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Sponsor: Sanofi Pasteur **Drug substance(s):** High-Dose Influenza Vaccine Quadrivalent	**Study Identifiers:** U1111-1183-5556, IND 17556, NCT03282240 **Study code:** QHD00013

Title of the study: Safety and Immunogenicity of High-Dose Quadrivalent Influenza Vaccine Administered by Intramuscular Route in Subjects Aged 65 Years and Older

Study center(s):

This was a multi-center study conducted at 35 sites in the United States. One additional site in Florida was initiated and approved by the Institutional Review Board, but the site was closed due to natural disaster (hurricane) prior to enrollment of any subject.

Study period:

Date first subjectS enrolled: 08/Sep/2017

Date last subjects completed: 19/Apr/2018

Phase of development: Phase III

Objectives:

Primary Objective:

Immunogenicity

To demonstrate that QIV-HD induces an immune response (as assessed by hemagglutination inhibition [HAI] geometric mean titers [GMTs] and seroconversion rates) that is non-inferior to responses induced by the TIV-HD1 and TIV-HD2 for the 4 virus strains at 28 days post-vaccination in all subjects.

Secondary Objectives:

Immunogenicity

1) To demonstrate that each B strain in QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-HD that does not contain the corresponding B strain in all subjects.
2) To describe the immune response induced by QIV-HD, TIV-HD1, and TIV-HD2 by HAI measurement method in all subjects.
3) To describe the immune response 28 days after vaccination by virus seroneutralization (SN) measurement method in a randomized subset of subjects from each study group.

Safety

To describe the safety profile of all subjects in each trial group.

Methodology:

QHD00013 was a randomized, modified double-blind, active-controlled, multi-center study conducted in 2670 healthy subjects aged 65 years and older to assess the safety and immunogenicity of the high-dose quadrivalent influenza vaccine (QIV-HD) compared to one of the high-dose trivalent influenza vaccines (TIV-HDs) containing either the B strain from the primary lineage (TIV-HD1, which was the licensed vaccine [Fluzone® High-Dose] for the 2017-2018 Northern Hemisphere [NH] influenza season) or the B strain from the alternate lineage (TIV-HD2, which was an investigational TIV-HD containing an alternate B strain).

An unblinded administrator at each site administered the vaccine.

All subjects were to provide a pre-vaccination (baseline) blood sample at Day (D) 0 and a post-vaccination blood sample at Visit (V) 02 (D28 [+7 days]) for HAI testing. A randomized subset of these subjects (Expanded Immunogenicity Subset) from each group (approximately 100 subjects per study group) was selected for SN and enzyme-linked lectin assay (ELLA) testing.

Solicited reactions were collected up to 7 days after vaccination, and unsolicited adverse events (AEs) were collected up to V02, which is the active phase of the trial (V01 to V02 [D0-D28]). Serious adverse events (SAEs) and adverse events of special interest (AESIs*) were collected throughout the trial (D0 through approximately D180 [6-month follow-up period]).

*Note: AESIs were captured as SAEs. These included new onset of Guillain-Barré syndrome (GBS), encephalitis / myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis.

Interactive response technology (IRT) was used to randomly assign subjects to one of the 3 trial groups and to assign subject numbers in each of the groups. Electronic data capture (EDC) was used for the collection of data.

Number of subjects:	Planned: 2616
	Randomized: 2670
	Treated: 2670
Evaluated:	Immunogenicity: 2648
	Safety: 2670

Diagnosis and criteria for inclusion:

A potential subject had to meet all of the following criteria to be considered for trial enrollment:

1) Aged ≥ 65 years on the day of inclusion
2) Informed consent form has been signed and dated
3) Able to attend all scheduled visits and to comply with all trial procedures

Study treatments

Investigational Product: High-Dose Influenza Vaccine Quadrivalent, (Zonal Purified, Split Virus) 2017–2018 Strains (QIV-HD)

Form: Liquid; essentially clear and slightly opalescent in color

Composition: Each 0.7 mL dose of QIV-HD contained:

Strains were based on World Health Organization (WHO) / Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommendations for the 2017-2018 NH influenza season.

Active substances:

A/Michigan/45/2015 X-275 (H1N1) strain	60 µg HA
A/Hong Kong/4801/2014 (NYMC X-263B) (H3N2) strain	60 µg HA
B/Brisbane/60/2008 strain	60 µg HA
B/Phuket/3073/2013 strain	60 µg HA

Excipients:

Buffered saline solution	quantity sufficient (qs) to appropriate volume
Octylphenol Ethoxylate (Triton X-100®)	not more than (NMT) 350 µg

Preservative is not used in the manufacture of QIV-HD.

Route of administration: Intramuscular (IM), injected into the upper arm area

Control product(s):

Control product 1: High-dose trivalent inactivated influenza vaccine (licensed Fluzone® High-Dose, TIV-HD1)

Form: Liquid; essentially clear and slightly opalescent in color

Composition: Each 0.5 mL dose of TIV-HD1 contained:

Strains were based on WHO/ VRBPAC recommendations for the 2017-2018 NH influenza season.

Active Substances:

A/Michigan/45/2015 X-275 (H1N1) strain	60 µg HA
A/Hong Kong/4801/2014 (NYMC X-263B) (H3N2) strain	60 µg HA
B/Brisbane/60/2008 strain	60 µg HA

Excipients:

Buffered saline solution	qs to appropriate volume
Octylphenol Ethoxylate (Triton X-100®)	NMT 250 µg

Preservative is not used in the manufacture of licensed TIV-HD1.

Route of administration: IM, injected into the upper arm area

Control product 2: High-dose trivalent inactivated influenza vaccine (Investigational TIV-High-Dose with alternate B strain, TIV-HD2)

Form: Liquid; essentially clear and slightly opalescent in color

Composition: Each 0.5 mL dose of TIV-HD2 contained:

Strains were based on WHO / VRBPAC recommendations for the 2017-2018 NH influenza season.

