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Sponsor: Sanofi Pasteur	Study Identifiers: U1111-1111-4478, IND 4518, NCT00976027
Drug substance(s): High-dose trivalent inactivated influenza vaccine	Study code: FIM07
Title of the study: Multi-Year Efficacy Study of Fluzone® High-Dose Trivalent Vaccine Compared With Fluzone® Vaccine In Adults ≥ 65 Years of Age	
Study center(s): This was a multi-center trial conducted at 99 centers in the United States.	
Study period: Date first subjects enrolled: 22/Sep/2009 Date last subjects completed: 28/May/2010	
Phase of development: Phase IIIb	
<p>Objectives:</p> <p>Primary Objectives:</p> <p>The primary objective of this study was to compare the clinical efficacy of Fluzone High-Dose vaccine to that of Fluzone vaccine in elderly adults, with respect to laboratory-confirmed influenza illness caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations.</p> <p><i>(The objective could not be met given that the study was terminated after the first year of study conduct, with no cases ascertained contributing to the objective.)</i></p> <p>Secondary Objectives:</p> <ol style="list-style-type: none"> 1) To compare the clinical efficacy of Fluzone High-Dose vaccine to that of Fluzone vaccine in elderly adults, with respect to laboratory-confirmed influenza illness caused by <i>any</i> influenza viral types/subtypes 2) To compare the clinical efficacy of Fluzone High-Dose vaccine to that of Fluzone vaccine in elderly adults, with respect to culture-confirmed influenza illness caused by viral types/subtypes antigenically similar to those contained in the respective annual vaccine formulations <p><i>(This objective could not be met given that the study was terminated after the first year of study conduct with no cases ascertained contributing to the objective.)</i></p> <p>Observational Objectives:</p> <ol style="list-style-type: none"> 1) To describe the rates in each vaccine group of the following events that are associated with cases of laboratory-confirmed influenza caused by viruses antigenically similar to those contained in the respective annual vaccine formulations: <ul style="list-style-type: none"> • Pneumonia • New onset or exacerbation of pre-existing cardio-respiratory conditions • Rates of health care utilization (emergency room visits, non-routine medical office visits, hospitalizations) and associated costs <p><i>(This objective could not be met given that the study was terminated after the first year of study conduct, with no cases ascertained contributing to the objective.)</i></p>	

- 2) To describe the rates in each vaccine group of the following events that are associated with all cases of ILI (with or without laboratory confirmation):
 - Pneumonia
 - New onset or exacerbation of pre-existing cardio-respiratory conditions
 - Rates of health care utilization (emergency room visits, non-routine medical office visits, hospitalizations) and associated costs
- 3) To compare the clinical efficacy of Fluzone High-Dose vaccine to that of Fluzone vaccine in elderly adults, with respect to culture-confirmed influenza illness caused by any influenza viral types/subtypes
- 4) To describe the rates in each vaccine group of all SAEs (including AESIs) that occur within 180 days post-vaccination, for each year of the study
- 5) To describe the rates in each vaccine group of all deaths that occur within 180 days post-vaccination, for each year of the study

Exploratory Objectives:

- 1) To estimate an HAI correlate of protection against laboratory-confirmed influenza illness caused by each viral type/subtype antigenically similar to those contained in the vaccine formulations for each respective year of the study.
(This objective could not be met given that the study was terminated after the first year of study conduct, with no cases ascertained contributing to the objective.)
- 2) To describe the rates in each vaccine group of the following events that are associated with all cases of CDC-defined ILI (with or without laboratory confirmation):
 - Pneumonia
 - New onset or exacerbation of pre-existing cardio-respiratory conditions
 - Rates of health care utilization (emergency room visits, non-routine medical office visits, hospitalizations) and associated costs

Methodology:

Phase IIIb, randomized, double-blind, active-controlled, multi-center trial in elderly adults (≥ 65 years of age). The trial was to span several influenza seasons; however, during Year 1 (2009–2010) of the study, no cases of influenza caused by strains similar to the vaccine components (primary endpoint) were detected. Since not a single case meeting the primary study endpoint was ascertained (pandemic H1N1 was the predominant circulating strain in 2009–2010), the study was terminated at the end of Year 1.

