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Prescribing decisions should be made based on the approved package insert.*

Sponsor/ Company:	Sanofi Pasteur	Study Code: GID26 Study Identifier: NCT00606359 EudraCT Number: 2006-003145-16
Proprietary Vaccine Name:	Inactivated, split-virion influenza vaccine for intradermal route	
Title of the Study: Immunogenicity of the Inactivated Split-Virion Influenza Vaccine Administered by the Intradermal Route in Renal Transplant Subjects		
Study centres: 2 sites in France		
Publications: None at the time of writing.		
Study period:	Date of first screening visit of the first subject: 02 October 2006 Date of first visit of the first subject: 15 October 2007 Date of last visit of the last subject: 17 December 2007	
Development phase:	Phase II	
Methodology / Trial Design: Multicenter randomized controlled open trial. First screening visit (SC1) to second screening visit (SC2) period: one group At SC1, the intramuscular (IM) commercialized vaccine (Vaxigrip®) 15 µg of hemagglutinin (HA) per strain and per 0.5 mL dose was administered to all subjects in order to identify non-responder subjects to the IM commercialized vaccine. Non-responder subjects were defined as subjects with an inhibition of hemagglutination (HAI) titer <40 (1/dil) for the H3N2 strain at SC2, 21 days after the vaccination with the IM commercialized vaccine. D0-D21 period (V01 to V02): non-responder subjects to the IM reference vaccine randomized in two groups:		
<ul style="list-style-type: none"> On D0, half of the non-responder subjects were administered with the intradermal (ID) investigational vaccine using the Becton Dickinson (BD) ID Micro-Injection System: 15 µg of HA per strain and per 0.1 mL dose. On D0, half of the non-responder subjects were administered with the IM reference vaccine: 15 µg of HA per strain and per 0.5 mL dose. 		
Objectives:		
Primary objective:		
To describe the immunogenicity of an injection of the ID 15µg investigational inactivated, split-virion influenza vaccine 21 days after vaccination in 18 to 60 years old renal transplant subjects identified as non-responder to previous vaccination with the IM reference vaccine (Vaxigrip®).		
Primary endpoints:		
Immunogenicity was evaluated using the HAI test in all subjects included in the trial. HAI antibody titers for the three strains were obtained 21 days after vaccination.		
The endpoints were:		
<ul style="list-style-type: none"> HAI individual titers on D0 and D21. Individual titer ratio: D21/D0. Seroconversion status (for subjects with a pre-vaccination titer <10 [1/dil], post-vaccination titer ≥40 [1/dil] on D21), or significant increase (for subjects with a pre-vaccination titer ≥10 [1/dil], ≥ four-fold increase from pre- to post-vaccination titer on D21). Seroprotection status: titer ≥40 (1/dil) on D21 for each strain. 		

Statistical methods for the primary objective:

Descriptive analysis

Secondary objective:

To describe the safety of an injection of the ID 15µg investigational inactivated, split-virion influenza vaccine in 18 to 60 years old renal transplant subjects identified as non-responder to previous vaccination with the IM reference vaccine (Vaxigrip®).

Secondary endpoint:***From SC1 to SC2:***

Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), time to onset, duration and relationship to vaccination of all serious adverse events (SAEs) were to be described within the 21 days following SC1. From SC2 to V01, only SAEs related to the IM reference vaccine (Vaxigrip®) were to be reported.

