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Sponsor/ Company:	Sanofi Pasteur	**Study Code:** GPF14 **Study Identifier:** NCT01053143 **WHO Universal Trial Number:** U1111-1111-6149
Proprietary Vaccine Name:	A/H1N1 pandemic influenza vaccine (split virion, inactivated, non-adjuvanted)	

Title of the Study: Bridging Study on Safety and Immunogenicity of an Intramuscular Inactivated, Split Virion Swine-origin A/H1N1 Influenza Non-Adjuvanted Vaccine in Healthy Adults in India

Study centres: This was a multi-center, with three trial centers in India. Due to delay in Ethics Committee review in coordinating Investigator center, only two centers have been initiated.

Publications: None at the time of report writing.

Study period: Date of First enrollment: 25 January 2010
Date of Last visit (contact): 06 August 2010

Development phase: Phase III Bridging Study

Methodology / Trial Design:

This was a multi-center, Phase III, open label, descriptive bridging study to assess the safety and immunogenicity of a non-adjuvanted A/H1N1 vaccine containing 15 µg of hemagglutinin (HA) per dose.

One hundred (100) healthy adults from 18 years of age and above were included.

All subjects received one injection on Day 0 (D0) and provided a pre-vaccination baseline blood sample on D0, as well as post-vaccination blood samples on D21 and on D180.

Clinical safety data were collected after vaccination. Serious adverse events (SAEs) were collected throughout the trial. A safety follow-up was performed 6 months after the vaccine administration.

This trial included an early review of safety data. Twelve days after the last subject was enrolled, a report summarizing all SAEs regardless of the causality that may have occurred in this study timeframe was reported in a timely manner to Indian Health Authorities and IECs/IRBs. This report was based on Safety data collected until D21. No immunogenicity results were available.

An Independent Data Safety Monitoring Board (DSMB) reviewed and evaluated safety on a regular basis during the trial.

This trial could be interrupted at any time if new data about the investigational product became available, and/or on advice of the Sponsor, the IECs/IRBs, or the governing regulatory authorities in India.

If the trial was prematurely terminated or suspended, the Sponsor was to promptly inform the Investigators, the IECs/IRBs, and the regulatory authorities of the reason for termination or suspension. If the trial was prematurely terminated for any reason, the Investigator was to promptly inform the trial subjects and assure appropriate therapy and follow-up.

Objectives:

Primary objective:

To describe the safety profile (injection site reactions, and systemic events) of the vaccine within 21 days following vaccination, and SAEs throughout the study in all subjects.

Primary endpoints:

Safety:

- Occurrence of unsolicited adverse event (AE) reported in the 30 minutes after vaccine injection
- Occurrence of solicited (prelisted in the subject diary and Case Report Form [CRF]) injection site reactions and systemic reactions within 7 days following vaccine injection
- Occurrence of unsolicited (spontaneously reported) AEs within 21 days following vaccine injection
- Occurrence of SAEs including adverse events of special interest (AESIs) within 21 days following vaccination, and up to the end of the trial 6 month after the vaccination.

Other endpoints recorded or derived were described at the time of statistical analysis plan. Depending on the item, these include: nature (MedDRA [Medical Dictionary for Regulatory Activities] preferred term), time of onset, duration, number of days of occurrence, grade of severity, relationship to vaccine, action taken, whether the AE led to early termination from the study, seriousness, or outcome.

Note: The following AESIs, considered as important medical events were to be considered as SAEs and reported to the Sponsor: anaphylaxis, Guillain-Barré syndrome (GBS), encephalitis, Bell's palsy, neuritis, convulsions, vasculitis, demyelinating disorders and confirmed vaccination failure.

Statistical methods for primary objective:

The overall study cohort (N=100) provided a probability of approximately 95% of observing any AE with a true incidence of 3%.

Secondary objectives:

- To describe the immune response to the vaccine 21 days after vaccination by hemagglutination inhibition (HAI) testing in all subjects
- To describe the antibody persistence 6 months after vaccination by HAI testing in all subjects.

Secondary endpoints:

Immunogenicity:

Antibody (Ab) titers against the A/H1N1 pandemic strain measured with HAI method were expressed as described below:

- HAI Ab titers were obtained on D0, D21 and D180 for all subjects
- The following endpoints were derived:
  - Individual D21/D0 titers ratio
  - Subjects with HAI Ab titer ≥40 (1/dilution [dil]) on D0, D21 and D180
  - Subjects with seroconversion or significant increase in HAI Ab titer, from D0 to D21:
    - Seroconversion defined for subjects with a pre-vaccination titer <10 (1/dil) on D0 as a post-vaccination titer ≥40 (1/dil)

      or
    - Significant increase defined for subjects with a pre-vaccination titer ≥10 (1/dil) as a ≥four-fold increase of the titer (post/pre)
  - Subjects with detectable HAI Ab, i.e. with a titer ≥10 (1/dil), on D0, D21 and D180.

Sample size (Number of Subjects):

Number planned	100
Number included	100
Number completed from D0-D21 period	100
Number completed from D21-180 period	96
Population of analyses	
Full Analysis Set (FAS)/Safety Analysis Set	100
Per Protocol (PP) Analysis Set	98
FAS for antibody persistence	96

Schedules of Vaccination and Specimen Collection:

Vaccination

Subjects received one vaccine injection on D0.

