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

Sponsor: Sanofi **Drug substance(s):** Monovalent subvirion H5N1 influenza vaccine (HA of Indonesia/05/2005 [H5N1] PR8-IBCDC-RG2 influenza virus) with AF03	**Study Identifiers:** NCT00664417 **Study code:** FUF04

Title of the study: Safety and Immunogenicity of Different Formulations of an Intramuscular A/H5N1 Inactivated, Split Virion Influenza Vaccine in Healthy Adults

Study center(s): 6 study centers located in United States

Study period:

Date first subject enrolled: 19/Apr/2008

Date last subject completed: 30/Jan/2009 (primary phase)

01/Mar/2010 (booster phase)

Phase of development: Phase I

Objectives:

- To describe the safety profile after each injection.
- To describe the immunogenicity/humoral immune response after each injection.
- To describe the antibody persistence.

Methodology: This was a randomized, observer-blinded, active-controlled, Phase I, formulation / dose ranging study. Six adjuvanted vaccine formulations were tested at 2.5 µg and 6.0 µg of hemagglutinin (HA) with the AF03 adjuvant at 0.5%, 1.0%, and 2.5%, respectively, and 2 control formulations at 2.5 µg and 6.0 µg of HA without adjuvant. All formulations were tested in a two-dose schedule (21 days apart). An additional group received two doses of a normal saline placebo (21 days apart).

	Study groups						**Control groups**		
Group #	1	2	3	4	5	6	7	8	9
Antigen Dose1 (µg)	2.5	2.5	2.5	6.0	6.0	6.0	2.5	6.0	N/A4
Adjuvant2	0.5%	1.0%	2.5%	0.5%	1.0%	2.5%	N/A3	N/A3	N/A
Planned Number of Subjects	50	50	50	50	50	50	25	25	25

1 Study groups 1 to 6 and Control groups 7 and 8 received the investigational H5N1 vaccine (HA of Indonesia/05/2005 [H5N1] PR8-IBCDC-RG2 influenza virus)
2 Adjuvant: AF03
3 Control non-adjuvanted doses.
4 Control group 9 received normal saline solution as placebo.

The study population was 375 healthy adult volunteers aged 18 to 40 years.

All subjects were asked to return 6 and 12 months after their first vaccination dose for safety follow up and a blood draw. After the 12 month follow-up, subjects from groups 1, 2, 4, 5, 7, and 9 were not asked to further participate in the trial.

Number of subjects**:**	Planned: 375
	Randomized: 375
	Treated: 372
Evaluated:	
	Safety: 372

Diagnosis and criteria for inclusion:

Inclusion Criteria

1) Healthy adult aged 18 to 40 years on the day of inclusion

2) Provides signed informed consent prior to study procedures

3) Able to attend all scheduled visits and comply with all trial procedures

4) For a woman of child-bearing potential, avoid becoming pregnant (use of an effective method of contraception or abstinence) for at least 4 weeks prior to the first vaccination, until at least 4 weeks after last vaccination

Exclusion criteria

1) Known systemic hypersensitivity to any of the vaccine components or history of a life-threatening reaction to the standard-dose Fluzone® vaccine or to a vaccine containing any of the same substances

2) For a woman of child-bearing potential, known pregnancy or positive serum/urine pregnancy test

3) Breast feeding woman

4) Participation in another clinical trial investigating a vaccine, drug, medical device, or a medical procedure in the 4 weeks preceding the (first) trial vaccination

5) Planned participation in another clinical trial during the present trial period

6) Known or suspected congenital or acquired immunodeficiency, immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 6 months, oral, parenteral, or inhaled steroids

7) Has an acute or chronic medical illness or any condition that would, in the opinion of the site investigator, place the subject at an unacceptable risk of injury or would interfere with the evaluation of responses or render the subject unable to meet the requirements of the protocol

8) Known or suspected current alcohol abuse or drug addiction that may interfere with the subject's ability to comply with trial procedures

9) History of receipt of blood or immunoglobulin or other blood-derived products within the 3 months prior to enrollment in this study that might interfere with the assessment of immune response

10) Receipt of any vaccine in the 4 weeks preceding the first trial vaccination

11) Planned receipt of any vaccine in the 4 weeks preceding or following any trial vaccination

12) Known Human Immunodeficiency Virus (HIV), HBs antigen, or Hepatitis C seropositivity

13) Personal or family history of Guillain-Barré Syndrome

14) Thrombocytopenia, bleeding disorder or anticoagulants in the 3 weeks preceding inclusion contraindicating IM vaccination

15) Active neoplastic disease or a history of any hematologic malignancy

16) Previous participation in a pandemic flu trial

17) History of H5N1 infection or exposure to presumed/confirmed H5N1 human/animal cases

18) Known seizure/epilepsy history and/or taking anti-seizure medication

19) Receipt of psychiatric drugs. Subjects receiving a single antidepressant drug and stable for at least 3 months prior to enrollment, without decompensating symptoms will be allowed to enroll in the study

20) Subject deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized without his/her consent

Temporary Exclusion Criteria:

A prospective subject should not be included in the study until the following conditions and/or symptoms are resolved

21) Acute febrile illness, including an oral temperature greater than ≥ 99.5 F (≥ 37.5 C), within 24 hours prior to vaccination

22) Signs and symptoms of an acute infectious respiratory illness

23) Received antibiotics therapy within 72 hours preceding the trial vaccination (excluding drops or topical)

24) Receipt of any allergy shots and/or seasonal allergy medication in the 7-day period prior to enrollment (vaccination), or scheduled to receive any allergy shots and/or seasonal allergy medication in the 7-day period after enrollment (vaccination). Subjects should be enrolled in the trial only if their allergy shots are given on a stable schedule outside the 7-day periods pre- and post-vaccination.

Study treatments

Investigational medicinal product(s): Monovalent subvirion H5N1 influenza vaccine (HA of Indonesia/05/2005 [H5N1] PR8-IBCDC-RG2 influenza virus) with AF03

Formulation: Liquid - single dose vials of pandemic influenza vaccine and PBS solution.

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

Dose regimen: Two injections

Noninvestigational medicinal product(s): Monovalent subvirion H5N1 influenza vaccine (HA of Indonesia/05/2005 [H5N1] PR8 IBCDC-RG2 influenza virus)

Formulation: Liquid - single dose vials of pandemic influenza vaccine and Phosphate Buffered Saline (PBS) solution.

Route(s) of administration: IM injected into the deltoid area.

Dose regimen: Two injections

Noninvestigational medicinal product(s): Placebo-normal saline (NS)

Formulation: NS solution

Route(s) of administration: IM injected into the deltoid area.

Dose regimen: Two injections.

Noninvestigational medicinal product(s): Monovalent Subvirion H5N1 influenza vaccine A/Bar-Headed Goose/Qinghai Lake/1A/05 (163222)(H5N1)

Formulation: Liquid - single dose vials of pandemic influenza vaccine and PBS solution.