Active Substances:

A/Michigan/45/2015 X-275 (H1N1) strain	60 µg HA
A/Hong Kong/4801/2014 (NYMC X-263B) (H3N2) strain	60 µg HA
B/Phuket/3073/2013 strain	60 µg HA

Excipients:

Buffered saline solution	qs to appropriate volume
Octylphenol Ethoxylate (Triton X-100®)	NMT 250 µg

Preservative is not used in the manufacture of TIV-HD2.

Route of administration: IM, injected into the upper arm area

Duration of treatment/participation: The duration of each subject's participation was approximately 6 months (D0 through D180)

Criteria for evaluation:

Primary Endpoints:

Immunogenicity

- HAI antibody (Ab) titers obtained on D28
- Seroconversion (titer < 10 [1/dil] at D0 and post-injection titer ≥ 40 [1/dil] at D28, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold rise in titer [1/dil] at D28)

Secondary Endpoints:

Immunogenicity Assessment by HAI (for all subjects)

- HAI Ab titers obtained on D0 and D28
- Individual HAI titers ratio D28/D0
- Seroconversion (titer < 10 [1/dil] at D0 and post-injection titer ≥ 40 [1/dil] at D28, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold-rise in titer [1/dil] at D28)
- Seroprotection (titer ≥ 40 [1/dil]) at D0 and D28

Immunogenicity Assessment by SN (for the Expanded Immunogenicity Subset)

Neutralizing Ab titers were measured for each influenza strain with the SN method in a randomly selected subset of subjects from each study group. They were obtained on D0 and D28.

- Individual neutralization test (NT) Ab titer on D0 and D28
- Individual NT Ab titer ratio (fold-rise in serum NT post-vaccination relative to D0) at D28
- Subjects with NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) at D28
- Fold-rise in NT Ab titer [post/pre] ≥2 and ≥ 4 at D28
- Detectable NT (NT Ab titer ≥ 10 [1/dil]) at D0 and D28

Safety

Safety was described for all subjects:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination.
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the trial, of solicited (prelisted in the subject's diary card and Case Report Book [CRB]) injection site reactions and systemic reactions occurring up to 7 days after vaccination.
- Occurrence, nature (MedDRA PT), time to onset, duration, intensity, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the trial, of unsolicited AEs up to 28 days after vaccination.
- Occurrence, nature (MedDRA PT), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the trial, of SAEs throughout the trial.
- Occurrence, nature (MedDRA PT), and relationship to vaccination of AESIs throughout the trial.

Statistical methods:

The statistical analyses were performed in 2 steps:

The first step was the analysis of the main HAI immunogenicity and safety results obtained on data collected within approximately 28 days following vaccination (from D0 to V02). The study blind was broken at that time.

The second step was assessing the remaining objectives of the study.

No statistical adjustment for the interim analysis was necessary because there were no planned repeat analyses of the same hypotheses.

The Per-protocol Analysis Set (PPAS) and Full Analysis Set (FAS) was used for the immunogenicity analyses. The Safety analysis set (SafAS) was used for all safety analyses.

For the purposes of the statistical methods section, the 4 virus strains in the QIV-HD trial groups and the TIV-HD trial groups was labeled as follows:

A/Michigan/45/2015 (H1N1) strain	A1
A/Hong Kong/4801/2014 (H3N2) strain	A2
B/Brisbane/60/2008 strain	B1
B/Phuket/3073/2013 strain	B2

Primary Objective

Non-inferiority of QIV-HD to TIV-HD1 and/or TIV-HD2

The immunogenicity of QIV-HD was compared to that of TIV-HD1 and / or TIV-HD2. For each A strain, the comparison was made with the pooled TIV-HD groups. For each B strain, the comparison was made with the TIV-HD group containing the corresponding B strain.

For each strain, a non-inferiority approach was used to compare the post-vaccination GMTs and the seroconversion rates between the groups using a 1-sided Type I error rate of 0.025 with the given individual hypothesis:

$$H_0^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{TIV-HD}} \leq \frac{1}{1.5}$$
$$\Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{TIV-HD}) \leq -log_{10}(1.5)$$

$$H_A^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{TIV-HD}} > \frac{1}{1.5}$$
$$\Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{TIV-HD}) > -log_{10}(1.5)$$

$$H_0^s : \pi^s_{QIV-HD} - \pi^s_{TIV-HD} \leq -0.1$$
$$H_A^s : \pi^s_{QIV-HD} - \pi^s_{TIV-HD} > -0.1$$

with:

s: strain in {A1, A2, B1 and B2}

If s in {A1 and A2}, TIV-HD represents the pooled TIV-HD1 and TIV-HD2 groups

If s = B1, TIV-HD represents the TIV-HD1 group

If s = B2, TIV-HD represents the TIV-HD2 group

π: The seroconversion rate

The statistical methodology was based on the use of the 2-sided 95% confidence intervals (CIs) of the ratio of post-vaccination GMTs and difference in seroconversion rates between QIV-HD and TIV-HD groups. The 95% CIs was calculated by normal approximation of log-transformed titers for GMTs and by the Newcombe-Wilson score method without continuity correction for

seroconversion rates. The margins used for hypothesis testing were 1.5 for GMTs and 10% for seroconversion rates to demonstrate non-inferiority.

The non-inferiority objective was achieved only if it was demonstrated for 4 strains and for both GMTs and seroconversion rates. Analyses were performed for both FAS and PPAS, but the conclusion was made from PPAS results.

A sensitivity analysis was performed with adjustment on the pre-vaccination HAI titers.

Secondary Objectives

Immunogenicity

Superiority of QIV-HD to TIV-HD1 or TIV-HD2

The superiority analyses was to be demonstrated in all subjects. For each B strain, the immunogenicity of QIV-HD was compared to that of TIV-HD group which does not contain the corresponding B strain.