Participants were randomized in a 2:1 ratio to receive one dose of either Fluzone High-Dose or Fluzone vaccine prior to the start of the influenza season and were followed until the end of the season. Enrollment continued until the year's enrollment goals were reached (07 November 2009).

A subset of approximately one-third of subjects randomly selected across participating sites provided a serum sample for immunogenicity testing 28 days post-vaccination.

Subjects were instructed to contact the site (passive surveillance) if they experienced symptoms of influenza-like illness (ILI) during the annual surveillance period. In addition, they were contacted weekly over this same time period by a call center representative (active surveillance). If a subject met the criteria for ILI, the site was to arrange for a nasopharyngeal (NP) swab to be taken within 5 days (between Day 0 and Day 4) of ILI episode onset, for laboratory confirmation of influenza.

The definition of ILI is a new onset (or exacerbation of a pre-existing condition) of at least one systemic **AND** one respiratory symptom from the following lists:

Systemic Symptoms	Respiratory Symptoms
Fever $> 37.2^{\circ}\text{C}$ ($> 99.0^{\circ}\text{F}$)	Stuffy or runny nose (nasal congestion or rhinorrhea)
Feverishness (feeling of warmth)	Sore throat

Chills (shivering)	Cough
Tiredness (fatigue)	Sputum production
Headache	Wheezing
Muscle aches (myalgia)	Chest tightness
	Shortness of breath (breathlessness)
	Chest pain with breathing

The first occurrence of qualifying symptoms occurring at the same time was defined as the “ILI episode start date” (Day 0).

All NP specimens were submitted for analysis by both culture and polymerase chain reaction (PCR), and a positive result on either test were considered a confirmed case of influenza.

Positive cultures or positive PCR samples underwent additional testing (typing and subtyping) to determine if the virus detected was antigenically similar to any of those contained in the vaccine formulation for the season.

All serious adverse events (SAEs) were collected from Day 0 of study entry until the end of the subject’s participation in 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:	Planned: 9000
	Randomized: 9172
	Treated: 9158
Evaluated:	Efficacy: 9021
	Safety: 9158

Diagnosis and criteria for inclusion:

An individual must have fulfilled *all* of the following criteria in order to be eligible 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 an 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 contains the following components:

A/Brisbane/59/07 (H1N1)	Hemagglutinin: 60 µg
A/Uruguay/716/2007 X-175C (H3N2)	Hemagglutinin: 60 µg
B/Brisbane/60/2008	Hemagglutinin: 60 µg

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

Control Product: Fluzone is a licensed 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 contains the following components:

A/Brisbane/59/07 (H1N1)	Hemagglutinin: 15 µg
A/Uruguay/716/2007 X-175C (H3N2)	Hemagglutinin: 15 µg
B/Brisbane/60/2008	Hemagglutinin: 15 µg
Route of administration: IM, injected into the deltoid area	
Duration of participation: The duration of each subject's participation in the study year was 6 to 8 months, depending on the time of enrollment.	
<p>Criteria for evaluation:</p> <p>Primary Endpoints:</p> <p>Occurrences of culture- or PCR-confirmed influenza illness (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are antigenically similar to those contained in the vaccine formulations.</p> <p><i>(This endpoint was not included in the analysis given that no cases of influenza caused by vaccine similar strains were detected.)</i></p> <p>Secondary Endpoints:</p> <ol style="list-style-type: none"> Occurrences of culture- or PCR-confirmed influenza illness (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes Occurrences of culture-confirmed influenza illness (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are antigenically similar to those contained in the vaccine formulations <p><i>(This endpoint was not included in the analysis given that no cases of influenza caused by vaccine similar strains were detected.)</i></p> <p>Observational Endpoints:</p> <ol style="list-style-type: none"> <i>In association with cases of culture- or PCR-confirmed influenza, antigenically similar to those contained in the respective annual vaccine formulations:</i> Episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as rates of health care utilization from 14 days post-vaccination until the end of each respective influenza season <p><i>(This endpoint was not included in the analysis given that no cases of influenza caused by vaccine similar strains were detected.)</i></p> <ol style="list-style-type: none"> <i>In association with all cases of ILI:</i> Episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as rates of health care utilization from 14 days post-vaccination until the end of each respective influenza season Occurrences of culture-confirmed influenza illness (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes SAEs (including AESIs), from Day 0 to Day 180 Deaths from all causes, from Day 0 to Day 180 <p>Exploratory Endpoints:</p> <ol style="list-style-type: none"> HAS 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 for the year. <p><i>(This endpoint was not included in the analysis given that no cases of influenza caused by vaccine similar strains were detected.)</i></p> <ol style="list-style-type: none"> In association with all cases of CDC-defined ILI (fever and cough and/or sore throat in the absence of a known cause other than influenza): Episodes of pneumonia and new onset or exacerbation of pre-existing cardio-respiratory conditions, as well as rates of health care utilization and associated costs from 14 days post-vaccination until the end of each respective influenza season. 	