Route(s) of administration: IM injected into the deltoid area.

Dose regimen: Two injections.

Duration of treatment: 2 days

Duration of observation: The duration of each subject's participation in the trial was approximately 12 months for subjects in groups 1, 2, 4, 5, 7, and 9 and approximately 21 months for subjects in groups 3, 6, and 8.

Criteria for evaluation:

Safety:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, action taken, and relationship to vaccine of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination.
- Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited (prelisted in the subject's diary and electronic case report form [eCRF]) injection site and systemic reactions occurring up to 7 days after each vaccination.
- Occurrence, nature (MedDRA preferred term), time to onset, duration, intensity, action taken, and relationship to vaccine (for systemic AEs only) of unsolicited (spontaneously reported) AEs occurring up to 21 days after each vaccination.
- Occurrence, nature (MedDRA PT), time to onset, duration, intensity, relationship to vaccine, seriousness criteria, and outcome of serious adverse events (SAEs) throughout the trial (up to 6 months post-booster vaccination).

Immunogenicity:

Two-dose schedule response:

Antibody (Ab) titers against the A/H5N1 strain were expressed as described below:

- Anti-Hemagglutination (anti-HA) Ab titers obtained on Day 0 (D0), D21, and D42 were performed using the hemagglutination inhibition (HAI) assay using horse erythrocytes (HIH) for all subjects. The following endpoints were derived:

  Individual titers ratios D21/D0, D42/D0, and D42/D21

  Titer ≥ 40* (1/dil) on D0, D21, and D42

  Significant increase of titer (titer ≥ 10 [1/dil] on D0 and ≥ 4-fold increase of the titer after injection) or a seroconversion rate (titer < 10 [1/dil] at D0 and post-injection titer ≥ 40 [1/dil]) at D21, and D42

  Detectable Abs (titer ≥ 10* [1/dil]) on D0, D21, and D42

  Note: *A titer ≥ 40 (1/dil) is considered as the seroprotective level.

- Seroneutralization (SN Method) Ab titers obtained on D0, D21, and D42. The following endpoints were derived:

  Individual titers ratios D21/D0, D42/D0, and D42/D21

  4-fold increase of titers from D0 to D21 and to D42

  Detectable Abs (titer ≥ 10 [1/dil]) on D0, D21, and D42

Cross-reactivity at D42: Ab titers against other A/H5N1 strain(s) from other clade(s) were performed (using the HIH and SN methods) to assess cross-reactivity

Ab persistence:

Ab titers obtained at Month 6 (M6, D180) and M12 (D365) (for all subjects), at M15 (D456) and 6 months post-booster (M21 [D636]) (for Subjects in groups 3, 6, and 8 only).

Detectable Abs (for HIH and SN methods: titer ≥ 10 [1/dil])

Anti-HA Ab (HIH method) titer ≥ 40 (1/dil)

Neutralizing Ab (SN method) titer ≥ 20 (1/dil) ≥ 40 (1/dil)

Booster injection response (for Subjects in groups 3, 6, and 8 only):

Ab titers against the A/H5N1 strain after booster injection will be expressed as described below:

- Anti-HA Ab titers (HIH method) obtained at Visit 6 (V06, D456, pre-booster vaccination), V07 (D464, 8 days post-booster vaccination), and V08 (D477, 21 days post-booster vaccination). The HIH assay was performed for all subjects. The following endpoints were derived:

  Individual titers ratios V07/V06, and V08/V06

  Titer ≥ 40* (1/dil) on V06, V07, and V08

  Significant increase of titer (titer ≥ 10 [1/dil] at V06 and ≥ 4-fold increase of the titer after injection) or a seroconversion rate (titer < 10 [1/dil] at V06 and post-injection titer ≥ 40 [1/dil]) at V07 and V08

  Detectable Abs (titer ≥ 10* [1/dil]) on V06, V07, and V08

- SN Ab titers obtained at V06 (D456, pre-booster vaccination), V07 (D464, 8 days post-booster vaccination), and V08 (D477, 21 days post-booster vaccination). The following endpoints were derived:

  Individual titers ratios V07/V06, and V08/V06

  4-fold increase of titers from V06 to V07, and to V08

  Detectable Abs (titer ≥ 10 [1/dil]) on V06, V07, and V08

Cross-reactivity was assessed at D456 (pre-booster vaccination), D464 (8 days after the booster vaccination), and D477 (21 days after the booster vaccination), using the HIH and SN methods against other A/H5N1 strain(s) from other clade(s).

Statistical methods:

This was a Phase I dose-ranging study and was not designed to test a specific hypothesis. Rather, it was intended to examine the safety of this vaccine and to achieve initial estimates of its dose-dependent immune response for future investigations.

Sample size rationale:

The overall study cohort (N = 375) provided a probability of approximately 98% of detecting any adverse events (AE) with an incidence of 1% in the study, 95% for the pooled adjuvanted group (N=300), 78% for either of the 2.5 µg pooled adjuvanted group or the 6.0 µg pooled adjuvanted group (N=150), and 53% for the pooled non-adjuvanted group (N=75).

Summary:

Population characteristics:

Demographics:

Primary Series:

In general, the demographics were comparable among study groups. In terms of sex, the majority of study groups had a lower number of males than females per group (ranged from 32.7 [16/49] to 65.3% [32/49] of male subjects and from 34.7% [17/49] to 67.3% [33/49] of female subjects).

The mean age of the subjects in each group at enrollment ranged from 26.9 to 31.9 years, with subjects aged a minimum and maximum of 18.0 and 40.0 years, respectively.

Most subjects in each group were Caucasian (45.8% [11/24] to 68.6% [35/51]), followed by Hispanic (19.2% [5/26] to 29.2% [7/24]); Asian, Black, American Indian or Alaska Native, and Other races constituted the remainder of the safety analysis set.

Booster Phase:

In general, the majority of study groups had a lower number of males than females per group (ranged from 32.3% [10/31] to 47.1% [8/17] of male subjects and from 52.9% [9/17] to 67.7% [21/31] of female subjects).

The mean age of the subjects in each group at enrollment ranged from 29.2 to 31.3 years, with subjects aged a minimum and maximum of 20.0 and 42.0 years, respectively.

Most subjects in each group were Caucasian.

Disposition:

Primary Series

A total of 375 subjects (49 to 52 subjects per adjuvanted group and 24 to 26 subjects per control group) were enrolled at 6 sites between 19 April 2008 and 09 May 2008 and randomized to one of the nine study groups.

Among the 375 subjects who were randomized, a total of 372 subjects received at least one vaccination and were included in the safety analysis set: 372 subjects received Dose 1 and 343 subjects received Dose 2.

Booster Phase

There were 30 (57.7%), 33 (66.0%), and 18 (69.2%) subjects who returned to receive a booster dose of 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg, respectively.