A superiority approach was used to compare post-vaccination GMTs and seroconversion rates between groups using a 1-sided test with Type I error rate of 0.025 following the individual hypotheses:

$$H_0^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{TIV-HD}} \leq 1.5$$
$$\Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{TIV-HD}) \leq log_{10}(1.5)$$

$$H_A^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{TIV-HD}} > 1.5$$
$$\Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{TIV-HD}) > log_{10}(1.5)$$

$$H_0^s : \pi^s_{QIV-HD} - \pi^s_{TIV-HD} \leq 0.1$$

$$H_A^s : \pi^s_{QIV-HD} - \pi^s_{TIV-HD} > 0.1$$

with:

s: strain in {B1 and B2}

If s = B1, TIV-HD represents the TIV-HD2 group

If s = B2, TIV-HD represents the TIV-HD1 group

π: The seroconversion rate

The statistical methodology was based on the use of the 2-sided 95% CI of the ratio of post-vaccination GMTs and difference in seroconversion rates between the QIV-HD group and TIV-HD group. The 95% CIs were calculated using normal approximation of log-transformed titers for GMTs and using the Newcombe-Wilson score method without continuity correction for seroconversion rates. For each strain, the 2-sided 95% CI should lie above 1.5 for GMTs and above 10% for seroconversion rates.

The superiority objective was achieved if the superiority was demonstrated for both B strains and for both GMTs and seroconversion rates. Analyses were performed for both FAS and PPAS but the conclusion was made from FAS results.

Summary:

Disposition of Participants

The active phase of this study (V01 to V02 [D0-D28]) was conducted in 35 centers in the United States. The first subject in this study was enrolled on 08 September 2017 and the last subject visit occurred on 02 November 2017. A 6-month follow up telephone call was performed between 06 March 2018 and 19 April 2018. The duration of the active phase was 71 days with a mean duration of subject participation during this time period of 30.9 days. The total study duration was 224 days with a mean duration of subject participation of 183 days.

A total of 2670 subjects were enrolled in the study and randomized to one of the 3 groups: QIV-HD group (1777 subjects), TIV-HD1 group (443 subjects), or TIV-HD2 group (450 subjects). In addition, a total of 318 subjects were randomized to the expanded immunogenicity subset: 106, 105, and 107 subjects from the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively. Of the 318 randomized subjects, 303 subjects were included in the expanded immunogenicity subset.

For all subjects enrolled, 99.7% met all inclusion criteria and did not meet any of the exclusion criteria.

All subjects were vaccinated and received the correct vaccine according to the group which they were randomized.

Out of the 2670 randomized subjects, 16 (0.6%) subjects did not complete the study: 10 (0.6%), 3 (0.7%), and 3 (0.7%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively. Two subjects each in the QIV-HD group and the TIV-HD1 group withdrew due to an AE. Other reasons for discontinuation were lost to follow-up (3 subjects in the QIV-HD group), protocol deviation (4, 1, and 2 subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively), and voluntary withdrawal by subject not due to an AE (1 subject each in the QIV-HD and TIV-HD2 groups).

Data Sets Analyzed

The PPAS consisted of 2533 (94.9%) subjects randomized as follows: 1680 (94.5%), 423 (95.5%), and 430 (95.6%) subjects in QIV-HD, TIV-HD1, and TIV-HD2, respectively.

The FAS consisted of 2648 (99.2%) subjects randomized as follows: 1763 (99.2%), 439 (99.1%), and 446 (99.1%) subjects in QIV-HD, TIV-HD1, and TIV-HD2, respectively.

The expanded immunogenicity subset consisted of 303 (11.3%) subjects randomized as follows: 102 (5.7%), 102 (23.0%), 99 (22.0%) subjects in QIV-HD, TIV-HD1, and TIV-HD2, respectively.

All 2670 randomized subjects were vaccinated and, therefore, were included in the SafAS as follows: 1777, 443, and 450 subjects in QIV-HD, TIV-HD1, and TIV-HD2, respectively. The numbers and percentages of subjects with injection site reactions data was the same as for subjects with systemic reactions data: 1768 (99.5%), 440 (99.3%), and 449 (99.8%) subjects in QIV-HD, TIV-HD1, and TIV-HD2, respectively.

Demographic and Baseline Characteristics

Overall, there were fewer male than female subjects in the PPAS, with a total of 1066 (42.1%) male and 1467 (57.9%) female subjects. The distribution of fewer males than females was also observed across each study group.

Overall, the mean age was 73.0 years (range: 65.0; 100.0 years). The mean ages were comparable across all study groups.

The overall percentage of subjects between the ages of 65 to < 75 years was higher than the percentage of subjects ≥ 75 years of age (64.5% and 35.5%, respectively). The distribution of both age ranges was similar between all study groups.

Most subjects in the study were White (90.7%), followed by Black or African American subjects (7.2%). All other races were each represented by ≤ 0.7% of subjects. The majority of subjects were not Hispanic or Latino (97.0%).

Medical History

A total of 1470 (55.1%) of all randomized subjects had at least one pre-specified medical history reported, most of which 1245 (46.6%) were ongoing at inclusion. Medical history data were similar across all study groups.

Influenza Vaccination History

Seasonal influenza vaccination history data for subjects in the PPAS from the year previous to this study (ie, since 01 August 2016) are presented. In the PPAS, a total of 1881 (74.3%) subjects received influenza vaccination in the previous year. Previous influenza vaccination data were similar across all study groups.

Concomitant Medications

A total of 2010 (75.3%) subjects were taking protocol-defined, reportable concomitant medications. Most of the subjects (1936 [72.5%]) were still taking reportable concomitant medications at the end of the study.

Primary objective:

Non-inferiority

For the A strains, the primary objective was evaluated using pooled data from TIV-HD1 and TIV-HD2. For each of the B strains, the primary objective was evaluated based on the TIV-HD groups that contain the corresponding B strain.

The primary objective of non-inferiority of QIV-HD to TIV-HD as assessed by GMTs and seroconversion rates was met as the lower limit of the 95% CI was above 0.667 for the ratio of GMTs and above -10% for the differences of seroconversion rates for all influenza strains.

