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Sponsor: Sanofi Pasteur	**Study Identifiers:** U1111-1183-5525, NCT03233217
Drug substance(s): High-Dose Influenza Vaccine Quadrivalent	**Study code:** QHD00008

Title of the study: Safety and Immunogenicity of High-Dose Quadrivalent Influenza Vaccine (SP0178) Administered by Intramuscular or Subcutaneous Route in Subjects Aged 65 Years and Older in Japan

Study center(s): This was a multi-center study involving 2 sites in Japan.

Study period:

Date first subjects enrolled: 15/Sep/2017

Date last subjects completed: 28/Nov/2017

Phase of development: Phase I/II

Objectives:

Safety

To describe the safety profile of subjects in each group.

Immunogenicity

To describe the immune responses induced by each group (as assessed by HAI geometric mean titers [GMTs] and seroconversion rates) for the 4 common virus strains at 28 days post-vaccination.

Methodology:

QHD00008-DFI15130 was a Phase I/II, randomized, modified double-blind, multi-center study conducted in 175 healthy adults aged 65 years and older to assess the safety and immunogenicity of the high-dose quadrivalent influenza vaccine (QIV-HD) administered by intramuscular (IM) method and QIV-HD administered by subcutaneous (SC) method. A local standard-dose quadrivalent influenza vaccine (QIV-SD) administered by SC method served as the control arm.

In order to assess the safety and tolerability of QIV-HD in Japanese adults aged 65 years and older in an initial smaller cohort, the first 10 subjects enrolled were randomized 1:1 to receive either QIV-HD by IM route or QIV-HD by SC route (Cohort 1). After review of the local and systemic adverse events (AEs) occurring for 7 days post-vaccination (Day [D] 0 to D7) in Cohort 1, enrollment of the remaining 165 subjects randomized 1:1:1 to receive QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route (Cohort 2) occurred.

The subjects in Cohort 1 followed the same study schedules and procedures as the subjects in Cohort 2.

All subjects provided a pre-vaccination (baseline) blood sample at D0 and a post-vaccination blood sample at Visit (V) 3 (D28 [+ 7 days]) for hemagglutination inhibition (HAI) testing.

Solicited reactions were collected up to 7 days after vaccination and unsolicited AEs were collected up to V3. Serious adverse events (SAEs) and adverse events of special interest (AESIs)* were collected throughout the study (D0 through V3).

*Note: AESIs had the same detailed information collected as SAEs. AESIs included new onset of: Guillain-Barré syndrome, encephalitis/myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis.

For Cohort 1, interactive response technology (IRT) was used to assign subjects to one of 2 study groups (QIV-HD by IM route or QIV-HD by SC route) and to assign subject numbers in each of the groups. However, the randomization was performed without stratification.

For Cohort 2, IRT was also used to assign subjects to one of 3 study groups (QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route) and to assign subject numbers in each of the groups. The randomization was stratified by age (<75, ≥75), sex (Male, Female), and sites.

Electronic data capture (EDC) was used for the collection of data.

Number of subjects:	Planned: 175
	Randomized: 175
	Treated: 175
Evaluated:	Immunogenicity: 175
	Safety: 175

Diagnosis and criteria for inclusion:

An individual had to fulfill all of the following criteria in order to be eligible for study enrollment:

I 01. Aged ≥65 years on the day of inclusion

I 02. Informed consent form (ICF) has been signed and dated

I 03. Able to attend all scheduled visits and to comply with all study procedures

Study treatments

Investigational Product: High-Dose Influenza Vaccine Quadrivalent, (Zonal Purified, Split Virus) 2017-2018 Strains (QIV-HD), provided in a pre-filled single-dose syringe.

Form: Suspension

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

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

Active substances:

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

Excipients:

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

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

Route(s) of administration: IM or SC, injected into the upper arm (IM injected into the deltoid area or SC injected into the posterior region)

Control Product: Local Standard-Dose Inactivated Influenza Vaccine Quadrivalent, 2017-2018 Strains (QIV-SD), provided in a pre-filled single-dose syringe.