Reasons for withdrawal

Primary Series:

A total of 332 subjects completed the study up to the D42 visit (40 [81.6%] to 47 [94.0%] subjects in each adjuvanted group and 21 [84.0%] to 25 [96.2%] subjects in each control group).

The most frequently reported reason for discontinuation among all study groups was due to non compliance with the protocol, reported for 15 subjects (0.0% to 8.2% [4/49] of subjects per group); followed by adverse events, lost to follow-up, and voluntary withdrawal not due to an AE, reported for ≤ 3 subjects per group (0.0% to 6.1% [3/49] subjects per group); no discontinuations were due to an SAE.

Booster Phase:

The majority of subjects in all study groups completed the trial: 29 (96.7%), 28 (90.3%), and 15 (88.2%) subjects from the 3.8 µg/2.5% group, 7.5 µg/2.5% group, and 7.5 µg group, respectively. The most frequently reported reason for subject withdrawal was due to lost to follow-up or voluntary withdrawal (not due to AE).

Deviations:

Primary Series:

A total of 91 subjects had at least one protocol deviation affecting statistical analyses during the primary phase and, therefore, were excluded from the Per-Protocol Analysis Set (PPAS).

In general, the incidence of protocol deviations was evenly distributed among study groups. The most common deviation was subjects with visit out of window, reported by 41 subjects (3.8% [2/52] to 26.9% [7/26] of subjects); followed by subjects who did not receive both vaccines, reported by 32 subjects (0.0% to 16.0% [8/50] of subjects). Subjects who did not meet entry criteria and subjects with other protocol violations were each reported by a total of 17 and 9 subjects among all groups before the booster phase.

Booster Phase:

The majority of subjects with protocol deviations had visits out of window for the blood draws. These subjects were still included in the full analysis set

Randomization/Vaccination Administration Errors

Primary Series:

Three subjects were randomized and did not receive any injection (One subject in the 2.5 µg/0.5% group and two subjects in the 2.5 µg/2.5% group), and one subject was randomized to the 6.0 µg/2.5% group, but received the 2.5 µg/2.5% vaccine at Vaccination 1 and 2.

Booster Phase:

There was 1 subject randomized to the 7.5 µg/2.5% group, however received a booster dose of 3.8 µg/2.5%, as this subject had received the 2.5 µg/2.5% dose in the primary series.

Safety results:

Immediate adverse events (AEs)

There were no AEs observed within 30 minutes after injections for any subject in this study.

Solicited Reactions Between D0 and D7 After Each Injection:

Solicited Injection Site Reactions:

Primary Series:

In general, the percentages of subjects reporting at least one solicited injection site reaction were higher in the adjuvanted groups than in the control groups; and, regardless of antigen strength, increasing adjuvant amount led to increased injection site reactions. While patterns observed after Injection 2 were similar to those after Injection 1, the percentages of reactions in the adjuvanted groups were higher after Injection 1 (52.2% [24/46] to 83.7% [41/49] of subjects) than after Injection 2 (33.3% [14/42] to 68.3% [28/41]); and percentages for the control groups were similar after Injections 1 and 2 (30.4% [7/23] to 34.6% [9/26], and 19.0% [4/21] to 37.5% [9/24], respectively).

For all study groups, the most frequently reported solicited injection site reaction after either injection was injection site pain. All other solicited injection site reactions after both injections were reported by ≤ 10 subjects in each of the adjuvanted groups and by ≤ 6 subjects in each of the control groups. The majority of reactions were reported as Grade 1, started within 3 days of injection, lasted 1 to 3 days, and required no action to be taken. Reports of reactions present at D8 or later were rare.

Booster Phase:

Solicited injection site reactions were reported by 71.4% (20/28), 69.2% (18/26), and 29.4% (5/17) of subjects in the 3.8 µg/2.5%, 7.5 µg/2.5%, and unadjuvanted 7.5 µg groups, respectively. The most frequently reported solicited injection site reaction for all study groups was injection site pain, reported by 71.4% (20/28), 65.4% (17/26), and 23.5% (4/17) of subjects who received 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg doses, respectively. Most pain was reported as Grade 1 (all pain was Grade 1 for the 7.5 µg group), with Grade 2 pain reported by 17.9% (5/28) and 23.1% (6/26) of subjects who received 3.8 µg/2.5% and 7 5 µg/2.5% doses, respectively. No Grade 3 pain was reported.

For the adjuvanted and unadjuvanted groups, erythema, swelling and induration were reported at similar frequencies (7.1% to 19.2% of subjects). Ecchymosis was the least frequently reported reaction for all groups. Most solicited injection site reactions were reported as Grade 1. Grade 3 solicited injection site reactions were reported by 2 subjects: one subject reported erythema and the other subject reported swelling and induration.

Most solicited injection site reactions occurred between Day 0 and Day 3 and lasted 1 to 3 days. There were no solicited injection site reactions reported for 8 days or more.

Solicited Systemic Reactions:

Primary Series:

Overall, the percentages of subjects experiencing at least one solicited systemic reaction were similar among the adjuvanted (53.3% [24/45] to 63.6% [28/44] of subjects) and control groups (50.0% [12/24] to 61.5% [16/26] of subjects). While patterns observed after Injection 2 were similar to those after Injection 1, the percentages of solicited systemic reactions in all groups were higher after Injection 1 than after Injection 2.

For the adjuvanted groups, headache, myalgia, and malaise were the most frequently reported solicited systemic reactions after either injection; shivering and fever were reported by ≤ 6 subjects in each group. For the control groups, headache and myalgia were the most frequently reported solicited systemic reactions after both injections; all other reactions were reported by ≤ 6 subjects in each group. The majority of reactions were reported as Grade 1, started within 3 days of injection, lasted 1 to 3 days, and required no action to be taken. Reports of reactions present at D8 or later were rare.

Booster Phase:

Solicited systemic reactions were reported by 46.4% (13/28), 53.8% (14/26), and 37.5% (6/16) of subjects who received doses of 3.8 µg/2.5%, 7.5 µg/2.5%, and unadjuvanted 7.5 µg, respectively.

The most frequently reported solicited systemic reaction for subjects in the 7.5 µg/2.5% and 7.5 µg groups was headache; myalgia was the most frequently reported solicited systemic reaction by the 3.8 µg/2.5% group. Fever and shivering were the least frequently reported solicited systemic reactions (reported by ≤ 6.3% of subjects. Most solicited systemic reactions were reported as Grade 1, occurred between Day 0 and Day 3 and lasted 1 to 3 days. There were no solicited systemic reactions reported for 8 days or more.

Unsolicited AEs between D0 to D21 After Each Injection: Primary Series

Unsolicited Injection Site Reactions:

Overall, there was no difference between adjuvanted groups and control groups in regards to unsolicited injection site reactions. Between D0 and D21after Injection 1, three (5.9%) subjects in the 2.5 µg/2.5% group reported at least one unsolicited injection site reaction (injection site pruritus, injection site rash, and injection site erythema), all of which were Grade 1 and required no action to be taken. There were no unsolicited injection site reactions in any other adjuvanted or control groups after Injections 1 and 2.