Blood sampling for immunogenicity

All subjects provided a pre-vaccination blood sample on D0 (prior to vaccination), and a blood sample on D21 and on D180.

Visits

For all subjects, there were an inclusion visit (V01), a home visit on D8 for the review of the D0 to D7 safety data Diary Cards (DC), and a follow up visit (V02) on D21 and a 6- month follow up visit (V03) on D180 for blood sample collection and collection of
SAEs, including AESIs.

Duration of Participation in the Trial:

The duration of each subject's participation in the trial was approximately 6 months.

Product Under Investigation:

A/H1N1 pandemic Influenza vaccine (split virion, inactivated)

Form/Dose/Route:

Suspension for injection/0.5 mL/ Intramuscular (IM), into the deltoid area

Batch number: E5925-1

Control Product: Not applicable

Other Product(s): Not applicable

Statistical methods

All analyses were descriptive. The immunogenicity populations (PP Analysis Set, FAS and FAS for antibody persistence) are used for the immunogenicity analyses, and the Safety Analysis Set is used for the safety analyses. For the main parameters, 95% confidence intervals (CIs) of point estimates were calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for proportions.

Safety

Safety was described for all vaccinated subjects in this study.

Solicited reactions (solicited injection site and systemic reactions), unsolicited AEs, including SAEs, were collected.

Solicited reactions were reported for 7 days after vaccination. For each individual solicited reaction, and all solicited injection site reactions and all solicited systemic reactions collectively, the prevalence for each severity for Days 0

to 7 after vaccination were presented. Each solicited reaction from Day 0 to 7 after each vaccination was categorized as none, Grade 1, Grade 2 or Grade 3. When more than one severity was reported within a time period, the highest severity was used. Occurrence, time of onset, number of days of occurrence for each reaction, and action taken were tabulated. Exact two-sided 95% CIs were also computed for the percentages of subjects with each event.

Unsolicited AEs (occurring within 30 minutes after vaccination and up to 21 days after vaccination) were summarized. SAEs reported throughout the trial up to 6 months after vaccination were summarized.

Immunogenicity

The point estimates and their 95% CIs were presented for the following:

- Geometric mean of titers (GMT) on D0, D21 and D180
- Geometric mean of individual titers ratio (GMTR) D21/D0
- Percentage of subjects with detectable Ab (titer ≥10 [1/dil]) on D0, D21 and D180
- Percentage of subjects with titers ≥40 (1/dil) on D0, D21 and D180
- Percentage of subjects achieving significant increase in titer (titer ≥10 [1/dil] on D0 and ≥4-fold increase of the titer after injection) or seroconversion (titer <10 [1/dil] on D0 and post-injection titer ≥40 [1/dil]) on D21.

Data Analysis

A first statistical analysis was performed when safety results within 21 days after vaccination were obtained and database was locked for clinical and safety data without immunogenicity data.

A second statistical analysis was performed when the D0 and D21 immunogenicity results were available.

A third and final statistical analysis was performed when 6-month follow-up safety and D180 immunogenicity results were obtained.

Calculation of Sample Size:

Although there were no statistically powered hypotheses in this study, the study sample size (N=100) provided a probability of approximately 95% of observing any AE having a true incidence of 3%.

Assuming a dropout rate of approximately 10%, a total of 90 evaluable subjects was anticipated.

Results:

A total of 100 subjects were included in the study (50 subjects in Center 002 and 50 subjects in Center 003) and vaccinated. No subjects were included in Center 001. All subjects completed the D0-D21 period of the study. The FAS and Safety Analysis Set include all subjects. Two subjects were excluded from the PP Analysis Set (they had no antibody titers available on D0 and/or D21).

Four subjects were not present at the 6-month follow-up visit (D180). The FAS for antibody persistence includes 96 subjects. Antibody titers were available for 95 subjects on D180.

Demographics and Baseline Characteristics

The median age at inclusion visit 1 (V01) was 33.3 years. The age ranged from 18.1 years to 57.0 years. There were 59 male (59.0%) *versus* 41 (41.0%) female subjects.

Baseline characteristics were similar in both centers, with more male than female subjects (respectively, 56% *versus* 44% in Center 002, and 62% *versus* 38% in Center 003) and a median age of 34.0 years in Center 002 and of 32.0 years in Center 003.

Safety: Primary Objective

Solicited Reactions

A total of 44 subjects (44.0%) experienced at least one solicited reaction within 7 days after injection.

- Injections site reactions:

Solicited injections site reactions were reported in 27 subjects (27.0%). Only pain was reported in these 27 subjects, except for one subject who experienced both pain and swelling reactions. Most injection site reactions occurred within 4 days after injection, were of Grade 1, and lasted 3 days or less. None was of Grade 3 severity. All injection site reactions resolved spontaneously within a maximum number of days of occurrence of 8 days.

