRs) and corresponding 2-sided 95% confidence intervals (CIs) were estimated using the method given by Blackwelder. Relative vaccine effectiveness (rVE) was calculated as (1−RR)×100.

Analyses were performed on the FAS according to the vaccine assigned at randomization. The FAS comprised all subjects who received study vaccine. Estimates were obtained for each study season and for both seasons combined. Statistical significance was defined as a 2-sided 95% CI excluding the null value (1 for RR and 0 for rVE), i.e., at a 2.5% level for any endpoint to detect signals. No adjustment for multiplicity was applied.

Summary:

Study FIM12 was a randomized, modified double-blind, active-controlled, multi-center, Phase IIIb/IV study that compared the efficacy of Fluzone High-Dose vaccine relative to standard-dose Fluzone vaccine in adults ≥ 65 years of age. The study met its primary objective, demonstrating superior efficacy of Fluzone High-Dose vaccine relative to Fluzone vaccine for the prevention of laboratory-confirmed influenza in adults ≥ 65 years of age. The point estimates of secondary efficacy objectives were supportive of the primary observation, with estimates for rVE being positive across different clinical illness definitions and different methods of influenza confirmation. In addition, the rVE point estimates were consistently positive across both study years and across influenza types.

Supplementary analyses of data from Study FIM12, which are presented in this addendum, evaluated the effectiveness of Fluzone High-Dose vaccine compared to Fluzone vaccine in preventing all-cause hospitalization and serious cardiorespiratory events possibly related to influenza infection.

Rates of All-Cause Hospitalization and Serious Cardiorespiratory Events Possibly Related to Influenza

Rates (events per 1000 subject-seasons) of all-cause hospitalization did not differ between the Fluzone High-Dose vaccine group and the Fluzone vaccine group in Year 1 (109.89 vs. 109.47 per 1000 subject-seasons [RR, 1.00; 95% CI: 0.91–1.10]), whereas they were significantly lower for the Fluzone High-Dose vaccine group in Year 2 (83.90 vs. 97.15 per 1000 subject-seasons [RR, 0.86; 95% CI: 0.79–0.95]) and for both study years combined (95.68 vs 102.73 per 1000 subject-seasons [RR, 0.931; 95% CI: 0.872–0.995]).

In Year 2, significantly lower rates (events per 1000 subject-seasons) in the Fluzone High-Dose vaccine group were observed for all selected serious cardiorespiratory events possibly related to influenza combined (Fluzone High-Dose vaccine group: 25.64 per 1000 subject-seasons; Fluzone vaccine group: 32.46 per 1000 subject-seasons [RR, 0.79; 95% CI: 0.66–0.94]), and both years combined (Fluzone High-Dose vaccine group: 26.77 per 1000 subject-seasons; Fluzone vaccine group: 32.51 per 1000 subject-seasons [RR, 0.82; 95% CI: 0.73–0.93]). In addition, significantly lower rates in the Fluzone High-Dose vaccine group were observed for serious pneumonia events in Year 1 (Fluzone High-Dose vaccine group: 4.00 per 1000 subject-seasons; Fluzone

vaccine group: 7.45 per 1000 subject-seasons [RR, 0.54; 95% CI: 0.34–0.84]), Year 2 (Fluzone High-Dose vaccine group: 4.81 per 1000 subject-seasons; Fluzone vaccine group: 7.32 per 1000 subject-seasons [RR, 0.66; 95% CI: 0.45–0.97]), and both years combined (Fluzone High-Dose vaccine group: 4.44 per 1000 subject-seasons; Fluzone vaccine group: 7.38 per 1000 subject-seasons [RR, 0.60; 95% CI: 0.45–0.81]), and for serious asthma/COPD/bronchial events in Year 2 (Fluzone High-Dose vaccine group: 3.89 per 1000 subject-seasons; Fluzone vaccine group: 6.17 per 1000 subject-seasons [RR, 0.63; 95% CI: 0.41–0.97]). A significantly lower rate for Fluzone vaccine compared to Fluzone High-Dose vaccine was observed only for the occurrence of serious asthma/COPD/bronchial events in Year 1 (Fluzone High- Dose vaccine group: 5.51 per 1000 subject-seasons; Fluzone vaccine group: 2.90 per 1000 subject-seasons [RR, 1.90; 95% CI: 1.12–3.22]).

When rates were calculated using the number of subjects with at least 1 episode of a specified event per 1000 subject-seasons, the rate of all-cause hospitalization for both years combined was significantly lower in the Fluzone High-Dose vaccine group than in the Fluzone vaccine group (Fluzone High-Dose vaccine group: 76.80 per 1000 subject-seasons; Fluzone vaccine group: 84.04 per 1000 subject-seasons [RR, 0.91; 95% CI: 0.85–0.98]).

Effectiveness of Fluzone High-Dose Vaccine Relative to Fluzone Vaccine

For both years combined, there was a significant reduction in the total number of serious cardiorespiratory events (rVE, 17.7% [95% CI: 6.6%–27.4%]) among Fluzone High-Dose vaccine recipients compared to Fluzone vaccine recipients, including a significant reduction in serious pneumonia events (rVE, 39.8% [95% CI: 19.3%–55.1%]). In addition, a borderline significant reduction in all-cause hospitalization (rVE, 6.9%; 95% CI: 0.5%–12.8%) was observed. Similar results were obtained when rates were defined by number of subjects with at least 1 episode of a specified event per 1000 subject-seasons (serious pneumonia events: rVE, 38.7%; 95% CI: 17.2%–54.7%; serious cardiorespiratory events: rVE, 18.8%; 95% CI: 6.7%–29.3%; all-cause hospitalization: rVE, 8.6%; 95% CI: 1.6%–15.1%).

Issue date: 06-Jul-2020