Unsolicited Systemic AEs:

Unsolicited systemic AE profiles were similar in all groups, in terms of percentages of subjects.

For the adjuvanted groups, unsolicited systemic AEs were reported most frequently in the system organ class (SOCs) of Respiratory, thoracic and mediastinal disorders (31 subjects total), Infections and infestations (20 subjects total), and General disorders and administration site conditions (14 subjects total), with similar numbers of subjects in each group. All unsolicited systemic AEs (by preferred term) were reported by ≤ 5 subjects in each group. For the control groups, unsolicited systemic AEs were reported by a total of ≤ 4 subjects for each SOC, and all unsolicited systemic AEs (by preferred term) were reported by ≤ 2 subjects in each group.

For all study groups, the majority of the reported unsolicited systemic AEs started within seven days of injection, lasted 1 to 3 days, and required either no action to be taken or medication. The majority of systemic AEs were reported as Grade 1. Those reported as Grade 3 were rare, with zero to two subjects per group. Zero to five subjects per group reported unsolicited systemic adverse reactions, the majority of which were reported as Grade 1; however, one subject in the 6.0 µg/1.0% group experienced Grade 3 myalgia (muscle pain) on Day 0, which lasted 3 days, required no action to be taken, and led to withdrawal from the study, and one subjects in the Placebo group experienced Grade 3 influenza like illness on Day 1, which

lasted 4 days and required medication.

Unsolicited AEs between D0 to D21 After Booster

Unsolicited AEs were reported by 3.3% (1/30), 12.9% (4/31), and 17.6% (3/17) of subjects who received 3.8 µg/2.5%, 7.5 µg/2.5%, and unadjuvanted 7.5 µg, respectively. Of these, 3.3% (1/30) and 3.2% (1/31) of subjects in the 3.8 µg/2.5% and 7.5 µg/2.5% groups, respectively, had unsolicited adverse reaction (ARs)

There was 1 subject in the 7.5 µg/2.5% group who reported a Grade 3 unsolicited injection site reaction (injection site warmth) that occurred on Day 1 after injection and lasted for 2 days. This unsolicited AE was considered as related to the vaccination by the investigator, and the subject took medication for this AR. This was the only subject who reported an unsolicited injection site reaction out of any group.

Most unsolicited systemic AEs were Grade 1 and were considered as unrelated to the vaccination except for 1 subject in the 3.8 µg/2.5% group who reported Grade 2 dizziness (dizzy and lightheaded) on the day of vaccination that lasted 2 days. The subject took no action for this AR and recovered. Other unsolicited systemic AEs included headache, upper abdominal pain, dyspepsia, cough, pharyngolaryngeal pain, rash, and ear infection.

AEs Leading to Study Withdrawal:

Primary Series:

In general, the number of subjects with unsolicited AEs leading to withdrawal within 21 days after any injections was similar among all study groups, with reports for one to two subjects within each group, with the exception of the 6.0 µg/2.5% and 6µg groups, for which there were no reports.

Adjuvanted groups

There were six subjects in the adjuvanted groups who were withdrawn from the study due to an AE, all of which occurred after Injection 1, including:

- Two subjects in the 2.5 µg/0.5% group: one subject due to subject illness (nasopharyngitis, stuffy nose, and sore throat) and one subject due to fever, dry throat, intermittent fatigue, sweats, and decrease in appetite
- One subject in the 2.5 µg/1.0% group due to Methicillin-resistant Staphylococcus aureus (MRSA) infection requiring antibiotic therapy
- One subject in the 2.5 µg/2.5% group due to possible allergic reaction to vaccine unknown at inclusion
- One subject in the 6.0 µg/0.5% group due to weakness after first day of injection
- One subject in the 6.0 µg/1.0% group due to development of severe muscle pain and fever

Control groups

There were two subjects in the control groups who were withdrawn from the study due to an AE, including:

- One subject in the 2.5 µg group due to cold-like symptoms
- One subject in the Placebo group due to flu-like reactions

Booster Phase:

There were no AEs leading to study withdrawal.

SAEs:

SAEs within 21 Days After Vaccine Injections:

During this time period, one subject in the 6.0 µg/0.5% group experienced an SAE in the SOC of injury, poisoning and procedural complications. The reported SAE was right wrist hematoma (post-operative) 15 days after Injection 2, which was considered to be unrelated to the vaccine by the Investigator. This SAE required hospitalization, and the subject recovered. There were no SAEs reported for any subject within 21 days after either injection in the remaining adjuvanted groups or control groups

SAEs between D42 and D180 After Vaccine Injection 1:

During this time period, a total of two subjects reported an SAE:

- One subject in the 2.5 µg/1.0% group experienced acute febrile illness 52 days after Injection 2. This SAE was considered to be unrelated to the vaccine by the Investigator, required hospitalization, and the subject recovered.
- One subject in the 2.5 µg/2.5% group experienced acute herniated lumbar disc, right L5-S1 78 days after Injection 2. This SAE was considered to be unrelated to the vaccine by the Investigator, required hospitalization, and the subject recovered.

There were no SAEs reported for any subject in the remaining adjuvanted groups or control groups.

SAEs between D180 and D365 After Vaccine Injection 1:

During this time period, 1 subject reported an SAE:

Subject 005-00043 (2.5 µg/2.5% group) experienced spontaneous abortion/fetal demise 198 days after Injection 2. This SAE was considered to be unrelated to the vaccine, and the subjected recovered.

In addition, subject 006-00004 from the 6.0 µg/1.0% group was being followed for pregnancy and experienced premature labor 376 days following Injection 1. The subject was hospitalized for this SAE. This SAE was considered to be unrelated to the vaccine, and the subjected recovered.

Pregnancies:

A total of 13 pregnancies were reported to the Sponsor. Pregnancy outcomes were reported for 10 of the 13 cases. All subjects who reported pregnancies and for whom outcome data were available had normal babies (except 1 subject, see SAE below). Three subjects have been lost to follow-up and the outcomes of their pregnancies are unknown.

Of these, there were 3 subjects who reported non-serious AEs during their pregnancy: heartburn, elevated blood pressure, and hyperemesis. All were resolved, and 2 subjects delivered normal babies, while 1 subject's delivery outcome was not known (subject lost to follow-up). Out of these pregnancies, 2 subjects experienced SAEs as described above (spontaneous abortion/fetal demise and premature labor).

Deaths:

There were no deaths reported for any subject in this study.

Immunogenicity: Primary Series

At baseline (pre-vaccination D0), all subjects were H5N1 vaccine-naïve according to HIH method. Using the SN method, 1 to 2 subjects per group (2.2% to 4.3%) had seropositivity (titer ≥ 10) to H5N1 at D0 before vaccination were found in the 2.5 µg/1.0%, and 2.5 µg/2.5%, 6.0 µg/0.5%, 6.0 µg/1.0%, and 6.0 µg/2.5% and 2.5 µg groups. A pre-vaccination titer ≥ 20 was also observed at D0 for 2 subjects (4.3%) in the 2.5 µg/1.0% group and 1 subject (2.2%) in the 6.0 µg/0.5% group.