Statistical methods:

The primary endpoint was not included in the statistical analysis because no cases of influenza caused by vaccine similar strains were detected. This section therefore specifies only the analysis of the secondary, observational, and exploratory objectives which could be evaluated with the data observed.

Secondary Objectives:

The statistical methods for the secondary efficacy objective #1 are presented below. Since no cases of influenza caused by vaccine similar strains were detected, the statistical methods for the secondary efficacy objective #2 are not presented.

The efficacy of Fluzone High-Dose relative to Fluzone was estimated 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

The CI was calculated by an exact method conditional on the total number of cases in both groups

Observational Objectives:

The statistical methods for the observation objectives #2 through #5 are presented below. Since no cases of influenza caused by vaccine similar strains were detected, the statistical methods for the observational efficacy objective #1 are not presented.

For each observational objective and endpoint (rates of pneumonia, SAEs, etc.), percentages of subjects in each treatment group reporting the specified conditions and events are presented, together with 95% CIs for relative risk (RR).

The statistical methods for observational objective #3 (efficacy with respect to culture-confirmed influenza illness caused by any influenza viral types/subtypes) was as for secondary efficacy objective #1 described above.

Exploratory Objectives:

The statistical methods for the exploratory objective #2 are presented below. Since no cases of influenza caused by vaccine similar strains were detected, the statistical methods for the exploratory efficacy objective #1 are not presented.

For the exploratory objective to describe rates of pneumonia etc. associated with CDC-defined influenza, the statistical methods were as for the observational objectives above.

Summary:

Population characteristics:

Disposition

A total of 9172 subjects were enrolled (6117 in the Fluzone High-Dose vaccine group and 3055 in the Fluzone vaccine group) by the 99 investigators of this study. The number of subjects enrolled per investigator ranged between 20 and 100 subjects (0.2% to 1.1% of the total population).

The first subject in this study was enrolled on 22 September 2009, and the last subject contact was on 28 May 2010.

Out of the total 9172 subjects who were randomized, 9158 subjects (99.8% of subjects in each study group) received vaccine and were included in the Full Analysis Set (FAS); however, 3 of these subjects (1 in the Fluzone High-Dose group and 2 in the Fluzone group) did not receive the vaccine to which they were randomized.

A total of 626 (6.8%) of the vaccinated subjects discontinued the study before the end of the study year: 411 (6.7%) subjects in the Fluzone High-Dose group and 215 (7.0%) subjects in the Fluzone group. The most frequently reported reason for discontinuation was lost to follow-up reported for 3.4% (311/9172) of subjects. Other reasons were voluntary withdrawal not due to an AE,

reported for 1.9% (173/9172) of subjects; non-compliance with the protocol, reported for 0.9% (87/9172) of subjects; SAEs, reported for 0.6% (53/9172) of subjects; and other AE, reported for 2 subjects.

The principal investigator for site 86 has been "Disqualified/Totally Restricted" by FDA from participating in further US IND clinical trials. Second versions of the principle tables, "Efficacy of Fluzone High-Dose Relative to Fluzone" and "Safety Overview After Vaccine Injection", were therefore prepared excluding the data from this site. The regulatory action by the FDA occurred after completion of the study and prior to preparation of this final report.

