*These results are supplied for informational purposes only.*
*Prescribing decisions should be made based on the approved package insert in the country of prescription.*

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| **Sponsor:** Sanofi<br>**Drug substance(s):** A/H5N1 inactivated, split-virion influenza virus | **Study Identifiers:** NCT00545701<br>**Study code:** GPA11 |
| **Title of the study:** Immunogenicity and Safety in Adults of an Intramuscular A/H5N1 Inactivated, Split Virion Pandemic Influenza Vaccine Batch Representative of Industrial Scale Production | |
| **Study center(s):** 2 study centers in Australia | |
| **Study period:**<br>Date first subject enrolled: 15/Oct/2007<br>Date last subject completed: 02/Jun/2008 | |
| **Phase of development:** Phase 2 | |
| **Objectives:**<br>• To describe the immune response 21 days after each vaccination.<br>• To describe the safety profile (injection site reactions, and systemic events) during the 21 days following each vaccination, and serious adverse events throughout the study. | |
| **Methodology:** Two centers, open-label. | |
| **Number of subjects:** | Planned sample size: 100 subjects<br>Included subjects: 100<br>Number of discontinued subjects: 4<br>Subjects included in the per protocol analysis set (PPAS): 97 post-dose 1, 91 post-dose 2<br>Subjects included in the full analysis set (FAS): 99<br>Subjects included in the safety analysis set (SafAS): 99 |
| **Diagnosis and criteria for inclusion:**<br>• Aged 18 to 60 years on day of inclusion.<br>• Informed Consent Form signed.<br>• Able to attend all scheduled visits and to comply with all trial procedures.<br>• For a woman, inability to bear a child or negative urine pregnancy test.<br>• For a woman of child-bearing potential, use of an effective method of contraception or abstinence for at least 4 weeks prior to and at least 4 weeks after each vaccination. | |
| **Duration of treatment and observation**<br>All subjects but one received the first of the two vaccinations separated by 21 days at Day 0 and Day 21.<br>Three blood samples (30 mL each) were drawn immediately prior to the first vaccination (Day 0) and at each subsequent visit for serology analyses, i.e. before the second dose (Day 21) and 21 days after the second dose (Day 42).<br>The total duration was approximately 7 months (6 months after the second vaccination at Day 21). | |

**Study treatments**

**Investigational medicinal product(s):** A/H5N1 inactivated split virion pandemic influenza vaccine made in embryonated eggs with aluminum hydroxide adjuvant

Formulation: Ready-to-use multidose 7 mL format vials containing 10 × 0.5 mL doses of vaccine

Route(s) of administration: Intramuscular injection into the deltoid muscle (injected volume: 0.5 mL)

**Criteria for evaluation:**

**Immunogenicity**:

- Anti-hemagglutinin (HA) antibody titers against the A/H5N1 strain measured by the Hemagglutination Inhibition method using horse erythrocytes (HIH) were obtained from duplicate testing on Day 0, Day 21, and Day 42, and summarized at the subject level by individual geometric mean (GM) of duplicates at each time point. The following endpoints were derived:
    - Subjects with titer <8 (1/dil) on Day 0, Day 21, and Day 42.
    - Individual titer ratios Day 21/Day 0, Day 42/Day 0, and Day 42/Day 21.
    - Proportion of subjects with titer ≥32 1/dilution [dil]) on Day 0, Day 21 and Day 42.
    - Seroconversion (for subjects with a titer <8 [1/dil] on D0: post-injection titer ≥32 [1/dil]) or significant increase (for subjects with a titer ≥8 [1/dil]: ≥4-fold increase of the titer) on Day 21 and Day 42.
- Neutralizing antibody titers measured by the Seroneutralization method (SN) were obtained from single testing on D0, D21, and D42 and provided at the subject level at each timepoint. The following endpoints were derived:
    - Subjects with titer <10 (1/dil) on Day 0, Day 21 and Day 42.
    - Individual titer ratios Day 21/Day 0, Day 42/Day 0, and Day 42/Day 21.
    - 2- and 4-fold increase from Day 0 to Day 21 and to Day 42.

**Safety**:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, severity, and relationship to vaccination for any unsolicited systemic adverse events (AE) reported in the 30 minutes after each injection.
- The occurrence, time to onset, number of days of occurrence, severity, and seriousness of solicited (pre-listed in the subject diary and Case Report Form [CRF]) injection site reactions and systemic reactions occurring within 7 days following each injection were reported
- The occurrence, nature (MedDRA preferred term), severity, relationship to vaccination and seriousness of unsolicited (spontaneously reported) adverse events within 21 days following each injection were reported)
- The occurrence, nature, time to onset, and relationship to vaccination of serious adverse events (SAEs) during the whole study period were reported.
- The occurrence of the following reactions (MedDRA preferred terms given in parentheses) following each injection was more especially reported (as defined by the European Medicines Agency [EMEA] Note for Guidance [CPMP/BWP/214/96]).
- Injection site induration ≥5 cm for at least 4 consecutive days following each injection.
- Injection site ecchymosis (injection site hemorrhage) in the 3 days following each injection.
- Temperature >38°C for 24 hours or more (pyrexia) in the 3 days following each injection.
- Malaise in the 3 days following each injection.
- Shivering (chills) in the 3 days following each injection.