Humoral Immune Response 21 Days After Each Injection:

Humoral Response 21 Days after Injection 1: **Antibody Response Against A/H5N1 Vietnam (cross-reactivity)**

Primary Series

HIH Method

At D21 after Injection 2 (D42), the geometric mean titer (GMTs) for all groups were relatively low (ranging from 6.0 to 8.7), where those of the adjuvanted groups were only slightly higher than those of the control groups (5.0 to 5.4). The percentages of subjects that had titers ≥ 10 (detectable Ab titers) increased with increasing AF03 adjuvant doses. For the adjuvanted groups, the percentages of subjects that had titers ≥ 10 and ≥ 40 against the A/Vietnam strain ranged from 13.6% (6/44) to 44.4% (20/45) and from 2.1% (1/47) to 6.7% (3/45) of subjects, respectively. For the control groups, 12.0% (3/25) of subjects from the 6.0 µg group had a titer ≥ 10. There were no subjects from the other control groups who had a titer ≥ 10, and no subjects from any control group with a titer ≥ 40.

SN Method

At D21 after Injection 2 (D42), the GMTs for all groups were relatively low (ranging from 6.0 to 8.7), where those of the adjuvanted groups were only slightly higher than those of the control groups (5.0 to 5.4). In general, the percentages of subjects that had titers ≥ 10 (detectable Ab titers) increased with increasing AF03 adjuvant dose. For the adjuvanted groups, the percentages of samples that had titers ≥ 10 and ≥ 40 were shown to be cross reactive against the A/Vietnam strain for 29.5% (13/44) to 71.1% (32/45) and 8.5% (4/47) to 28.9% (13/45) of subjects, respectively; and, for the control groups, titers ≥ 10 were achieved for 4.5% (1/22) to 16.0% (4/25) of subjects in the 2.5 µg and 6.0 µg groups, respectively, and 4.0% (1/25) of subjects in the placebo group. There were no subjects from the control groups who had a titer ≥ 40.

While the humoral immune response (HIH Method) within 21 days after Injection 1 was low for all study groups, the response was higher in the adjuvanted groups than in the 3 control groups:

- The D21 GMTs ranged from 6.2 to 11.9 and from 5.0 to 5.1, respectively.
- The geometric mean titer ratio (GMTRs) (D21/D0) were 1.1 to 1.6, and 1.0, respectively.
- The percentage of subjects who achieved seroprotection was 0.0% to 21.3% (10/47) of subjects and no subjects, respectively.
- For all study groups, the percentages of subjects achieving significant increase or seroconversion after Injection 1 were 0.0% to 21.3% [10/47] of subjects and 0.0% in the adjuvanted and control groups, respectively.
- The percentages of subjects with titers ≥ 10 [1/dil] were 20.0% [9/45] to 57.4% [27/47] of subjects and zero to one (3.8%) subject, respectively.

Within the adjuvanted groups, the humoral immune response showed an increase with increased percentages of AF03 adjuvant (i.e., from 0.5% to 1.0% and 2.5%). For the majority of the endpoints, these percentages were highest in the 6 µg antigen groups:

- The D21GMTs for the 2.5 µg doses ranged from 6.0 to 9.0 (from 0.5% to 2.5% adjuvanted groups, respectively); and the D21 GMTs for the 6.0 µg doses ranged from 6.3 to 11.9 (from 0.5% to 2.5% adjuvanted groups, respectively).
- The GMTRs (D21/D0) for the 2.5 µg doses ranged from 1.1 to 1.4 and (from 0.5% to 2.5% adjuvanted groups, respectively); and the GMTRs for the 6.0 µg doses ranged from 1.1 to 1.6 (from 0.5% to 2.5% adjuvanted groups, respectively, with the latter being the highest GMTR overall).
- The percentage of subjects who achieved seroprotection was low for all groups, with the highest percentage in the 2.5% adjuvanted groups (13.0% [6/46] and 21.3% [10/47] of subjects in the 2.5 µg and 6.0 µg antigen groups, respectively).
- The percentage of subjects who achieved significant increase or seroconversion (D0 to D21) was similar in the 2.5 µg and 6.0 µg antigen groups, with the highest percentage in the 2.5% adjuvanted groups (13.0% [6/46] and 21.3% [10/47] of subjects in the 2.5 µg/2.5% in the 6.0 µg/2.5% groups, respectively).

The percentages of subjects with detectable titers were similar for all adjuvanted groups, with the highest percentages in the 2.5 µg/2.5% and 6.0 µg/2.5% groups (57.4% [27/47] of subjects).

Similar immune response patterns were observed for the SN Method; however, responses were higher with the SN Method than with the HIH Method.

Humoral Response 21 Days after Injection 2:

Similar humoral immune response (HIH Method) patterns were observed at D21 post-Injection 2 (Day 42) as were observed at D21 post-Injection 1 (i.e., higher responses in adjuvanted groups than in control groups); however, responses were further amplified at a higher rate for the adjuvanted groups than for the control groups:

- The D42 GMTs ranged from 30.8 to 99.3 and from 5.0 to 6.2 respectively.
- The GMTRs (D42/D0) ranged from 3.3 to 10.2 and 1.0 to 1.1, respectively.
- The percentages of subjects who achieved seroprotection increased for the adjuvanted groups (52.5% [21/40] to 84.4% [38/45] of subjects post-Injection 2); however the number and percentage remained at zero subjects for the control

groups

- From baseline to 21 days post-Injection 2 (D42) in the adjuvanted groups, a significant increase in titer or seroconversion was achieved by 52.5% (21/40) to 84.4% (38/45) of subjects.
- Titers were detectable in the majority of subjects in all adjuvanted groups (77.5% [31/40] to 95.6% [43/45] of subjects); however, percentages had a limited increase for the control groups (0.0% to 20.0% [5/25] of subjects).