For the A/H1N1 strain, the GMTs of QIV-HD and TIV-HD pooled were 312 and 374, respectively. The GMT ratio was 0.83; and the lower limit of the 95% CI was 0.744, which is above the pre-established non-inferiority threshold of 0.667. The seroconversion rates for QIV-HD and TIV-HD pooled were 50.4% and 53.7%, respectively. The percent difference for the seroconversion rates was -3.27%; and the lower limit of the 95% CI was -7.37%, which is above the pre-established threshold of -10%.

For the A/H3N2 strain, The GMTs of QIV-HD and TIV-HD pooled were 563 and 594, respectively. The GMT ratio was 0.95; and the lower limit of the 95% CI was 0.842, which is above the pre-established non-inferiority threshold of 0.667. The seroconversion rates for the QIV-HD and TIV-HD pooled were 49.8% and 50.5%, respectively. The percent difference for the seroconversion rates was -0.71%; and the lower limit of the 95% CI was -4.83%, which is above the pre-established threshold of -10%.

For the B/Brisbane/60/2008 strain, The GMTs of QIV-HD and TIV-HD1 were 516 and 476, respectively. The GMT ratio was 1.08; and the lower limit of the 95% CI was 0.958, which is above the pre-established non-inferiority threshold of 0.667. The seroconversion rates for QIV-HD and TIV-HD1 were 36.5% and 39.0%, respectively. The percent difference for the seroconversion rates was -2.41%; and the lower limit of the 95% CI was -7.66%, which is above the pre-established threshold of -10%.

For the B/Phuket/3073/2013 strain, The GMTs of QIV-HD and TIV-HD2 were 578 and 580, respectively. The GMT ratio was 1.00; and the lower limit of the 95% CI was 0.881, which is above the pre-established non-inferiority threshold of 0.667. The seroconversion rates for QIV-HD and TIV-HD2 were 46.6% and 48.4%, respectively. The percent difference for the seroconversion rates was -1.75%; and the lower limit of the 95% CI was -7.04%, which is above the pre-established threshold of -10%.

In addition, a sensitivity analysis using GMTs at V02 after vaccination adjusted for the baseline showed similar results for the PPAS and FAS and also demonstrated non-inferiority. For the A/H1N1 strain, the 95% CI of the GMT ratio did not include 1, but the 95% CI of the difference in seroconversion rates includes 0. The slight difference shown by the A/H1N1 strain's GMT ratio between QIV-HD and TIV-HD is not considered clinically relevant as the lower bound of the 95% CI remained above the non-inferiority margin.

Secondary objectives:

Secondary Objective 1: Superiority

The secondary objective of demonstrating that each B strain in QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-HD that does not contain the corresponding B strain in all subjects was met as the lower limit of the 95% CI was above 1.5 for the ratios of GMTs and above 10% for the seroconversion rates for both B influenza strains.

The B/Brisbane/60/2008 GMTs of QIV-HD and TIV-HD2 were 515 and 253, respectively. The GMT ratio was 2.03; and the lower limit of the 95% CI was 1.802, which is above the pre-established superiority threshold of 1.5.

The B/Phuket/3073/2013 GMTs of QIV-HD and TIV-HD1 were 573 and 280, respectively. The GMT ratio was 2.04; and the lower limit of the 95% CI was 1.804, which is above the pre-established superiority threshold of 1.5.

The B/Brisbane/60/2008 seroconversion rates for QIV-HD and TIV-HD2 were 36.3% and 15.5%, respectively. The percent difference in seroconversion rates was 20.78%; and the lower limit of the 95% CI was 16.5%, which is above the pre-established superiority threshold of 10%.

The B/Phuket/3073/2013 seroconversion rates for QIV-HD and TIV-HD1 were 46.7% and 17.4%, respectively. The percent difference was 29.27%; and the lower limit of the 95% CI was 24.78%, which is above the pre-established superiority threshold of 10%.

In addition, a sensitivity analysis using GMTs at V02 after vaccination adjusted for the baseline showed similar results for the PPAS and FAS and also demonstrated superiority.

Secondary Objective 2: Descriptive Analysis of the Immune Response by HAI Measurement Method

HAI GMTs at V01 (Pre-vaccination)

At baseline, GMTs were similar between the QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled groups for all the strains.

Results were similar in the FAS.

HAI GMTs at V02 post-vaccination

At V02 post-vaccination, GMTs for the A/H1N1 strain increased as compared to baseline GMTs and were similar between the QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled groups: 312, 387, 362, and 374, respectively.

At V02 post-vaccination, GMTs for the A/H3N2 strain increased as compared to baseline GMTs and were similar between the QIV-HD, TIV-HD1, TIV-H2, and TIV-HD pooled groups: 563, 588, 600, and 594, respectively.

At V02 post-vaccination, GMTs for the B/Brisbane strain were similar between the QIV-HD and TIV-HD1 groups, but the GMTs for the QIV-HD group were higher than for the TIV-HD2 group: 516 for the QIV-HD group, 476 for the TIV-HD1 group, and 253 for the TIV-HD2 group.

At V02 post-vaccination, GMTs for the B/Phuket strain were similar between the QIV-HD and TIV-HD2 groups but the GMTs for the QIV-HD group were higher than for the TIV-HD1 group: 578 for the QIV-HD group, 580 for the TIV-HD2 group, and 282 for the TIV-HD1 group.

Results were similar in the FAS.

HAI geometric mean titer ratios (GMTRs) (geometric mean of individual titer ratios of post-vaccination/pre-vaccination)

At V02 post-vaccination, GMTRs were similar between QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled for the 2 common influenza A strains with GMTRs ranging from 4.38 (95% CI: 4.11; 4.66) to 5.57 (95% CI: 4.85; 6.39) for the A/H1N1 strain and 4.65 (95% CI: 4.35; 4.98) to 4.94 (95% CI: 4.32; 5.65) for the A/H3N2 strain.