Form: Suspension

Composition: Each 0.5 mL dose of QIV-SD contains

Strains determined based on Japan National Institute of Infectious Diseases (NIID) recommendations for the 2017-2018 NH influenza season.

• A/Singapore/GP1908/2015 (IVR-180) (H1N1) pdm09 strain	15 µg HA
• A/Hong Kong/4801/2014 (NYMC X-263) (H3N2) strain	15 µg HA
• B/Phuket/3073/2013 strain	15 µg HA
• B/Texas/2/2013 strain	15 µg HA
• Buffered saline solution	quantity sufficient to appropriate volume

Route(s) of administration: SC, injected into the upper arm (posterior region)

Duration of participation: Duration for per subject is 28 days [+ 7 days]

Criteria for evaluation:

Safety

Safety was described for all subjects.

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, maximum 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, maximum intensity, action taken, and whether the reaction led to early termination from the study, of solicited (prelisted in the subject's diary card and 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 study, 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 study, of SAEs throughout the study (D0 through V3)
- Occurrence, nature (MedDRA PT), and relationship to vaccination of AESIs throughout the study (D0 through V3)

Immunogenicity

- HAI antibody titers obtained on D0 and D28
- Individual titer ratios of HAI at 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 increase in titer [1/dil] at D28)
- Seroprotection (titer ≥40 [1/dil]) at D0 and D28

Statistical methods:

No hypotheses for safety and immunogenicity were planned. All analyses were descriptive.

Safety

The safety results in subjects who received QIV-HD (either IM or SC) or the QIV-SD were described. The main parameters were described with the 95% confidence interval (CI) based on the Clopper-Pearson method. The safety analysis set (SafAS) was used for the safety analyses.

Immunogenicity

Immunogenicity in terms of GMTs, seroconversion, and seroprotection rates were summarized for each strain. The 95% CIs for the GMTs were calculated using normal approximation of log-transformed titers. The 95% CIs for the proportions were based on the Clopper-Pearson method. The GMT ratios were obtained between groups with the 95% CIs calculated using normal approximation of log-transformed titers. The differences in the seroconversion rates between groups were computed along with the 2-sided 95% CIs by the Newcombe-Wilson method without continuity correction. Additional parameters were displayed as appropriate. Details of the above analyses were described in a Statistical Analysis Plan (SAP). The per-protocol analysis set (PPAS) and full analysis set (FAS) were applied for the immunogenicity analyses. The main immunogenicity analyses were conducted on Cohort 2 for the PPAS. Immunogenicity analyses were also conducted on Cohort 2 for the FAS and on all 175 subjects.

Summary:

Population characteristics:

Disposition

The study was conducted at 2 centers between 15 September 2017 (first visit, first subject) and 28 November 2017 (last visit, last subject).

A total of 10 subjects were enrolled and randomized into one of 2 groups in Cohort 1: 5 subjects in the QIV-HD by IM route (QIV-HD IM) group, and 5 subjects in the QIV-HD by SC route (QIV-HD SC) group.

A total of 165 subjects were enrolled and randomized into one of 3 groups stratified according to age (<75, ≥75), sex (Male, Female), and site in Cohort 2: 55 subjects in the QIV-HD IM group, 55 subjects in the QIV-HD SC group, and 55 subjects in the QIV-SD by SC route (QIV-SD SC) group.

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

Data Sets Analyzed

All 175 subjects in Cohort 1+Cohort 2 received the study vaccine and, therefore, were included in the SafAS: 60 subjects in the QIV-HD IM group, 60 subjects in the QIV-HD SC group, and 55 subjects in the QIV-SD SC group.

A total of 164 (99.4%) subjects in Cohort 2 were included in the PPAS: 55 subjects in the QIV-HD IM group, 55 subjects in the QIV-HD SC group, and 54 subjects in the QIV-SD SC group.