Within the adjuvanted groups, the humoral immune responses 21 days after Injection 2 showed similar patterns as those 21 days after Injection 1 (i.e., increased response with increased percentages of AF03 adjuvant [i.e., from 0.5% to 1.0% and 2.5%], and for the majority of the endpoints, these percentages were highest in the 6 µg antigen groups); however, all responses were amplified further after Injection 2:

- The D42 GMTs for the 2.5 µg doses ranged from 30.8 to 86.4 (from 0.5% to 2.5% adjuvanted groups, respectively); and the D42 GMTs for the 6.0 µg doses ranged from 30.8 to 99.3 (from 0.5% to 2.5% adjuvanted groups, respectively).
- The GMTRs (D42/D0) for the 2.5 µg doses ranged from 3.6 to 8.9 (from 0.5% to 2.5% adjuvanted groups, respectively); and the GMTRs for the 6.0 µg doses ranged from 3.3 to 10.2 (from 0.5% to 2.5% adjuvanted groups, respectively, with the latter being the highest GMTR overall).
- The percentage of subjects who achieved seroprotection was highest in the 2.5% adjuvanted groups (80.0% [36/45] and 84.4% [38/45] of subjects in the 2.5 µg and 6.0 µg antigen groups, respectively). For all other adjuvanted groups, percentages ranged from 52.5% (25/47) to 74.4% (32/43) of subjects.
- The percentage of subjects who achieved significant increase or seroconversion (D0 to D42) was 80.0% (36/45) and 84.4% (38/45) of subjects in the 2.5 µg/2.5% and in the 6.0 µg/2.5% groups, respectively. The percentages in all other groups were lower, with a range from 52.5% (21/40) to 74.4% (32/43) of subjects.
- Titers were detectable in the majority of subjects in all adjuvanted groups (ranged from 77.5% [31/40] to 95.6% [43/45] of subjects in the 2.5 µg antigen groups and from 88.6% [39/44] to 95.6% [43/45] of subjects in the 6.0 µg antigen groups), with the 2.5% adjuvanted groups being the highest percentages for each antigen dose.

Similar patterns were observed at 21 days post-Injection 2 using the SN Method; however, percentages were higher with the SN Method than with the HIH Method.

Antibody Response Against A/H5N1 Vietnam (cross-reactivity)

Primary Series

HIH Method

At D21 after Injection 2 (D42), the GMTs for all groups were relatively low (ranging from 6.0 to 8.7), where those of the adjuvanted groups were only slightly higher than those of the control groups (5.0 to 5.4). The percentages of subjects that had titers ≥ 10 (detectable Ab titers) increased with increasing AF03 adjuvant doses. For the adjuvanted groups, the percentages of subjects that had titers ≥ 10 and ≥ 40 against the A/Vietnam strain ranged from 13.6% (6/44) to 44.4% (20/45) and from 2.1% (1/47) to 6.7% (3/45) of subjects, respectively. For the control groups, 12.0% (3/25) of subjects from the 6.0 µg group had a titer ≥ 10. There were no subjects from the other control groups who had a titer ≥ 10, and no subjects from any control group with a titer ≥ 40.

SN Method

At D21 after Injection 2 (D42), the GMTs for all groups were relatively low (ranging from 6.0 to 8.7), where those of the adjuvanted groups were only slightly higher than those of the control groups (5.0 to 5.4). In general, the percentages of subjects that had titers ≥ 10 (detectable Ab titers) increased with increasing AF03 adjuvant dose. For the adjuvanted groups, the percentages of samples that had titers ≥ 10 and ≥ 40 were shown to be cross reactive against the A/Vietnam strain for 29.5% (13/44) to 71.1% (32/45) and 8.5% (4/47) to 28.9% (13/45) of subjects, respectively; and, for the control groups, titers ≥ 10 were achieved for 4.5% (1/22) to 16.0% (4/25) of subjects in the 2.5 µg and 6.0 µg groups, respectively, and 4.0% (1/25) of subjects in the placebo group. There were no subjects from the control groups who had a titer ≥ 40.

Antibody Persistence (up to M12):

Antibody titers (HIH and SN methods) were obtained at Month 6 (M6 [D180]) and Month 12 (M12 [D365]) for all subjects.

While immune response decreased over time (at M6) for all study groups, responses for all endpoints were higher for the adjuvanted groups than for the control groups:

The general percentage of subjects with detectable Ab titers at M6 were similar for the 2.5 µg and 6.0 µg adjuvanted groups at each adjuvant percentage, with the highest percentages in the 2.5 µg/2.5% and 6.0 µg/2.5% groups:

For the 2.5 µg adjuvanted doses, the M6 GMTs (HIH Method) ranged from 6.7 to 12.4 (from the 0.5% to 2.5% adjuvanted groups, respectively, with the latter being the highest GMT overall); and for the 6.0 µg adjuvanted doses, the M6 GMTs ranged from 6.3 to 11.6 (from 0.5% to 2.5% adjuvanted groups, respectively). In the control groups, M6 GMTs (HIH Method) ranged from 5.0 to 5.6.

The proportion of subjects with detectable Ab titers were 61.0% [25/41] and 59.0% [23/39] of subjects in the 2.5 µg/2.5% and 6.0 µg/2.5% groups, respectively, and percentages in all other adjuvanted groups ranged from 20.0% (9/45) to 38.5% (15/39) of subjects. For the control groups, 0.0% to 4.5% (1/22) of subjects had detectable Ab titers.

The percentages of subjects with seroprotection were 19.5% [8/41] and 15.4% [6/39] of subjects in the 2.5 µg/2.5% and 6.0 µg/2.5% groups, respectively, and percentages in all other adjuvanted groups ranged from 0.0% to 4.4% (2/45) of subjects. For the control groups, 0.0% to 4.5% (1/22) of subjects achieved seroprotection.

For the proportion of subjects with SN Ab titers ≥ 20 (1/dil), the percentages were 87.8% [36/41] and 84.6% [33/39] of subjects in the 2.5 µg/2.5% and 6.0 µg/2.5% groups, respectively, and percentages in all other adjuvanted groups ranged from 54.1% (20/37) to 79.5% (31/39) of subjects. For titers ≥ 40 (1/dil), the percentages were 70.7% [29/41] and 64.1% [25/39] of subjects in the 2.5 µg/2.5% and 6.0 µg/2.5% groups, respectively, and percentages in all other adjuvanted groups ranged from 28.2% (11/39) to 48.7% (19/39) of subjects. The percentage of subjects with SN Ab titers ≥ 20 (1/dil) and ≥ 40 (1/dil) for all control groups was low, with 4.5% (1/22) to 13.0% (3/23) of subjects with a titer ≥ 20 (1/dil) and with one subject per group with a titer ≥ 40 (1/dil).

At M12:

The GMTs using the HIH method for subjects in all groups were 5.3, 5.6, and 6.4 for subjects in the 2.5 µg/0.5%, 2.5 µg/1.0%, and 2.5 µg/2.5% groups, respectively; 5.0, 5.5, and 6.0 for subjects in the 6.0 µg/0.5%, 6.0 µg/1.0%, and 6.0 µg/2.5% groups, respectively; and 5.0 for all subjects in the 2.5 µg, 6.0 µg, and placebo groups.

There were 2 subjects who were seroprotected according to the HIH method: 2.4% (1/41) of subjects from the 2.5 µg/1.0% group and 2.6% (1/47) of subjects from the 6.0 µg/2.5% group. No other subjects had levels of seroprotection from any group.