At V02 post-vaccination, the GMTR for the QIV-HD and TIV-HD1 groups for the B/Brisbane/60/2008 influenza strain were similar, but the GMTR for the QIV-HD group was higher than that for the TIV-HD2 group: GMTR for QIV-HD was 3.17 (95% CI: 2.99; 3.35), GMTR for TIV-HD1 was 3.35 (95% CI: 2.99; 3.76), and GMTR for TIV-HD2 was 1.65 (95% CI: 1.52; 1.78).

At V02 post-vaccination, the GMTR for the QIV-HD and TIV-HD2 groups for the B/Phuket/3073/2013 influenza strain were similar, but the GMTR for the QIV-HD group was higher than that for the TIV-HD1 group: GMTR for QIV-HD was 3.82 [95% CI: 3.62; 4.03), GMTR for TIV-HD1 was 1.86 [95% CI: 1.73; 2.02), and GMTR for TIV-HD2 was 3.82 [95% CI: 3.43; 4.24).

Results were similar in the FAS.

Seroconversion Rates

Seroconversion is defined as a titer < 10 (1/dil) at D0 and post-injection titer ≥ 40 (1/dil) at D28, or HAI titer ≥ 10 (1/dil) at D0 and a ≥4-fold rise in HAI titer (1/dil) at D28.

At V02 post-vaccination, the seroconversion rates were similar between QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled for the A/H1N1 influenza strain. The seroconversion rates were 50.4% (95% CI: 48.0, 52.8) for QIV-HD, 56.2% (95% CI: 51.3, 61.0) for TIV-HD1, 51.2% (95% CI: 46.3, 56.0) for TIV-HD2, and 53.7% (95% CI: 50.2, 57.1) for TIV-HD pooled.

At V02 post-vaccination, the seroconversion rates were similar between QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled for the A/H3N2 influenza strain. The seroconversion rates were 49.8% (95% CI: 47.3, 52.2) for QIV-HD, 52.9% (95% CI: 48.0, 57.7) for TIV-HD1, 48.1% (95% CI: 43.3, 53.0) for TIV-HD2, and 50.5% (95% CI: 47.1, 53.9) for TIV-HD pooled.

At V02 post-vaccination, the seroconversion rate for the QIV-HD and TIV-HD1 groups for the B/Brisbane/60/2008 influenza strain were similar, but the seroconversion rate for the QIV-HD group was higher than that for the TIV-HD2 group: seroconversion rate for QIV-HD was 36.5% (95% CI: 34.2, 38.9), seroconversion rate for TIV-HD1 was 39.0% (95% CI: 34.3, 43.8), and seroconversion rate for TIV-HD2 was 15.2% (95% CI: 11.9, 18.9).

At V02 post-vaccination, the seroconversion rate for the QIV-HD and TIV-HD2 groups for the B/Phuket/3073/2013 influenza strain were similar, but the seroconversion rate for the QIV-HD group was higher than that for the TIV-HD1 group: seroconversion rate for QIV-HD was 46.6% (95% CI: 44.2, 49.0), seroconversion rate for TIV-HD2 was 48.4% (95% CI: 43.5, 53.2), and seroconversion rate for TIV-HD1 was 17.6% (95% CI: 14.1, 21.6).

Results were similar in the FAS.

Seroprotection

At V01, the percentage of subjects with seroprotection titer of ≥ 1:40 were comparable between all study groups for the 2 common influenza A strains and the B strains.

For the A/H1N1 strain, the percentages of seroprotection were 69.4%, 67.9%, and 70.1% for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively. For the A/H3N2 strain, the percentages of seroprotection were 77.4%, 78.1%, and 77.8% for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

For the B/Brisbane strain, the percentages of seroprotection were 88.9%, 87.9%, and 88.8% for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively. For the B/Phuket strain, the percentages of seroprotection were 89.6%, 88.1%, and 90.9% for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

At V02 post-vaccination, the percentages of subjects who were seroprotected were higher than the percentage of subjects who were seroprotected at baseline for the 2 common influenza A strains and the B strains.

For the QIV-HD, TIV-HD1, and TIV-HD2 groups, the percentages of subjects who achieved seroprotection were 95.1%, 96.7%, and 95.6% against the A/H1N1 strain, respectively; 96.9%, 96.9%, and 96.7% against the A/H3N2 strain, respectively; 99.0%, 99.1%, and 96.5% against the B/Brisbane strain, respectively; and 99.3%, 96.7%, and 99.1% against the B/Phuket strain, respectively.

Similar results were seen in the FAS.

Immunogenicity by Covariate Factors

Age

The GMTs at V02 (post-vaccination) and seroconversion rates for subjects ≥ 75 years of age tended to be lower compared with subjects 65 to < 75 years of age for all strains except for B/Brisbane's results in the TIV-HD2 group (since B/Brisbane was not included in the TIV-HD2) and for B/Phuket's results in the TIV-HD1 group (since TIV-HD1 does not contain B/Phuket).

In general, the seroprotection rates at baseline and at V02 (post-vaccination) are similar in all study groups for both age subgroups.

Sex

In general, the post-vaccination GMTs and seroconversion rates were numerically higher in female than male subjects for any strain. The seroprotection rates were similar between male and female subjects in any study group for any strain.

Race

In general, the post-vaccination GMTs and seroconversion rates were numerically higher in non-Caucasian subjects compared with Caucasian subjects.

Previous Influenza Vaccination Status

In general, the GMTs at V02 (post-vaccination) and the seroconversion rates tended to be higher in subjects with no history of previous influenza vaccination the prior year compared with subjects with a history of an influenza vaccination the prior year.

Almost all of the subjects (94.2% or higher) reached seroprotection at V02 regardless of the previous influenza vaccination status.

Baseline Seropositivity Status (Ab titer ≥ 1:10)

The number of subjects who were seronegative at baseline was low and thus no conclusions can be made. The post-vaccination GMTs and seroprotection rates were lower for subjects who were seronegative at baseline in any group for any strain. However, the seroconversion rates were higher for subjects who were seronegative at baseline in any group for any strain.