A total of 174 (99.4%) subjects in Cohort 1+Cohort 2 were included in the PPAS: 60 subjects in the QIV-HD IM group, 60 subjects in the QIV-HD SC group, and 54 subjects in the QIV-SD SC group.

A total of 175 (100%) subjects in Cohort 1+Cohort 2 were included in the FAS: 60 subjects in the QIV-HD IM group, 60 subjects in the QIV-HD SC group, and 55 subjects in the QIV-SD SC group.

Demographics

Overall, there were fewer female than male subjects in the SafAS in Cohort 1+Cohort 2, with a total of 95 (54.3%) male and 80 (45.7%) female subjects. The distribution of fewer females than males was also observed across each study group.

The mean age was 70.2 years (range: 65; 79 years). The mean ages and percentages of subjects greater than 75 years of age were comparable across all study groups.

The mean BMI was 23.68 kg/m^2 (range: 18.2; 33.2 kg/m^2). The mean BMIs and the distribution of BMI were comparable across all study groups.

Medical and Vaccination History

Almost all of the subjects (100%, 98.3%, and 98.2% in the QIV-HD IM, QIV-HD SC, and QIV-SD SC groups, respectively) had at least one past and current significant medical history, most of which (100%, 96.7%, and 96.4% of subjects in the QIV-HD IM, QIV-HD SC, and QIV-SD SC groups, respectively) were ongoing at inclusion.

The percentages of subjects who had received an influenza vaccination in the previous year (2016/2017 influenza season) were similar between the QIV-HD SC and QIV-SD SC groups (31.7% and 30.9%, respectively), but lower in the QIV-HD IM group (16.7%).

Concomitant Medications

The percentages of subjects who were taking concomitant medications which were considered reportable were 20.0%, 16.7%, and 25.5% of subjects in the QIV-HD IM, QIV-HD SC, and QIV-SD SC groups, respectively. The majority of concomitant medications were anti-hyperlipidemia medications of the statin family (18.3%, 15.0%, and 18.2% of subjects in the QIV-HD IM, QIV-HD SC, and QIV-SD SC groups, respectively), followed by medications impacting or that may have an impact on the evaluation of the safety such as antipyretics, analgesics, and NSAIDs (5.0%, 3.3%, and 9.1% of subjects in the QIV-HD IM, QIV-HD SC, and QIV-SD SC groups, respectively).

Safety:

Solicited Injection Site Reactions

Within 7 days after vaccination, the percentages of subjects who reported at least one solicited injection site reaction were 41.7% (25/60) in the QIV-HD IM group, 66.7% (40/60) in the QIV-HD SC group, and 41.8% (23/55) in the QIV-SD SC group in the SafAS in Cohort 1+Cohort 2.

The most frequently reported solicited injection site reaction was pain, reported by 30.0% of subjects (18/60) in the QIV-HD IM group, 45.0% of subjects (27/60) in the QIV-HD SC group, and 27.3% of subjects (15/55) in the QIV-SD SC group; followed by erythema, with 18.3% of subjects (11/60) in the QIV-HD IM group, 31.7% of subjects (19/60) in the QIV-HD SC group, and 20.0% of subjects (11/55) in the QIV-SD SC group; and swelling, with 15.0% of subjects (9/60) in the QIV-HD IM group, 28.3% of subjects (17/60) in the QIV-HD SC group, and 23.6% of subjects (13/55) in the QIV-SD SC group.

Most of the solicited injection site reactions were of Grade 1 or Grade 2 intensity, which started within the first 3 days after vaccination and resolved spontaneously within 7 days of onset. There were few reports of Grade 3 solicited injections site reactions, with 5.0% of subjects (3/60) in the QIV-HD IM group, and 10.0% of subjects (6/60) in the QIV-HD SC group. Grade 3 reactions were reported as follows:

- Erythema was reported in 8 subjects: 3 subjects (5.0%) in the QIV-HD IM group and 5 subjects (8.3%) in the QIV-HD SC group
- Swelling was reported in 4 subjects: 1 subject (1.7%) in the QIV-HD IM group and 3 subjects (5.0%) in the QIV-HD SC group
- Induration was reported in 2 subjects: 1 subject (1.7%) in the QIV-HD IM group and 1 subject (1.7%) in the QIV-HD SC group

There were no Grade 3 solicited injections site reactions reported in the QIV-SD SC group.