For the SN method, GMTs were 14.1, 10.9, 29.1, 11.4, 16.9, 29.0, 5.6, 5.6, and 5.0 for subjects in the 2.5 µg/0.5%, 2.5 µg/1.0%, 2.5 µg/2.5%, 6.0 µg/0.5%, 6.0 µg/1.0%, 6.0 µg/2.5%, 2.5 µg, 6.0 µg, and placebo groups, respectively.

The proportion of subjects with SN Ab titers ≥ 20 (1/dil) and ≥ 40 (1/dil) decreased among all adjuvanted groups at M12 compared to M6. The percentage of subjects with titers ≥ 20 (1/dil) were similar for the 2.5 µg and 6.0 µg groups at the 0.5% and 1.0% adjuvant level, ranging from 22.0% (9/41) to 37.1% (13/35). For titers ≥ 20 (1/dil), the highest percentages of subjects were in the 2.5 µg/2.5% and 6.0 µg/2.5% groups (59.0% [23/39] and 57.9% [22/38] of subjects, respectively). For titers ≥ 40 (1/dil), the highest percentages were in the 2.5 µg/2.5% and 6.0 µg/2.5% groups (46.2% [18/39] and 47.41% [18/38] of subjects, respectively), and percentages in all other adjuvanted groups were 25.7% (9/35), 17.1% (7/41), 5.3% (2/38), and 14.3% (5/35) of subjects for the 2.5 µg/0.5%, 2.5 µg/1.0%, 6.0 µg/0.5%, and 6.0 µg/1.0% groups, respectively. In the control groups, the percentage of subjects with SN Ab titers ≥ 20 (1/dil) was very low, with 6.3% (1/16) of subjects with titers ≥ 20 (1/dil) (from the 2.5 µg group only). No other subjects who received unadjuvanted vaccine or placebo had titers ≥ 20 (1/dil) or ≥ 40 (1/dil).

Antibody Persistence: Booster phase (Pre-Booster)

At D456, pre-booster, the GMTs using the HIH method for the H5N1/Indonesia strain were similar among groups: 6.9, 6.3, and 5.0 for the 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg groups, respectively.

One subject (3.2%) from the 7.5 µg/2.5% group had seroprotection according to the HIH method.

For the SN method, GMTs were 27.1, 25.1, and 5.0 for the 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg groups, respectively.

The proportion of subjects with SN Ab titers ≥ 20 (1/dil) and ≥ 40 (1/dil) were higher in the adjuvanted groups than in the unadjuvanted group.

On Day 456, 58.6% (17/29) and 54.8% (17/31) of subjects had SN titers ≥ 20 (1/dil) for the 3.8 µg/2.5% and 7.5 µg/2.5% groups, respectively. For titers ≥ 40 (1/dil), there were 41.4% (12/29) and 38.7% (12/31) of subjects in the 3.8 µg/2.5% and 7.5 µg/2.5% groups, respectively. Subjects who received unadjuvanted vaccine did not have titers ≥ 20 (1/dil)

Immunogenicity: Booster Phase

Antibody Response Against A/H5N1 Indonesia (Priming Strain)

The antibody response against the A/H5N1 Indonesia strain was analyzed at the following time points: pre-booster (D456), 8 days post boost (D464), and 21 days post boost (D477).

HIH Method

GMTs and GMTR s:

Pre-booster, the titers across groups were 6.9, 6.3, and 5.0 for the 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg groups, respectively. The 8- and 21-day post-booster GMTs were similar for the adjuvanted groups (range of 210.6 to 279.8) but were lower for the unadjuvanted group (10.0). All GMTs were lower at 6 months post-booster than at the 2 earlier time points post booster, and were lowest for the non-adjuvanted group (68.1, 67.7, and 8.5 for the 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg groups, respectively).

GMTRs of D464/D456 were 18.7, 23.2, and 1.5 for the 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg groups, respectively. For D477/D456, they were 19.6, 25.6, and 1.7, respectively. The GMTRs show that there was no change in the unadjuvanted group following a booster.

Seroprotection:

Pre-booster, there was only 1 subject from the 7.5 µg/2.5% group who had seroprotection.

Both 8 and 21 days following the booster, 89.7% (26/29) and 100% of subjects from the 3.8 µg/2.5% and 7.5 µg/2.5% groups, respectively, achieved seroprotection. In the unadjuvanted group, 13.3% (2/15) and 18.8% (3/16) subjects achieved seroprotection at 8 and 21 days following the booster, respectively.

Seroconversion or Significant Increase:

In the adjuvanted groups, 89.7% and 100% of subjects in the 3.8 µg and 7.5 µg adjuvanted groups achieved seroconversion or significant increase Day 456 to Day 464 and Day 456 to Day 477. In the unadjuvanted group, a seroconversion or significant increase was achieved for 13.3% (2/15) of subjects Day 456 to Day 464 and 18.8% (3/16) of subjects Day 456 to Day 477.

Detectable Antibodies:

Pre-booster, 27.6% (8/29) and 19.4% (6/31) of subjects had detectable antibodies in the 3.8 µg/2.5% and 7.5 µg/2.5% groups, respectively. There were no subjects in the unadjuvanted group with detectable antibodies. Eight and 21 days post-booster dose, 100% of the subjects from the adjuvanted groups, and 40.0% (6/15) and 43.8% (7/16) subjects in the unadjuvanted group, respectively, had detectable antibodies.

Six months post-booster dose, 89.3% (25/28), 96.6% (28/29) and 26.7% (4/15) of subjects in the 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg groups, respectively, had detectable antibodies.

SN method

GMTs and GMTRs:

Pre-booster, the titers across adjuvanted groups were 27.1 and 25.1 for the 3.8 µg/2.5%, and 7.5 µg/2.5% groups, respectively. For the 7.5 µg group, the GMT was 5.0. The 8 and 21 days post-booster GMTs were similar for the adjuvanted groups (range of 2464.7 to 2826.4) but were lower for the unadjuvanted group (50.0 and 58.7 for 8 and 21 days, respectively). All GMTs were lower at 6 months post-booster, and were lowest for the unadjuvanted group (582.8, 662.7, and 24.4 for the 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg groups, respectively).

GMTRs of D464/D456 for the groups were 75.0, 89.2, and 5.7 for the 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg groups, respectively for D477/D456, they were 79.4, 94.3, and 6.7, respectively. The GMTRs show that there was a relatively small change in the unadjuvanted group following a booster.

4-Fold Increase:

While percentages of subjects with a 4-fold increase of titers at D464 and D477 (from D456) was 100% for the 3.8 µg/2.5%, and 7.5 µg/2.5% groups, the percentage of subjects with a 4-fold increase of titers in the 7.5 µg group was 53.3% for D464 and 50.0% for D477. There was little to no 4-fold increase in titers from D464 to D477 for any group.

Antibody Response Against A/H5N1 Bar Headed Goose (Booster Strain)

The antibody response against the A/H5N1 Bar Headed Goose strain was analyzed at the following time points: pre-booster (D456), 8 days post boost (D464), and 21 days post boost (D477).