Secondary Objective 3: Descriptive Analysis of the Immune Response by SN Measurement Method

GMTs at V01 (Baseline)

At baseline, the GMTs were similar between QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled for the 2 common influenza A strains with GMTs ranging from 412 to 427 for the A/H1N1 strain and 497 to 593 for the A/H3N2 strain. GMTs were also similar for all the groups for the 2 B strains, ranging from 430 to 458 for the B/Brisbane strain and 155 to 192 for the B/Phuket strain.

GMTs at V02 Post-vaccination

At V02 post-vaccination, GMTs for the 2 common influenza A strains increased for the QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled. GMTs were also similar between each study group ranging from 1686 to 2229 for the A/H1N1 strain and 1301 to 1404 for the A/H3N2 strain. GMTs for the B strains in the QIV-HD group were similar to those in the TIV-HD groups except for the corresponding strain that was not included in the TIV-HD vaccine. For the B/Brisbane strain, GMTs for the QIV-HD and TIV-HD1 were similar (1288 and 1114, respectively) whereas GMTs for the QIV-HD were higher than those for the TIV-HD2 (1288 and 590, respectively). This is expected since TIV-HD2 does not contain the B/Brisbane strain. For the B/Phuket strain, GMTs for the QIV-HD and TIV-HD2 were similar (546 and 494, respectively) whereas GMTs for the QIV-HD were higher than those for the TIV-HD1 (546 and 259, respectively). This is expected since TIV-HD1 does not contain the B/Phuket strain.

GMTRs (Geometric means of individual titer ratios of post-vaccination/pre-vaccination)

GMTRs were similar between QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled for the 2 common strains influenza strains with GMTRs ranging from 4.06 to 5.40 for the A/H1N1 strain and 2.19 to 2.83 for the A/H3N2 strain. For the B/Brisbane strain, GMTRs for the QIV-HD and TIV-HD1 were similar (2.81 and 2.47, respectively) whereas GMTR for the QIV-HD was higher than that for the TIV-HD2 (2.81 and 1.37, respectively). This is expected since TIV-HD2 does not contain the B/Brisbane strain. For the B/Phuket strain, GMTRs for the QIV-HD and TIV-HD2 were similar (3.51 and 2.58, respectively) whereas GMTR for the QIV-HD was higher than that for the TIV-HD1 (3.51 and 1.66, respectively). This is expected since TIV-HD1 does not contain the B/Phuket strain.

Fold-Rise (V02 Post-vaccination)

The percentage of subjects with a 2-fold rise were comparable between all study groups for the 2 common influenza A strains, ranging from 64.6% (64/99) to 72.5% (74/102) for the A/H1N1 strain and 42.4% (42/99) to 51.0% (52/102) for the A/H3N2 strain.

For the B/Brisbane strain, the increase in the titers by 2-fold for QIV-HD and TIV-HD1 was similar (51.0% [52/102] and 51.0% [51/100], respectively) whereas the 2-fold increase in titer for QIV-HD was higher than that for TIV-HD2 (51.0% [52/102] and 24.2% [24/99], respectively).

For the B/Phuket strain, the increase in the titers by 2-fold for QIV-HD and TIV-HD2 was similar (63.7% [65/102] and 55.6% [55/99], respectively) whereas the 2-fold increase in titer for QIV-HD was higher than that for TIV-HD1 (63.7% [65/102] and 31.0% [31/100], respectively).

The percentage of subjects with a 4-fold rise were comparable between all study groups for the 2 common influenza A strains, ranging from 41.4% (41/99) to 50.0% (50/100) for the A/H1N1 strain and 23.2% (23/99) to 26.5% (27/102) for the A/H3N2 strain.

For the B/Brisbane strain, the increase in the titers by 4-fold for QIV-HD and TIV-HD1 was similar (27.5% [28/102] and 23.0% [23/100], respectively) whereas the 4-fold increase in titer for QIV-HD was higher than that for TIV-HD2 (27.5% [28/102] and 8.1% [8/99], respectively).

For the B/Phuket strain, the increase in the titers by 4-fold for QIV-HD and TIV-HD2 was similar (35.3% [36/102] and 29.3% [29/99], respectively) whereas the 4-fold increase in titer for QIV-HD was higher than that for TIV-HD1 (35.3% [36/102] and 11.0% [11/100], respectively).

Titers ≥ 1:10 and ≥ 1:40 at V01 (Baseline)

At baseline, the percentage of subjects with titers ≥ 1:10 were similar between all study groups, ranging from 98.0% to 100% for all the influenza strains.

Titers ≥ 1:10 and ≥ 1:40 at V02 Post-vaccination

For all the influenza strains, 100% and ≥ 97.1% of subjects achieved post-vaccination titers of ≥ 1:10 and ≥ 1:40, respectively.

Additional Immunogenicity Analyses using using ELLA

GMTs at V01 (Baseline)

At baseline, GMTs were similar between QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled ranging from 238 to 312 for the N1 antigen and 41.2 to 45.2 for the N2 antigen.

GMTs at V02 Post-vaccination

At V02 post-vaccination, GMTs increased for the QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled. GMTs were also similar between each study group ranging from 398 to 505 for the N1 antigen and 74.5 to 86.9 for the N2 antigen.

GMTRs

GMTRs were similar between QIV-HD, TIV-HD1, TIV-HD2, and TIV-HD pooled ranging from 1.61 to 1.71 for the N1 antigen and 1.65 to 2.12 for the N2 antigen.