Solicited Systemic Reactions

Within 7 days after vaccination, the percentage of subjects who reported at least one solicited systemic reaction were 18.3% (11/60) in the QIV-HD IM group, 33.3% (20/60) in the QIV-HD SC group, and 16.4% (9/55) in the QIV-SD SC group.

The most frequently reported solicited systemic reaction was myalgia, reported by 15.0% of subjects (9/60) in the QIV-HD IM group, 26.7% of subjects (16/60) in the QIV-HD SC group, and 12.7% of subjects (7/55) in the QIV-SD SC group; followed by headache, with 5.0% of subjects (3/60) in the QIV-HD IM group, 13.3% of subjects (8/60) in the QIV-HD SC group, and 1.8% of subjects (1/55) in the QIV-SD SC group; and malaise, with 1.7% of subjects (1/60) in the QIV-HD IM group, 6.7% of subjects (4/60) in the QIV-HD SC group, and 5.5% of subjects (3/55) in QIV-SD SC group.

All the solicited systemic reactions were of Grade 1 intensity except for one subject in the QIV-HD SC group who experienced at least 1 Grade 2 fever. Most of the solicited systemic reactions started within the first 3 days after vaccination and resolved spontaneously within 3 days of onset.

Immediate Unsolicited AEs

There were no immediate unsolicited AEs reported within 30 minutes after vaccination in any of the groups.

Unsolicited Non-serious Injection Site Reactions

Reports of subjects with at least one unsolicited non-serious injection site reaction were low, with 1.7% (1/60), 5.0% (3/60), and 1.8% (1/55) of subjects in the QIV-HD IM, QIV-HD SC, and QIV-SD SC groups, respectively.

The only unsolicited injection site reaction that was reported in each group was pruritus, all of which were of Grade 1 intensity, which started within the first 3 days after vaccination and resolved spontaneously within 4 days of onset.

Unsolicited Non-serious Systemic AEs

The percentages of subjects who reported at least one unsolicited non-serious systemic AEs were 5.0% (3/60), 3.3% (2/60), and 12.7% (7/55) in the QIV-HD IM, QIV-HD SC, and QIV-SD SC groups, respectively.

The unsolicited systemic AEs occurring with PTs ≥2% in any of the groups were in the System Organ Classes of:

- Infections and infestations and included: nasopharyngitis reported by 3.3% of subjects (2/60) in the QIV-HD SC group and 3.6% of subjects (2/55) in the QIV-SD SC group
- Respiratory, thoracic and mediastinal disorders and included: oropharyngeal pain reported by 3.6% of subjects (2/55) in the QIV-SD SC group

All of the unsolicited systemic AEs were of Grade 1 intensity, except for one subject in the QIV-SD SC group who experienced a Grade 2 unsolicited systemic AE. There were no Grade 3 unsolicited systemic AEs reported in any of the groups.

AEs Leading to Withdrawal from the Study

There were no AEs leading to study discontinuation within 28 days after vaccination in any of the groups.

Deaths, Other SAEs, and Other Significant AEs

There were no deaths or AESIs during this study.

During this study, one SAE occurred in one subject in the QIV-SD SC group. The subject experienced sudden hearing loss 3 days after vaccination and was hospitalized. The event was reported as recovering or resolving at V3, and was assessed as not related to the study vaccination by the Investigator.

Immunogenicity:

Although both the US and Japan use the WHO recommended list of "-Like strains" for inclusion in influenza vaccines, 3 of the Japan recommended strains (for the A/H1N1, A/H3N2, B/Victoria lineage strains) used in the local QIV-SD were not the same exact strains as the US recommended "-Like strains" used in QIV-HD. The B/Yamagata lineage strain was the same for both study vaccines. Sera from all the subjects were tested in the HAI assay against all strains used in the study vaccines regardless of which study vaccine the subject received.