Analysis Sets

Of the 9172 subjects randomized, 9158 subjects received any vaccine and were included in the FAS.

There were a total of 9021 (98.4%) subjects in the Per-Protocol Analysis Set (PPAS) (6013 [98.3%] and 3008 [98.5%] subjects in the Fluzone High-Dose and Fluzone groups, respectively).

The most frequent reason for exclusion from the PPAS was no surveillance contact, reported for 0.7% (68/9172) of subjects. Other reasons were reported for 0.2% (16/9172) to 0.3% (28/9172) of subjects. A total of 22 (0.2%) subjects 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.

Demographics and Baseline Characteristics

Demographics

In both study groups, the percentage of male subjects was slightly lower than females. Overall, in the FAS, the percentage of males was 46.3% (4243/9158) and the percentage of females was 53.7% (4915/9158).

The mean age of subjects in the Fluzone High-Dose and the Fluzone groups in the FAS was 72.8 years for both groups. Overall, the range of ages was from 64.3 to 99.9 years and was similar for the 2 groups.

The majority of subjects in both study groups were Caucasian, with 85.1% (5198/6108) and 84.9% (2590/3050) of subjects in the Fluzone High-Dose and Fluzone groups, respectively; followed by Hispanic, with 8.8% (540/6108) and 8.4% (256/3050) of subjects in the Fluzone High-Dose and Fluzone groups, respectively; and Black, with 4.7% (286/6108) and 5.4% (164/3050) of subjects in the Fluzone High-Dose and Fluzone groups, respectively. There was \leq 0.8% of subjects for any other race per study group.

Past and Current Medical History

Within the FAS, the most frequently reported condition was vascular disorders, with 65.3% (3990/6108) and 64.6% (1970/3050) of subjects in the Fluzone High-Dose and Fluzone groups, respectively. The majority of these reported vascular disorders were for high blood pressure/hypertension, with 64.3% (3925/6108) and 63.5% (1938/3050) of subjects in the Fluzone High-Dose and Fluzone groups, respectively; and the remaining percentages of reports were for peripheral vascular disease.

In addition, 24.0% of subjects in each study group had a history of cardiac disorders, with the most common disorders being ischemic heart disease (15.2% of subjects within each study group) and cardiac rhythm disorder (10.9% of subjects within each study group). In addition, the percentages of subjects with a respiratory condition were 16.3% (998/6108) and 15.3% (467/3050) of subjects in the Fluzone High-Dose and Fluzone groups, respectively, with the most common conditions being asthma (8.7% [532/6108] and 8.8% [267/3050]) and chronic obstructive pulmonary disease (8.1% [497/6108] and 7.6% [233/3050]).

Vaccination History

Prior to the start of the study, 88.7% (8119/9158) of subjects in the FAS (88.9% [5427/6108] and 88.3% [2692/3050] of subjects in the Fluzone High-Dose and Fluzone groups, respectively) had received a seasonal influenza vaccination in a previous year; and 57.5% (5262/9158) of subjects (57.5% [3514/6108] and 57.3% [1748/3050] of subjects in the Fluzone High-Dose and Fluzone groups, respectively) in the FAS received pneumococcal vaccination.

Efficacy

Secondary Objective #1:

The vaccine efficacy of Fluzone High-Dose relative to Fluzone, based on cases of laboratory-confirmed ILI caused by any viral types/subtypes in the PPAS, was 12.5% (95% CI -140.9; 65.7).

Excluding site 086 gave a similar estimate of relative vaccine efficacy (18.8%, 95% CI -126.1; 68.8).

Observational Objective # 2:

For events temporally associated with cases of Protocol-defined ILI, Fluzone High-Dose rates were slightly lower than Fluzone rates for new onset or exacerbation of cardio-respiratory conditions and hospitalizations (relative risks below 1); Fluzone High-Dose rates were slightly increased for emergency room visits and antiviral use (relative risks above 1); and rates were essentially the same for both vaccines for all other events (relative risks = 1). All CIs for these comparisons were wide and crossed 1, indicating that none of the differences in rates were significant.