Fold-Rise (V02 Post-vaccination)

For the N1 antigen, the percentages of subjects with a 2-fold rise were 50.0% (51/102), 49.0% (49/100), and 51.0% (50/98) for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

For the N2 antigen, the percentages of subjects with a 2-fold rise were 64.0% (64/100), 62.0% (62/100), and 50.0% (49/98) for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

For the N1 antigen, the percentages of subjects with a 4-fold rise were 11.8% (12/102), 16.0% (16/100), and 12.2% (12/98) for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

For the N2 antigen, the percentages of subjects with a 4-fold rise were 23.0% (23/100), 18.0% (18/100), and 9.2% (9/98) for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

Titers ≥ 1:10 and ≥ 1:40 at V01 (Baseline)

At baseline, the percentages of subjects with titers ≥ 1:10 were 100.0% for all study groups for the N1 antigen.

For the N2 antigen, the percentages of subjects with titers ≥ 1:10 were 98.0% (100/102), 97.0% (97/100), and 97.0% (96/99) for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

For the N1 antigen, the percentages of subjects with titers ≥ 1:40 were 100.0% (102/102), 99.0% (99/100), and 96.0% (95/99) for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

For the N2 antigen, the percentages of subjects with titers ≥ 1:40 were 65.7% (67/102), 63.0% (63/100), and 63.6% (63/99) for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

Titers ≥ 1:10 and ≥ 1:40 at V02 Post-vaccination

For the N1 antigen, 100% of subjects achieved post-vaccination titers of ≥ 1:10 and ≥ 1:40.

For the N2 antigen, ≥ 99.0% of subjects achieved post-vaccination titers of ≥ 1:10. The post-vaccination titers of ≥ 1:40 were 84.0% (84/100), 83.3% (85/102), and 83.7% (82/98) for the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

Safety

Solicited Reactions Between D0 and D7

Solicited Injection Site Reactions

Within 7 days after vaccination, the percentages of subjects who reported at least 1 solicited injection site reaction were 44.1% (779/1768) and 39.8% (354/889) in the QIV-HD and TIV-HD pooled groups, respectively.

The most frequently reported solicited injection site reaction was pain, reported by 41.3% and 36.4% in the QIV-HD and TIV-HD pooled groups, respectively. Injection site reactions that were less frequently reported by subjects in the QIV-HD and TIV-HD pooled groups were erythema (6.2% and 5.7%, respectively), swelling (4.9% and 4.7%, respectively), induration (3.7% and 3.5%, respectively), and bruising (1.3% and 1.1, respectively).

The majority of solicited injection site reactions in the study groups were of Grade 1 intensity, started within the first 3 days after vaccination, and resolved spontaneously within 7 days of onset.

There were few reports of Grade 3 solicited injection site reactions with 26 (1.5%) and 4 (0.4%) subjects in the QIV-HD and TIV-HD pooled groups, respectively. Grade 3 reactions were reported as follows:

- Pain was reported by 12 (0.7%) and 2 (0.2%) subjects in the QIV-HD and TIV-HD pooled groups, respectively.
- Erythema was reported by 11 (0.6%) and 2 (0.2%) subjects in the QIV-HD and TIV-HD pooled groups, respectively.
- Swelling was reported by 5 (0.3%) and 1 (0.1%) subjects in the QIV-HD and TIV-HD pooled groups, respectively. There was no Grade 3 swelling reported in the TIV-HD1 group.
- Induration was reported by 3 (0.2%) and 1 (0.1%) subjects in the QIV-HD and TIV-HD pooled groups, respectively. There was no Grade 3 induration reported in the TIV-HD1 group.

Solicited Systemic Reactions

Within 7 days after vaccination, the percentages of subjects who reported at least 1 solicited systemic reaction were 31.0% (548/1768) and 29.7% (264/889) in the QIV-HD and TIV-HD pooled groups, respectively.

The most frequently reported solicited systemic reaction was myalgia, reported by 22.7% and 18.9% of subjects in the QIV-HD and TIV-HD pooled groups, respectively; followed by headache, reported by 14.4% and 13.6% in the QIV-HD and TIV-HD pooled groups, respectively; and malaise, reported by 13.2% and 13.4% in the QIV-HD and TIV-HD pooled group, respectively. Systemic reactions that were less frequently reported by subjects in the QIV-HD and TIV-HD pooled groups were shivering (5.4% and 4.7%, respectively) and fever (0.4% and 0.9%, respectively).

The majority of solicited systemic reactions in the study groups were of Grade 1 intensity, started within the first 3 days after vaccination, and resolved spontaneously within 7 days of onset.

There were few reports of Grade 3 solicited systemic reactions, with 28 (1.6%) and 9 (1.0%) subjects in the QIV-HD and TIV-HD pooled groups, respectively. Grade 3 reactions were reported as follows:

- Myalgia was reported by 16 (0.9%) and 6 (0.7%) subjects in the QIV-HD and TIV-HD pooled groups, respectively.
- Malaise was reported by 13 (0.7%) and 4 (0.4%) subjects in the QIV-HD and TIV-HD pooled groups, respectively.
- Headache was reported by 11 (0.6%) and 4 (0.4%) subjects in the QIV-HD and TIV-HD pooled groups, respectively.
- Shivering was reported by 5 (0.3%) and 3 (0.3%) subjects in the QIV-HD and TIV-HD pooled groups, respectively. There was no Grade 3 shivering reported in TIV-HD2 group.
- Fever was reported by 3 (0.2%) and 2 (0.2%) subjects in the QIV-HD and TIV-HD pooled groups, respectively.

Unsolicited AEs Between D0 and D28

Overall, the percentages of subjects reporting at least 1 unsolicited AE were comparable across the study groups: 16.4% (292/1777), 17.8% (79/443), and 15.1% (68/450) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

Grade 3 unsolicited non-serious AEs were rare in all groups, with 14 (0.8%), 3 (0.7%), and 7 (1.6%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

Immediate Unsolicited AEs

A total of 7 subjects reported 10 unsolicited AEs within 30 minutes after vaccination; 5 subjects in the QIV-HD group reported 7 AEs and 2 subjects in the TIV-HD2 group reported 3 AEs. None of the AEs were Grade 3 in intensity:

Unsolicited Non-serious Injection Site AR

Within 28 days after vaccination, a total of 13 (0.7%), 4 (0.9%), and 3 (0.7%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively, reported at least 1 unsolicited non-serious injection site reactions. None of the ARs were of Grade 3 intensity.