HAI Geometric Mean Titer (GMT)

At V3 (post-vaccination), the GMTs for both the QIV-HD IM and QIV-HD SC groups were higher than the QIV-SD SC group for all strains regardless of testing the subjects' sera with either the QIV-HD strains or QIV-SD strains, with the ratios of GMTs (QIV-HD/QIV-SD) ranging from 1.98 (95% CI: 1.26; 3.10) to 2.89 (95% CI: 1.95; 4.28) for the QIV-HD IM group, and from 1.65 (95% CI: 1.06; 2.56) to 2.70 (95% CI: 1.88; 3.86) for the QIV-HD SC group in the PPAS in Cohort 2.

At V1 (pre-vaccination), the GMTs were similar between the QIV-HD IM, QIV-HD SC, and QIV-SD SC groups for all strains. At V3 (post-vaccination), the GMTs for all strains increased in each study group, with GMTRs (V3/V1) ranging from 7.51 (95% CI: 4.93; 11.45) to 16.93 (95% CI: 10.99; 26.10) for the QIV-HD IM group, from 4.68 (95% CI: 3.34; 6.56) to 9.25 (95% CI: 6.11; 14.00) for the QIV-HD SC group, and from 2.67 (95% CI: 2.00; 3.57) to 6.56 (95% CI: 4.36; 9.86) for the QIV-SD SC group.

The GMTs at V3 (post-vaccination) for the QIV-HD IM group were higher than QIV-HD SC group for all strains, with the ratio of GMTs (QIV-HD IM/QIV-HD SC) ranging from 1.03 (95% CI: 0.69; 1.53) to 1.40 (95% CI: 0.91; 2.13).

Seroconversion

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

At V3 (post-vaccination), the seroconversion rate for both the QIV-HD IM and QIV-HD SC groups were higher than the QIV-SD SC group for all strains regardless of testing the subjects' sera with either the QIV-HD strains or QIV-SD strains, with the difference (QIV-HD − QIV-SD) ranging from 17.9 (95%CI: 0.1; 34.4) to 42.9 (95%CI: 25.2; 57.0) for the QIV-HD IM group, and from 10.2 (95%CI: -8.1; 27.6) to 30.3 (95%CI: 11.6; 46.2) for the QIV-HD SC group.

The seroconversion rates for the QIV-HD IM group were higher than the QIV-HD SC group for all strains, with the difference (QIV-HD IM − QIV-HD SC) ranging from 1.8 (95% CI: −15.6; 19.1) to 21.8 (95% CI: 5.5; 36.8).

Seroprotection

Seroprotection is defined as a HAI titer ≥40 (1/dil) at D0 and D28.

At V1 (pre-vaccination), the seroprotection rates were similar between the QIV-HD IM, QIV-HD SC, and QIV-SD SC groups for the A/H1N1, B/Yamagata, and B/Victoria lineage strains. For the A/H3N2 lineage strains, the seroprotection rates for the QIV-HD SC group were slightly higher compared with the QIV-HD IM and QIV-SD SC groups.

At V3 (post-vaccination), high seroprotection rates (nearly100%) were achieved for all strains in the QIV-HD IM and QIV-HD SC groups. In the QIV-SD SC group, seroprotection rates were over 90% for all strains.

HA Antibody Response between Vaccine Strains

The GMTs at V3 (post-vaccination) and the GMTRs (V3/V1) showed some differences between use of the QIV-HD strains or QIV-SD strains in the HAI assay. For all 4 lineage strains, when sera was tested in the HAI assay against the strains used in the QIV-HD, the GMTs and the GMTRs (V3/V1) were higher in all groups than when tested against the QIV-SD strains.

The GMTs at V3 (post-vaccination), the GMTRs (V3/V1), and the seroconversion rates for the QIV-HD IM and QIV-HD SC groups were higher than the QIV-SD SC group for all strains regardless of whether sera was tested against the QIV-HD or QIV-SD strains.

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