From inclusion visit (V01) to V02 (V01+21D):

The endpoints were:

- Occurrence, nature (MedDRA preferred term), duration, severity, and relationship to vaccination of any systemic adverse event (AE) reported in the 30 minutes after vaccination.
- Occurrence of the following reactions in the 3 days following vaccination were reported following the European Medicines Agency (EMA) Note for Guidance on Harmonization of requirements for influenza vaccines (CPMP/BWP/214/96):
 - Injection site induration >5 cm observed for more than 3 days
 - Injection site ecchymosis
 - Fever (oral temperature >37.5°C, or rectal equivalent temperature >38.0°C) for 24 hours or more
 - Malaise
 - Shivering
- Occurrence, time to onset, number of days of occurrence, and severity of solicited (prelisted in the subject's diary card [DC] and Case Report Form [CRF]) injection site and systemic reactions occurring up to 7 days after vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, severity, and relationship to vaccination (only for systemic events) of unsolicited (spontaneously reported) AEs up to 21 days after vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration and relationship to vaccination of SAEs. Up to 21 days after vaccination

Sample size (Number of Subjects):**Planned sample size:**

- **Screening period (SC1 to SC2):** 200 renal transplant subjects for at least 6 months with stable renal function within the 3 months preceding vaccination had to receive the IM commercialized vaccine.
- **D0-D21 period (V01 to V02):** 67 subjects were identified as non-responder subjects, among the 200 subjects included for screening, were to be randomized in two groups: the ID 15µg group or the IM 15µg group.

Real sample size:**Screening Summary - All Screened Subjects**

	All (N= 201)	
	n	%
N screened subjects (SC1)	201	100
N vaccinated with IM vaccine at SC1	201	100
N present at SC2	196	97.5
N with blood sample drawn at SC2 (BL02)	196	97.5
N not eligible for V01 investigation*	134	66.7
N eligible for V01 investigation†	67	33.3
N eligible for V01 investigation but not included at V01	5	2.5
N included at V01	62	30.8

*Subjects responder to the study vaccine, with sample taken (BL02) out of the protocol defined windows, with the inclusion criterion 4 not met, lost-to-follow up, refusal to continue to participate in the study, or with sample results not usable.

† Non-responder subjects: HAI titer <40 (1/dil) for H3N2 strain at SC2.

Summary of Subjects Disposition According to Injected Vaccine Group - All Injected Subjects

	ID 15µg (N= 31)	IM 15µg (N= 31)	All (N= 62)
N included at V01	31	31	62
N vaccinated	31	31	62
Subjects discontinued before V02 (D0 to D21)	0	0	0
Immunogenicity Analysis Sets* (All three strains)	31	31	62
Safety Analysis Set**	31	31	62
Subjects who completed the study***	31	31	62

* defined, for each strain, as the subset of subjects who received the vaccination and whose pre- and post-vaccination titers are available and not having received influenza vaccination within 6 months before vaccination

**defined as subjects who received the vaccination.

***defined as subjects not discontinued before V02.

Schedules of Vaccination and Specimen Collection:**Screening period (SC1 to SC2):**

- One vaccination: one dose (IM commercialized vaccine) on SC1
- Two blood samples were to be drawn in all subjects: immediately before vaccination (SC1) and 21 days after vaccination (SC2 [SC1+21D])
- Two planned visits (SC1 and SC2 [SC1+21D])

D0-D21 period (V01 to V02): trial vaccine administration

- One vaccination: one dose (ID investigational or IM reference vaccine) on D0
- Two blood samples were to be drawn in all vaccinated subjects: immediately before vaccination (V01/D0) and 21 days after vaccination (V02/D21)
- Two planned visits (V01 and V02)

Product Under Investigation:

Northern Hemisphere (NH) 2007-2008 influenza formulation (V01/D0): Inactivated, split virion Influenza vaccine for ID route administered with the ID Micro-Injection System.

Form/Dose/Route:

Suspension for injection in pre-filled syringe using a Micro-Injection System/0.1 mL/ID into the upper arm (deltoid area)

Batch number:

S4198

Control Product:

NH 2007-2008 influenza formulation (V01/D0): Inactivated, split virion Influenza vaccine for IM route.

