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Sponsor/ Company:	Sanofi Pasteur	**Study Code:** GRT86 **Study Identifier:** NCT00946179
Proprietary Vaccine Name:	Influenza vaccine (split virion, inactivated)	

Title of the Study: Immunogenicity and Safety of the Influenza Vaccine (Split Virion, Inactivated), Northern Hemisphere 2009-2010 Formulation (Intramuscular Route)

Study centres: This was a multicenter trial conducted in two centers in Switzerland.

Publications: None at the time of report writing.

Study period: Date of First enrollment: 08 May 2009
Date of Last visit (contact): 05 June 2009

Development phase: Phase II

Methodology / Trial Design:

Open-label, uncontrolled, multicenter trial. 130 subjects, two age groups (65 subjects aged 18 to 60 years and 65 subjects aged 61 years or older) were vaccinated with one injection of the influenza vaccine (split virion, inactivated) Northern Hemisphere (NH) 2009-2010 formulation.

Objectives:

1) To evaluate the compliance, in terms of immunogenicity, of the influenza vaccine (split virion, inactivated) NH 2009-2010 formulation with the requirements of the Committee for Proprietary Medicinal Products (CPMP) Note for Guidance (NfG) CPMP/BWP/214/96 in two adult groups, one aged from 18 to 60 years and the other aged 61 years or older
2) To describe the safety of the influenza vaccine (split virion, inactivated) NH 2009-2010 formulation in both adult groups.

Endpoints:

Immunogenicity

Immunogenicity was evaluated before and 21 days after injection of the influenza vaccine using the Hemagglutination Inhibition (HAI) assay. For each vaccine strain, anti-Hemagglutinin (HA) antibody titers were expressed as HAI titers obtained in duplicate on D0 and D21, summarized at the subject level by individual geometric mean of duplicates on D0 and D21.

The derived endpoints were:

- Individual titer ratio D21/D0,
- Seroprotection status: titer ≥40 (1/dil) on D0 and D21,
- Seroconversion for subjects with a titer <10 (1/dil) on D0: post-injection titer ≥40 (1/dil) on D21 or significant increase for subjects with a titer ≥10 (1/dil) on D0: ≥4-fold increase of post-injection titer on D21.

Safety

Safety was evaluated within 21 days following injection of the influenza vaccine (split virion, inactivated) NH 2009-2010 formulation in subjects aged 18 to 60 years and in subjects aged 61 years or older.

- The occurrence of the following reactions during the first 3 days following vaccination were more specifically reported (as defined by the CPMP NfG CPMP/BWP/214/96):
  - Injection site induration ≥5 cm observed for more than 3 consecutive days
  - Injection site ecchymosis
  - Temperature >38°C for 24 hours or more
  - Malaise
  - Shivering
- Occurrence of unsolicited Adverse Events (AEs) reported in the 30 minutes after injection
- Occurrence of solicited (prelisted in the subject diary and the Case Report Form [CRF]) injection site reactions and systemic reactions within 7 days following injection
- Occurrence of unsolicited (spontaneously reported) AEs within 21 days following injection,
- Occurrence of serious AEs (SAEs) within 21 days following injection.

Depending on the item, these endpoints were described according to nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time of onset, duration, number of days of occurrence, Grade of intensity, relationship to vaccine, action taken, whether the AE led to early withdrawal from the study, seriousness, or outcome.

Sample size (Number of Subjects):

Planned sample size: 130 subjects (65 in the 18 to 60 years group, 65 in the 61 years or older group)

Number of subjects included: 130 subjects (65 in the 18 to 60 years group, 65 in the 61 years or older group)

Number of subjects completed: 128 subjects

Number of subjects discontinued: 2 subjects

Immunogenicity analysis set: 127 subjects

Safety analysis set: 130 subjects

Schedules of Vaccination and Specimen Collection:

One vaccination on D0, two visits.
Two blood samplings: one on D0 (before vaccination) and the second on D21 (±1).

Duration of Participation in the Trial:

The total duration of follow-up by subject was between 20 and 24 days.

Product Under Investigation:

Influenza vaccine (split virion, inactivated), NH 2009-2010 formulation

Form/Dose/Route:

Suspension for injection in prefilled syringe/0.5 mL/ Intramuscular (IM) into the deltoid muscle

Batch number: S4285F01

Control Product: Not applicable

Other Product(s): Not applicable

Statistical methods

The analysis was descriptive. No hypothesis was tested.

For each vaccine strain and in each age group, the recommendations were to meet at least one of the three CPMP criteria:

Age (years)	18 to 60	61 or older
Seroconversion rate* or significant increase of titer† on D21	>40%	>30%
Mean geometric increase‡ between D0 and D21	>2.5	>2
Percentage of seroprotected subjects∫ on D21	>70%	>60%

*: For subjects with a pre-vaccination titer <10 (1/dilution [1/dil]), proportion of subjects with a post- vaccination titer ≥40 (1/dil)

†: For subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥4-fold increase of post- vaccination titer

‡: Geometric mean of individual ratios (post-/pre-vaccination titers)

∫: Proportion of subjects achieving a post-vaccination titer ≥40 (1/dil)

The above parameters were presented with 95% confidence intervals (CIs) for each age group.

Calculation of the 95% CIs for each age group was done using:

- the standard approximate method for geometric mean titers (GMTs) and geometric mean titer ratios (GMTRs),
- the exact binomial distribution for percentages (Clopper Pearson)

The sample size was determined in accordance with the CPMP NfG (CPMP/BWP/214/96).