Observational Objective #3:

The vaccine efficacy of Fluzone High-Dose relative to Fluzone, based on culture-confirmed ILI caused by any viral types/subtypes in the PPAS, was 7.1% (95% CI -175.0; 65.6).

Exploratory Objective #2:

For events temporally associated with cases of CDC-defined ILI, Fluzone High-Dose rates were slightly lower than Fluzone rates for pneumonia, any health-care visit, emergency room visits, non-routine medical office visits, any medication use, use of antipyretics, NSAIDs or analgesics, and use of antibiotics (relative risks below 1); Fluzone High-Dose rates were slightly increased for new onset or exacerbation of cardio-respiratory conditions and antiviral use (relative risks above 1); and rates were essentially the same for both vaccines for the occurrence of hospitalizations (relative risk = 1). All CIs for these comparisons were wide and crossed 1, indicating that none of the differences in rates were significant.

Safety

Observational Objectives #4 and #5:

There were 493/6108 (8.1%) and 236/3050 (7.7%) subjects in the Fluzone High-Dose and Fluzone groups, respectively, who experienced at least 1 SAE throughout the entire study period.

Within 180 days after vaccination, 408/6108 (6.7%) and 197/3050 (6.5%) subjects in the Fluzone High-Dose and Fluzone groups, respectively, experienced at least 1 SAE. The majority of these SAEs required or prolonged hospitalization (6.1% [371/6108] and 6.0% [182/3050] of subjects in the Fluzone High-Dose and Fluzone groups, respectively). All other SAE seriousness categories (excluding deaths), were reported for 0.0% to 0.5% (31/6108) and 0.0% to 0.4% (12/3050) of subjects in the Fluzone High-Dose and Fluzone Groups, respectively. Similar results were reported for SAEs throughout the study.

For the Fluzone High-Dose group, SAEs within 180 days after vaccination were most frequently reported in the SOC of Cardiac disorders and Infections and infestations (1.1% [69/6108] of subjects for each SOC), with the most frequently reported event within these SOCs being congestive cardiac failure (0.3% [18/6108] of subjects) and pneumonia (0.2% [14/6108]), respectively. Other SAEs were reported in the SOCs of Gastrointestinal disorders; Neoplasms benign, malignant, and unspecified (including cysts and polyps); Nervous system disorders; Respiratory, thoracic and mediastinal disorders; Musculoskeletal and connective tissue disorders; and Injury, poisoning and procedural complications (0.5% [33/6108] to 0.8% [47/6108] of subjects). The remaining SOCs were reported for \leq 0.4% (22/6108) of subjects. Similar results were reported throughout the study.

For the Fluzone group, SAEs within 180 days after vaccination were also most frequently reported in the SOC of Cardiac disorders (1.5% [46/3050]), with the most frequently reported event within this SOC being congestive cardiac failure (0.3% [9/3050] of subjects). Other SAEs were reported in the SOCs of Infections and infestations; Gastrointestinal disorders; Nervous system disorders; Injury, poisoning and procedural complications; Respiratory, thoracic and mediastinal disorders; Musculoskeletal and connective tissue disorders; Neoplasms benign, malignant, and unspecified (including cysts and polyps) (0.6% [17/3050] to 0.8% [24/3050] of subjects). The remaining SOCs were reported for \leq 0.5% (14/3050) of subjects. Similar results were reported throughout the study.

Deaths

Throughout the study, there were a total of 31/6108 (0.5%) and 12/3050 (0.4%) deaths in the Fluzone High-Dose and Fluzone groups, respectively; none of which were considered by the Investigator and Sponsor to be related to the vaccination. Of these deaths, a total of 24/6108 (0.4%) and 10/3050 (0.3%) deaths occurred within 180 days after vaccination in the Fluzone High-Dose and Fluzone groups, respectively.