HIH Method

Pre-booster dose, most subjects had a titer <10; there was 1 subject in the 7.5 µg/2.5% who had a titer ≥ 40. GMTs were from 5.00 to 5.91 among all groups.

Eight days post-booster dose, only 1 subject (3.4%) in the adjuvanted groups had a titer < 10 (from the 3.8 µg/2.5% group), while 60.0% (9/15) of subjects in the unadjuvanted group had a titer <10. The percentage of subjects that had ≥ 40 (seroprotective level) was 96.7% (29/30) of subjects in the 7.5 µg/2.5% group and 89.7% (26/29) of subjects in the 3.8 µg/2.5% group. Only 1 subject (6.7%) in the 7.5 µg group achieved seroprotection. The GMTs were higher in the adjuvanted groups (201 and 234 for the 3.8 µg/2.5% group and the 7.5 µg/2.5% group, respectively) than the unadjuvanted group (9.33). Most subjects in the adjuvanted groups achieved a significant increase or seroconversion pre-booster dose to 8 days post-booster dose (88.0% to 96.7%), compared to 6.7% in the unadjuvanted group. The GMT ratios for each group were 19.6 and 21.4 for the 3.8 µg/2.5% group and 7.5 µg/2.5% group, respectively, and 1.38 for the 7.5 µg group.

Twenty-one days post-booster dose, only 2 subjects (6.9%) in the adjuvanted groups had a titer < 10 (from the 3.8 µg/2.5% group), while 62.5% (10/16) of subjects in the unadjuvanted group had a titer <10. The percentage of subjects that had ≥ 40 (seroprotective level) was 100% (31/31) of subjects in the 7.5 µg/2.5% group and 89.7% (26/29) of subjects in the 3.8 µg/2.5% group. Four subjects (25.0%) in the 7.5 µg group achieved seroprotection. The GMTs were higher in the adjuvanted groups (201 and 280 for the 3.8 µg/2.5% group and the 7.5 µg/2.5% group, respectively) than the unadjuvanted group (11.6). Most subjects in the adjuvanted groups achieved a significant increase or seroconversion from pre-booster dose to 21 days post-booster dose (88.0% to 100%), compared to 25.0% in the unadjuvanted group. The GMT ratios for each group were 19.8 and 25.6 for the 3.8 µg/2.5% group and 7.5 µg/2.5% group, respectively, and 1.76 for the 7.5 µg group.

SN Method

Pre-booster dose, most subjects had a titer < 10; there were 3 (10/3%) and 2 (6.5%) subjects in the 3.8 µg/2.5% and 7.5 µg/2.5%, respectively, who had a titer ≥ 40. GMTs were 10.2, 9.00, and 5.00 for the 3.8 µg/2.5%, 7.5 µg/2.5%, and 7.5 µg groups, respectively.

Eight days post-booster dose, all subjects from the adjuvanted groups had detectable antibodies, while 46.7% (7/15) of subjects in the unadjuvanted group had no detectable antibodies (titer <10). The percentage of subjects that had a titer ≥ 40 was 100% of subjects in the adjuvanted groups, and 40.0% (6/15) in the 7.5 µg group. The GMTs were higher in the adjuvanted groups (1183 and 1321 for the 3.8 µg/2.5% group and the 7.5 µg/2.5% group, respectively) than the unadjuvanted group (22.7). All subjects in the adjuvanted groups achieved a significant increase from pre-booster dose to 8 days post-booster dose, compared to 40.0% in the unadjuvanted group. The GMT ratios for each group were 78.9 and 96.2 for the 3.8 µg/2.5% group and

7.5 µg/2.5% group, respectively, and 3.13 for the 7.5 µg group.

Twenty-one days post-booster dose, all subjects from the adjuvanted groups had detectable antibodies, while 50.0% (8/16) of subjects in the unadjuvanted group had no detectable antibodies (titer <10). The percentage of subjects that had titers ≥ 40 was 100% from the adjuvanted groups, and 37.5% of subjects in the 7.5 µg group. The GMTs were higher in the adjuvanted groups (1202 and 1449 for the 3.8 µg/2.5% group and the 7.5 µg/2.5% group, respectively) than the unadjuvanted group (25.0). All subjects in the adjuvanted groups achieved a significant increase pre-booster dose to 21 days post-booster dose, compared to 37.5% in the unadjuvanted group. The GMT ratios for each group were 80.2 and 105 for the 3.8 µg/2.5% group and 7.5 µg/2.5% group, respectively, and 3.53 for the 7.5 µg group.

Antibody Response Against A/H5N1 Vietnam (cross-reactivity)

Booster Phase

Note that data from the baseline were not available for this strain for the booster dose**.**

HIH Method

Day 464

Eight days post-booster dose, the percentage of subjects that had ≥ 40 (seroprotective level) was 73.3% (22/30) of subjects in the 7.5 µg/2.5% group and 69.0% (20/29) of subjects in the 3.8 µg/2.5% group. No subjects in the 7.5 µg group achieved seroprotection. The GMTs were higher in the adjuvanted groups (52.0 and 65.7 for the 3.8 µg/2.5% group and the 7.5 µg/2.5% group, respectively) than the unadjuvanted group (5.61).

Day 477

Twenty-one days post-booster dose, few subjects in the adjuvanted groups had a titer < 10 (10.3% of subjects from the 3.8 µg/2.5% group only), while most subjects in the unadjuvanted group had a titer <10 (87.5%). The percentage of subjects that had ≥ 40 (seroprotective level) was 71.0% (22/31) of subjects in the 7.5 µg/2.5% group and 72.4% (21/29) of subjects in the 3.8 µg/2.5% group. One subject (6.3%) in the 7.5 µg group achieved seroprotection. The GMTs were higher in the adjuvanted groups (52.7 and 73.2 for the 7.5 µg/2.5% group and the 3.8 µg/2.5% group, respectively) than the unadjuvanted group (6.35).

SN Method

Day 464

Eight days post-booster dose, the percentage of subjects that had titers ≥ 40 was 96.7% (29/30) of subjects in the 7.5 µg/2.5% group and 93.1% (27/29) of subjects in the 3.8 µg/2.5% group. Three subjects (20.0%) in the 7.5 µg group had titers ≥ 40. The GMTs were higher in the adjuvanted groups 255 and 317 for the 7.5 µg/2.5% group and the 3.8 µg/2.5% group, respectively) than the unadjuvanted group (13.8).

Day 477

Twenty-one days post-booster dose, the percentage of subjects that had titers ≥ 40 was 100% of subjects in the 7.5 µg/2.5% group and 89.7% (26/29) of subjects in the 3.8 µg/2.5% group. Three subjects (18.8%) in the 7.5 µg group achieved titers ≥ 40. The GMTs were higher in the adjuvanted groups (244 and 321 for the 7.5 µg/2.5% group and the 3.8 µg/2.5% group, respectively) than the unadjuvanted group (12.2).

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