**Statistical methods:**

The first statistical analysis of immunological and safety data was performed on results obtained 21 days after the second vaccination following database lock.

The second and final statistical analysis was produced after the 6-month safety follow-up to include safety data obtained 6 months after the second vaccination.

All the main analyses were descriptive; for the main parameters, 95% CIs of point estimates were calculated using normal approximation for quantitative data and exact binomial distribution (Clopper-Pearson method) for proportions.

For the immunological parameters, GMs of titer ratios between timepoints were calculated using normal approximation of the $Log_{10}$-transformed titers followed by back-transformation.

**Summary:**

**Subjects disposition and sample size:**

A total of 100 subjects were included in the study between 15 October 2007 and 19 October 2007 and were planned to receive two vaccinations at a 21-day interval of the 30µgHA+aluminum hydroxide vaccine.

The last contact (last 6-month follow-up) of the last subject took place on 02 June 2008. The primary vaccination period lasted 85 days.

A total of four subjects did not complete the study to V03. Two subjects discontinued the study before V02 (one due to non-compliance with the protocol and one was lost to follow-up after V01, but was contacted again for the 6-month safety follow-up), and two subjects discontinued the study between V02 and V03 (they were lost-to follow-up after V02, but were contacted again for the 6-month safety follow-up). In addition, two subjects did not receive the second vaccination due to ongoing injection site and systemic AEs but were followed for safety at Day 21 and provided the second blood sample as planned at Day 21; 96 subjects therefore received the second vaccination.

One subject returned for safety follow-up at Day 42; however, the other did not return for safety follow-up.

Overall, among the 99 subjects vaccinated at Day 0, 98 subjects (99%) completed the 6-month safety follow-up. Nine subjects presented with at least one protocol deviation during the primary vaccination series, and were therefore excluded from the PPAS population.

**Immunogenicity:**

Antibody response to vaccination as measured by hemagglutination inhibition using horse erythrocytes (HIH)

Few subjects (2.0%) had a detectable antibody titer, i.e. ≥8 (1/dil), prior to the first vaccination whereas at Day 42, 71.3% of subjects had a detectable antibody titer and 30.9% of subjects had a titer ≥32 (1/dil). At Day 42, one of the three EMEA immunogenicity criteria was fulfilled (GMT of individual ratio from Day 0 equal to 3.30). The lower limit of the 95% CI also met the criterion.

Antibody response to vaccination as measured by seroneutralization (SN)

Few subjects (1.0%) had a detectable antibody titer, i.e. ≥10 (1/dil), prior to the first vaccination, whereas at Day 42, 69.5% of subjects had a detectable titer and 55.8% of subjects had a 4-fold increase in titer between Day 0 and Day 42.

The trends for the SN data reflect those described for the HIH data.

**Safety results:**

No subject experienced an immediate unsolicited AE within 30 minutes following vaccination.

Only one SAE, hospitalization for tonsillitis, was reported up to D42. This event was considered as unrelated to vaccination. After D42, four SAEs unrelated to vaccination were reported. Out of the four SAEs, there were two full-recoveries, one recovery with sequelae and one subject was lost to follow-up.

Four SAEs were reported during the study, none was assessed related to vaccination according to both the Sponsor and the Investigator.

Most subjects experienced at least one solicited injection site reaction. The most frequently reported solicited injection site reactions were injection site pain and erythema, which occurred in 52.0% and 22.4% of subjects following the first vaccination, respectively. At Day 42, the most frequently reported solicited injection site reaction was injection site pain, reported by 39.4% of subjects. The incidence of remaining solicited injection site reactions was lower than 15%. No Grade 3 solicited reactions were reported.

Approximately 50% of subjects experienced a solicited systemic reaction in the 7 days following any vaccination. After the first vaccination, the most frequently reported solicited systemic reactions were headache, myalgia and malaise which occurred in 27.6%, 21.4% and 20.4% of subjects, respectively. Six subjects reported at least one Grade 3 solicited reaction after the first vaccination.

For all solicited systemic reactions, the incidence was either slightly lower following the second compared to the first vaccination or similar following both vaccinations. After the second vaccination, three subjects experienced at least one solicited systemic reaction reported as Grade 3.

Virtually all solicited reactions started within 3 days of vaccination, were reported as Grade 1 reactions and resolved spontaneously with no action being taken, except for headache which resolved following medication intake, mainly within 3 days or less.

Most subjects did not report any adverse reactions listed in the EMEA guidance within 3 days following the first and the second vaccinations.

Unsolicited events occurring within 21 days after any vaccination were reported for 56.1% of subjects. All but one unsolicited event were systemic events, and most events were not related to vaccination.

Two subjects reported at least one unsolicited AE of Grade 3 severity after the first vaccination: one subject reported Grade 3 vomiting and nausea related to vaccination which resolved spontaneously within 2 days, and one subject reported Grade 3 tonsillitis, which resolved following hospitalization and was considered as an SAE. One subject reported Grade 3 upper respiratory tract infection after the second vaccination, which was not related to vaccination and resolved following medication intake.

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