- Systemic reactions:

Solicited systemic reactions were reported in 37 subjects (37.0%). Malaise, myalgia and headache were the most frequent solicited systemic reactions (25.0%, 25.0% and 24.0% of subjects, respectively). Fever (≥38.0°C) had a low incidence (2.0% of subjects). Most systemic reactions occurred within 4 days after injection, were of Grade 1, and lasted 3 days or less. Most systemic reactions resolved spontaneously. None lasted more than 7 days. Grade 3 systemic reactions were reported in three subjects (3.0% of subjects), i.e. shivering, headache and myalgia in one subject, headache and myalgia in a second subject, and headache, malaise and myalgia in a third subject. These Grade 3 reactions resolved spontaneously within a maximum of 3 days.

The incidence of solicited reactions was slightly lower in Center 002 (36.0% of subjects) than in Center 003 (52.0%), for injection site reactions (18.0% *versus* 36.0%) as well as for systemic reactions (28.0% *versus* 46.0%).

Unsolicited AEs/reactions:

No immediate unsolicited events occurred within 30 minutes after vaccination.

Unsolicited events were reported in nine subjects (9.0%) within 21 days after vaccination. All unsolicited events were systemic. None was serious and none was assessed as related to vaccination by the Investigator. Rhinitis was the most frequent unsolicited event (6.0% of subjects), followed by cough (2.0% of subjects). Gastritis, stomatitis, pyrexia, pharyngitis and pain in extremity were reported each in 1.0% of subjects. Only one subject (1.0%) experienced a Grade 3 non serious unsolicited event (fever) associated to coryza and cough, which was transient and was treated by medication.

The incidence of unsolicited events was slightly higher in Center 002 (16.0% of subjects) than in Center 003 (2.0%).

Immunogenicity: Secondary Objectives

D0-D21 Period:

Before vaccination (D0), 49.0% of subjects had a detectable anti-HA antibody titer (≥10 [1/dil]) and 33.7% of subjects were seroprotected (anti-HA antibody titer ≥40 [1/dil]). Twenty-one days after vaccination (D21), all subjects achieved seroprotective anti-HA antibody titers (≥40 [1/dil]).

GMTs increased from 20.9 (1/dil) on D0 to 948 (1/dil) on D21. GMTR (increase from D0 to D21) was 45.4. A seroconversion or significant increase in anti-HA antibody titers from D0 was observed in 92.9% subjects. Differences were observed on D0 between Center 2 and Center 3.

Before vaccination (D0), the proportion of subjects with a detectable anti-HA antibody titer (≥10 [1/dil]) was slightly higher in Center 003 (60.4% of subjects) than in Center 002 (38.0%). The proportion of subjects with a seroprotective anti-HA antibody titer (≥40 [1/dil]) was also slightly higher in Center 003 (45.8% of subjects) than in Center 002 (22.0%). GMT was slightly higher in Center 003 (32.9 [1/dil]) than in Center 002 (13.5 [1/dil]).

After vaccination (D21), all subjects were seroprotected (anti-HA antibody titer ≥40 [1/dil]) in both centers and GMTs were comparable in Center 002 (1091 [1/dil]) and Center 003 (818 [1/dil]). Overall, a seroconversion or a significant increase in antibody titers was observed in 98.0% of subjects in Center 002 and 87.5% of subjects in Center 003.

D21-D180 Period: Antibody Persistence

Six months after vaccination (D180), all subjects except one (98.9%) had a detectable anti-HA antibody titer (≥10 [1/dil]). Seroprotective titers (≥40 [1/dil]) were observed in a high proportion of subjects (96.8%) on D180. GMT had decreased from 966 (1/dil) on D21 to 260 (1/dil) on D180.

Immunogenicity Results per Center

No differences were observed between Center 002 and Center 003.

On D21, all subjects were seroprotected in both centers and GMTs were similar in Center 002 (1091 [1/dil]) and Center 003 (846 [1/dil]).

On D180, the proportion of subjects seroprotected was high and similar in Center 002 (96.0%) and Center 003 (97.8%). GMTs were similar in Center 002 (320 [1/dil]) and Center 003 (206 [1/dil]) on D180.

Deaths, Other SAEs and Other Significant AEs:

No deaths, no SAEs and no AESIs were reported during the D0-D180 period.

Conclusions:

- One injection of the non-adjuvanted A/H1N1 pandemic influenza vaccine was well tolerated in healthy adults from India.
- Solicited reactions (mainly pain, headache, malaise and myalgia) were most often transient and of Grade 1 severity. The incidence of Grade 3 solicited reactions (systemic reactions only) was very low.
- No SAEs and no AESIs were reported over the D0-D180 period.
- A strong immune response was induced after one dose of vaccine. All subjects achieved seroprotective anti-HA antibody titers 21 days after vaccination.
- The protective immune response induced after vaccination is long-lasting. Six months after vaccination, a high proportion of subjects (96.8%) were still protected even if anti-HA antibody titers had decreased
- Safety and immunogenicity results obtained in the present study are similar to those obtained in adults aged 18 to 60 years (GPF07 study conducted in Europe) during the clinical development of the non-adjuvanted A/H1N1 pandemic influenza vaccine and no safety concerns were identified.

Date of Report: 15 October 2010.