Unsolicited Non-serious Systemic AEs

Within 28 days after vaccination, a total of 269 (15.1%), 70 (15.8%), and 65 (14.4%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively, reported at least 1 unsolicited non-serious systemic AE.

The most common (occurring in > 1% of subjects) unsolicited systemic AEs were in the system organ classes of:

- Infections and infestations and included upper respiratory tract infection, reported by 19 (1.1%), 9 (2.0%), and 3 (0.7%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

- Respiratory, thoracic and mediastinal disorders and included: cough, reported by 30 (1.7%), 10 (2.3%), and 5 (1.1%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively; and nasal congestion, reported by 8 (0.5%), 5 (1.1%), and 3 (0.7%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

Most of the unsolicited non-serious systemic AEs were of Grade 1 or 2 intensities. Grade 3 unsolicited non-serious systemic AEs were reported by a total of 14 (0.8%), 3 (0.7%), and 7 (1.6%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively.

Unsolicited Non-serious Systemic ARs

Unsolicited non-serious systemic ARs were reported by a total of 22 (1.2%), 4 (0.9%), and 6 (1.3%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively. None of the ARs were of Grade 3 intensity.

AEs Leading to Withdrawal from the Study

Within 28 days after vaccination, there were a total of 3 AEs leading to withdrawal from the study: 1 subject in the QIV-HD group died suddenly of natural causes, 1 subject in the TIV-HD1 group experienced Myocardial infarction, and 1 subject in the TIV-HD1 group experienced a rib fracture. All AEs leading to withdrawal from the study were considered SAEs and were assessed as not related to the study vaccination by the Investigator.

Deaths, Other SAEs, and other Significant AEs

Deaths

A total of 5 deaths were reported during the study: 3 subjects in the QIV-HD group and 2 subjects in the TIV-HD1 group.

Deaths within 28 Days after Vaccination at V01

Within 28 days after vaccination, there was 1 death in the QIV-HD group and 1 death in TIV-HD1 group. Both deaths were assessed as not related to the study vaccination by the Investigator.

- QIV-HD group: Subject 840001700005 died suddenly of natural causes 6 days after vaccination.
- TIV-HD1 group: Subject 840001100025 experienced myocardial infarction 25 days after vaccination. The subject was hospitalized and died on the same day.

Deaths after V02

During the 6-month follow-up period, there were 2 deaths reported in the QIV-HD group and 1 death reported in the TIV-HD1 group. All deaths were assessed as not related to the study vaccination by the Investigator.

- QIV-HD group: Subject 840002900005 experienced acute respiratory infection 168 days after vaccination. The subject was hospitalized and died 5 days later.
- QIV-HD group: Subject 840000100014 experienced prostate cancer 105 days after vaccination. The subject was hospitalized and died 6 days later.
- TIV-HD1 group: Subject 840000100039 experienced pneumonia 87 days after vaccination. The subject was hospitalized and died 18 days later.

SAEs Other Than Deaths

A total of 128 subjects experienced 162 SAEs during the study, 9 subjects within the first 7 days after vaccination at V01, 31 subjects within 28 days after vaccination, and 104 subjects after D28 through the 6-month follow-up. One SAE was considered as related to the vaccine by the Investigator, and 3 SAEs led to discontinuation from the study.

All and Related SAEs within 28 Days after Vaccination at V01

A total of 31 subjects experienced 37 SAEs within the first 28 days after vaccination on D0: 19 (1.1%) subjects in the QIV-HD group experienced 23 SAEs, 7 (1.6%) subjects in the TIV-HD1 group experienced 8 SAEs, and 5 (1.1%) subjects in the TIV-HD2 group experienced 6 SAEs; none were considered as related to the vaccine by the Investigator and 1 SAE in the TIV-HD1 group led to termination from the study:

- TIV-HD1 group: Subject 840001400009 suffered from fractured ribs 21 days after vaccination. The subject was diagnosed with worsening of left hip osteoarthritis and was hospitalized. The subject recovered 6 days later. This event led to termination from the study.

All and Related SAEs after V02

A total of 104 subjects experienced 125 SAEs after Visit 2: 65 subjects (3.7%) in the QIV-HD group experienced 80 SAEs, 23 (5.2%) subjects in the TIV-HD1 group experienced 26 SAEs, and 16 subjects (3.6%) in TIV-HD2 group experienced 19 SAEs In the QIV-HD group, 1 SAE was considered as related to the vaccine by the Investigator and 1 SAE led to termination from the study.

- QIV-HD group: Subject 840002700007 experienced small fiber inflammatory neuropathy 40 days after vaccination. The event was ongoing at the end of the study and was considered related to the vaccine by the Investigator but not related by the Sponsor.
- QIV-HD group: Subject 840000200008 suffered from post cardiotomy syndrome 39 days after vaccination. The subject was hospitalized and recovered within 4 days. This SAE was not considered related to the vaccine. This event led to termination from the study.

AESIs

During the 6-month follow-up period, a total of 3 AESIs were reported: 1 in QIV-HD group and 2 in TIV-HD2 group. All AESIs were assessed as not related to the study vaccination by the Investigators.

- QIV-HD group: Subject 840003700036 experienced facial paralysis and was diagnosed with Bell's palsy 60 days after vaccination. The subject was hospitalized and recovered 2 days later.
- TIV-HD2 group: Subject 840003400051 experienced facial paralysis 31 days after vaccination and was diagnosed with bilateral Bell's palsy. The subject was recovering from the condition by the end of the 6-month follow-up period.
- TIV-HD2 group: Subject 840002700070 experienced facial paralysis 171 days after vaccination and was diagnosed with Bell's palsy on the right side of the face. By the end of the 6-month follow-up period, the event was ongoing.

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