Form/Dose/Route:

Suspension for injection/0.5 mL/IM into the upper arm (deltoid area)

Batch number:

B0566

Other Product(s):

NH 2006-2007 influenza formulation (SC1): Influenza vaccine (split virion, inactivated) administered by the IM route

Form/Dose/Route:

Suspension for injection/0.5 mL/IM into the upper arm (deltoid area)

Batch number:

A0712

Statistical methods

The analysis was descriptive.

Immunogenicity:

The analysis was descriptive and presented by group with 95% confidence intervals (CIs) for the following parameters:

- Seroprotection rate (titer ≥ 40 [1/dil]) on D21
- Geometric mean of titer ratio (GMTR) D21/D0
- Seroconversion or significant increase rate from D0 to D21

Safety:

Safety results were descriptive for all the parameters.

Sample size:

The sample size was arbitrary set to 200 subjects for the screening period in order to obtain 80 non-responder subjects as initially planned (40 in each of the ID and IM groups) for the NH 2007-2008 influenza formulation. Following the first year results, 67 non-responder subjects could be selected for the 2007-2008 vaccination.

Results summary:**Disposition of subjects**

A total of 201 subjects aged from 18 to 60 years were included in the screening part of the trial. A total of 67 subjects were non-responder to the H3N2 strain of previous IM vaccination. Five subjects were not included in the second part of the study (V01 to V02). As a result, 62 subjects were randomized in two groups (31 subjects in the ID 15µg group and 31 subjects in the IM 15µg group). No subjects discontinued the trial before V02. Baseline characteristics at V01 were similar in the two groups in terms of gender and age. The male/female ratio was 2.4 in ID 15µg group and 2.1 in the IM 15µg group. At inclusion (V01), mean age in the ID 15µg group was 47.7 years (standard deviation of 8.7 years) and 48.3 years in the IM 15µg group (standard deviation of 8.4 years).

Primary Objective: Immunogenicity Results

Before vaccination, seroprotection rates and HAI GMTs were quite similar in the two groups and for each strain. A marked increase in HAI antibody titers was observed for the three strains in the two groups after vaccination. However the increase tended to be greater in the ID 15µg group as evidenced by the higher GMTR, seroconversion or significant increase rates and seroprotection rates in the ID 15µg group. Geometric mean of the individual titer ratios post-vaccination over pre-vaccination (GMTRs) obtained for the A/H3N2 strain tended to be higher in the ID 15µg group than in the IM 15µg group (3.50 versus 2.34). Seroconversion or significant increase rates from D0 to D21 obtained were higher in the ID 15µg group for the A/H3N2 strain (35.5%) compared to the IM 15µg group (19.4%). Marked increases in seroprotection rates were observed 21 days after vaccination with both ID 15µg and IM 15µg vaccines, with an increase inclined to be higher in the ID 15µg group. Seroprotection rates obtained for the A/H3N2 strain were of 51.6% in the ID 15µg group and of 35.5% in the IM 15µg group.

In the ID 15µg group, immunogenicity results were compliant with the EMEA Note for Guidance (CPMP/BWP/214/96). At least one criterion was met for each strain in this group. Specifically, for the A/H1N1 strain, two criteria were met in terms of GMTR (above 2.5) and seroprotection rate (proportion of subjects achieving an HAI titer ≥ 40). For the A/H3N2 and B strains, one criterion was met in each of these two strains in terms of GMTR and seroprotection rate, respectively. In the IM 15µg group, none of the criteria were fulfilled for any of the three strains.

Secondary Objective: Safety Results

Safety results presented hereafter are all described in the Safety Analysis Set (SafAS) population.

- Reactions listed in the EMEA Note for Guidance

A total of 22.6% of subjects in the two groups experienced at least one of the reactions listed in the EMEA Note for Guidance. The most frequently reported reactions, in the two groups, were shivering (16.1% in the ID 15µg group and 9.7% in the IM 15µg group) and malaise (12.9% in the ID 15µg group and 9.7% in the IM 15µg group).

Injection site ecchymosis was only reported in the IM 15µg group.