SAEs other than deaths

Within 180 days after vaccination, most subjects with non-fatal SAEs recovered completely (5.2% [316/6108] and 5.1% [155/3050] of subjects in the Fluzone High-Dose and Fluzone groups, respectively). A minority of subjects reporting an SAE recovered with sequelae (0.9% [54/6108] and 0.8% [23/3050] of subjects in the Fluzone High-Dose and Fluzone groups, respectively) or had the event still ongoing at the time of final contact (0.6% [36/6108] and 0.6% [17/3050] of subjects in the Fluzone High-Dose and Fluzone groups, respectively). Similar results were reported throughout the study.

Related SAEs

One subject in the Fluzone High-Dose group* and two subjects in the Fluzone group experienced at least 1 SAE that was considered by the Investigator and Sponsor to be related to the vaccination, all of which occurred within the 180 days after vaccination time period. None of these related SAEs resulted in discontinuation from the study.

*Note: For an additional subject in the Fluzone High-Dose group (reported chills in November 2009, which required hospitalization for an unknown diagnosis) the investigator did not provide a causality assessment. Although the Sponsor later assessed the SAE as unrelated, it was deemed as related in line with the study statistical analysis plan and, therefore, this subject is included in the table.

- One subject in the Fluzone High-Dose group was reported to have cardiac chest pain which started 1 day after the vaccination. This SAE required or prolonged hospitalization, and the subject recovered after 2 days.
- One subject in the Fluzone group was reported to have Bell's Palsy 34 days after the vaccination. This SAE was categorized as other important medical event and was ongoing at the time of study completion.
- One subject in the Fluzone group was reported to have immune thrombocytopenia 13 days after vaccination. This SAE required or prolonged hospitalization, and the subject recovered after 5 days.

AESIs

The occurrence of AESIs was rare in both study groups, with 0.1% (4/6108) and 0.1% (2/3050) of subjects reporting occurrences in the Fluzone High-Dose and Fluzone groups, respectively, throughout the study.

Bell's Palsy was reported within the 180 days after vaccination time period for 3 subjects in the Fluzone High-Dose group and 2 subjects in the Fluzone group. All 5 subjects completed the study, and, with the exception of one subject in the Fluzone group, all occurrences of Bell's Palsy were considered by the Investigator and Sponsor to be not related to the vaccine.

- One subject in the Fluzone High-Dose group was reported to have facial palsy 126 days after vaccination. This AESI, categorized as other important medical event, was ongoing at the time of study completion.
- One subject in the Fluzone High-Dose group was reported to have facial palsy (right side) 116 days after vaccination. This AESI, categorized as other important medical event, was ongoing at the time of study completion.
- One subject in the Fluzone High-Dose group was reported to have facial palsy 178 days after vaccination. This AESI, categorized as other important medical event which required or prolonged hospitalization, was ongoing at the time of study completion.
- One subject in the Fluzone group was reported to have facial palsy 176 days after vaccination. This AESI was categorized as other important medical event, and the subject recovered with sequelae.
- One subject in the Fluzone group was reported to have facial palsy 34 days after vaccination. This AESI, which was categorized as other important medical event, was considered to be related to the vaccination by the Investigator and Sponsor and was ongoing at the time of study completion.



Transverse myelitis was reported for subject 098-09020 in the Fluzone High-Dose group 191 days after vaccination. This AESI, which required or prolonged inpatient hospitalization, was considered by the Investigator and Sponsor to be not related to the vaccination, was ongoing at the time of study completion, and the subject completed study.

No other AESIs were reported for any subjects in either study group.

AEs leading to study discontinuation

Throughout the study, total of 0.6% (36/6108) and 0.6% (17/3050) of subjects in the Fluzone High-Dose and Fluzone groups, respectively, discontinued the study due to SAEs; none of which were considered by the Investigator and Sponsor to be related to the study vaccination. Of these subjects, 0.5% (30/6108) and 0.5% (15/3050) of subjects experienced the SAE within 180 days after vaccine injection.

Two (0.1%) subjects in the Fluzone group discontinued the study due to other AEs. One subject was unable to communicate appropriately for study purposes due to dementia, and the other subject had a gout flare and wanted to participate in a gout study.

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