Results:

A total of 130 subjects (65 aged 18 to 60 years and 65 aged 61 years or older) were included in the study between 08 May and 13 May 2009 to receive the NH 2009-2010 formulation of the inactivated influenza vaccine. The last visit of the last subject took place on 05 June 2009. Two subjects discontinued the study.

The mean age of subjects was 39.9 years in the 18 to 60 years group and 68.3 years in the 61 years or older group. The male/female sex ratio was 1.10 in the 18 to 60 years group and 1.95 in the 61 or older group, respectively. 45 subjects (69.2%) in the 18 to 60 years old group and 55 subjects (84.6%) in the 61 years or older group received influenza vaccination in the previous years. 6 subjects in the 18 to 60 years group and no subjects in the 61 years or older group reported an influenza infection during the last winter (from December 2008 to January 2009). Of these, three had been vaccinated in the preceding years.

Immunogenicity

Of the 130 subjects included in the study, three subjects had no blood samples available at the second study visit. A total of 127 subjects were included in the immunogenicity analysis set.

In the two age groups, at least one CPMP criterion was met, showing that the 2009-2010 formulation of the inactivated split-virion influenza vaccine complies with the CPMP recommendations.

In the two groups, the three CPMP criteria were met for the two A Strains. For the B strain, two CPMP criteria were met in the 18 to 60 years group (seroconversion rate or significant increase and GMTR) and one CPMP criterion was met in the 61 years or older group (GMTR).

However, when tested with the HAI method using split antigen, a validated and recognized HAI assay method known to be more sensitive for the measurement of antibody to some influenza B viruses, the three CPMP criteria were met for the B/Brisbane/60/2008 strain in both age groups.

Safety:

Serious Adverse Events (SAE)

No SAEs were reported during the study.

CPMP recommendations

A total of 8 subjects (12.3%) in the 18 to 60 years group and 9 subjects (13.8%) in the 61 years or older group reported at least one reaction listed in the CPMP recommendations. Malaise was the most frequently reported of the CPMP reactions with 9.2% and 10.8% of subjects in the 18 to 60 years and the 61 years or older groups, respectively.

Injection site ecchymosis and shivering were reported both in one subject in the 18 to 60 years group while ecchymosis was reported in 3 subjects (4.6%) in the 61 years or older group.

Injection site induration ≥5 cm observed for more than 3 days and pyrexia (temperature > 38°C) for at least one day were not reported in any group.

The majority of the reactions remained of Grade 1 intensity and resolved spontaneously within 1 to 3 days.

Solicited reactions within 3 days after vaccination

In the 18 to 60 years group, a total of 35 subjects (53.8%) experienced at least one solicited injection site reaction and 23 subjects (35.4%) experienced at least one solicited systemic reaction.

In the 61 years or older group, a total of 21 subjects (32.3%) experienced at least one solicited injection site reaction and 15 subjects (23.1%) experienced at least one solicited systemic reaction.

In the two groups, pain and erythema were the most frequently reported injection site reactions. Myalgia, headache and malaise were the most frequently reported systemic reactions in the 18 to 60 years group while myalgia, malaise and headache were the most frequently reported systemic reactions in the 61 years or older group. Most of them were present for 1 to 3 days over the solicited period. These reactions were mainly of Grade 1 intensity. Few cases of swelling, induration and ecchymosis were reported in the 61 years or older group but not in the 18 to 60 years group.

No grade 3 solicited reactions were reported in any group.

Solicited reactions more than 3 days after vaccination

More than 3 days after vaccination, no subjects among the two age groups reported any solicited injection site reaction. Eight subjects (12.3%) in the 18 to 60 years group and one subject (1.5%) in the 61 years or older reported at least one solicited systemic reaction.

No Grade 3 solicited reactions were reported in any group.

In the 18 to 60 years group:

Headache (10.8% of subjects) and myalgia (4.6% of subjects) were reported between D4 and D7 after vaccination. The majority of these events occurred on D4 or D5, was present for 1-3 days and was of Grade 1 and Grade 2 intensity.

In the 61 years or older group:

Myalgia and headache were reported by one subject (1.5%) between D4 and D7 after vaccination. These reactions occurred both on D4, were present 1 to 3 days over the solicited period and were of Grade 1 intensity.

No Grade 3 solicited systemic reactions were reported in any of the two groups.

Unsolicited Non-Serious adverse events within 21 days

No immediate unsolicited non-serious adverse events were observed in any of the two groups.

Overall, within 21 days after vaccination, 18 subjects (27.7 %) aged 18 to 60 years and 9 subjects (13.8%) aged 61 years or older experienced at least one unsolicited event within 21 days after vaccination. Four subjects (6.2%) reported at least one Grade 3 non-serious adverse events.

Ten subjects (15.4%) in the 18 to 60 years group reported at least one unsolicited reaction:

- For nine subjects, at least one unsolicited reaction occurred within 3 days after vaccination. Among these unsolicited reactions, one systemic reaction (fatigue) of Grade 3 intensity was reported. This reaction spontaneously resolved within 3 days after vaccination.

- For four subjects, including one who did not report any unsolicited event within 3 days after vaccination, at least one unsolicited systemic reaction was reported between D4 and D21 after vaccination.

Two subjects (3.1%) in the 61 years or older group reported at least one unsolicited systemic reaction. None were of Grade 3 intensity.

Conclusions:

The NH 2009-2010 formulation of the inactivated, split-virion influenza vaccine complies with the immunogenicity requirements of the European recommendations for each age group and for all three strains. Its safety profile is satisfactory.

Date of Report: 21 June 2009