- Solicited Reactions Within 7 Days after Vaccination

The proportion of subjects with at least one solicited injection site reaction within the 7 days following vaccination was 80.6% in the ID 15µg group and 48.4% in the IM 15µg group. Solicited injection site reactions were more frequent in the ID 15µg group than in the IM 15µg group particularly for injection site erythema (71.0% versus 16.1% of subjects), swelling (35.5% versus 9.7%), induration (35.5% versus 19.4% of subjects), and pruritus (29.0% versus 9.7%). Two severe solicited injection site reactions were reported in the ID 15µg group: one subject experienced severe swelling and one subject reported severe erythema.

The proportion of subjects with at least one solicited systemic reaction was 54.8% in the ID 15µg group and 51.6% in the IM 15µg group. In both groups, the most frequently reported systemic reactions were headache, myalgia, and malaise. One subject in the ID 15µg group and one subject in the IM 15µg group reported at least one severe solicited systemic reaction (severe myalgia and severe malaise, respectively).

- Unsolicited Reactions/Adverse Events Within 21 Days after Vaccination

Five subjects (16.1%) in the ID 15µg group and four (12.9%) in the IM 15µg group presented at least one unsolicited event within 21 days after injection. No subjects reported unsolicited injection site or systemic reactions.

In the ID 15µg group, reported unsolicited systemic events were listed in the categories “gastrointestinal disorders”, “infections and infestations”, “musculoskeletal and connective tissue disorders”, “skin and subcutaneous tissue disorders”. In the IM 15µg group, reported unsolicited systemic events were listed in the categories “gastrointestinal disorders”, “infections and infestations”, “musculoskeletal and connective tissue disorders”, and “respiratory, thoracic and mediastinal disorders”.

Two subjects (6.5%) in the ID 15µg group reported at least one severe unsolicited systemic event.

Deaths, Other SAEs and Other Significant AEs:

- Serious Adverse Events

No deaths were reported during the trial.

A total of three SAEs were reported:

- one not-related SAE (acute constipation associated with abdominal pain) after SC1
- two SAEs within 21 days following the vaccination (after V01): one, related to the trial vaccine, in the ID 15µg group (a subject experienced liver biological disorders rated as related to the trial vaccine by both the Investigator and the Sponsor) and one, not related to the study vaccine, in the IM 15µg group (vasovagal syncope associated with hypotension).

Conclusions:

In this Phase II study, conducted between 02 October 2006 and 17 December 2007, the primary objective was to describe the immunogenicity of one injection of the intradermal (ID) 15µg investigational inactivated, split-virion influenza vaccine 21 days after vaccination in 62 renal transplant subjects between 18 to 60 years old identified as non-responders following previous vaccination with the intramuscular (IM) reference vaccine (Vaxigrip®). The compliance with at least one EMEA requirements, as described in the Note for Guidance CPMP/BWP/214/96 for influenza vaccine in adults, was only observed in subjects who received the ID 15µg vaccine. The results of this Phase II study suggest that the same amount of antigen (15 µg per strain) administered via the ID route induces a more pronounced immune response with respect to administration via the IM route and may result in an increased seroprotection rate in subjects who were non-responders at baseline. The ID 15µg vaccine was as well tolerated as the IM 15µg vaccine in terms of proportions of subjects with solicited systemic reactions. Solicited systemic reactions were mainly mild to moderate and resolved within 3 days in the two groups.

The ID 15µg vaccine induced more solicited injection site reactions than the IM 15µg vaccine. Two severe solicited injection site reactions (one erythema and one swelling) were reported in the ID 15µg and none in the IM 15µg group. One suspected unexpected serious adverse reaction (SUSAR) was reported in the ID 15µg group (liver biological disorders).

Overall, the results of this Phase II study suggest that the ID route induces a higher immune response in renal transplant recipients than IM administration. Safety profile was satisfactory for the two administration routes.

Date of Report: 13 June 2008.