SANOFI PASTEUR

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Sponsor/ Company:	Sanofi Pasteur	**Study Code:** QID01 **Study Identifier:** NCT01712984
Proprietary Vaccine Name:	Influenza Virus Vaccine Quadrivalent, (Zonal Purified Subvirion) 2012–2013 Formulation + B strain from the alternate lineage (QIV-ID)	
Title of the Study: Immunogenicity and Safety Trial of Quadrivalent Influenza Vaccine Administered by Intradermal Route in Adult Subjects Aged 18 through 64 Years**.**		
Development phase:	Phase III	
Coordinating Investigator:	[redacted]	
Investigators and Trial Centers:	This was a multi-center trial involving 38 investigators at 38 sites. The full list of Investigators and centers is provided in an appendix of the full final report.	
Publications:	Gorse GJ, Falsey AR, Ozol-Godfrey A, Landolfi V, and Tsang PH. Safety and immunogenicity of a quadrivalent intradermal influenza vaccine in adults Vaccine. 2015 Feb 25;33 (9):1151-9.	
Trial period:	Date of First enrollment: 22 October 2012 Date of Last visit (contact): 28 May 2013	

Methodology / Trial Design:

QID01 was a randomized, double-blind, active-controlled, multi-center trial evaluating the immunogenicity and safety of the quadrivalent influenza vaccine by intradermal route (QIV-ID) in adults 18 through 64 years of age.

At enrollment, all eligible subjects were randomized to receive a single injection of either the QIV-ID or one of the trivalent influenza vaccines by intradermal route (TIV-IDs) containing either the B strain from the primary (Yamagata) lineage (TIV-ID1, which was the licensed vaccine [Fluzone® Intradermal] for the 2012–2013 season) or the B strain from the alternate (Victoria) lineage (TIV-ID2, which was an investigational TIV-ID containing an alternate B strain):

- Group 1 (QIV-ID): N=1674
- Group 2 (TIV-ID1): N=837
- Group 3 (TIV-ID2): N=837

At enrollment, a subset of 2/3 of subjects was randomly selected to provide a pre-vaccination (baseline) blood sample at Day 0 (D0) and a post-vaccination blood sample at D28.

Solicited reactions were collected up to 7 days after vaccination, and unsolicited adverse events (AEs) and reactions were collected up to 28 days after vaccination. Serious adverse events (SAEs) (including adverse events of special interest [AESIs*]) were collected throughout the trial (D0 through 6 month follow-up period).

*Note: AESIs were captured as SAEs. These were to include new onset of Guillain-Barré syndrome (GBS), Bell's palsy, encephalitis / myelitis, optic neuritis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

An interactive voice response system (IVRS) was used to randomly assign subjects to the QIV-ID group or the TIV-ID1 or TIV-ID2 groups and to assign subject numbers in each of the trial groups. Subjects were stratified by age (18 through 49 years [approximately 2/3 of subjects] and 50 through 64 years [approximately 1/3 of subjects]). Subjects were also randomized into the immunogenicity subset during the same IVRS call. Electronic data capture (EDC) was used for the collection of data.

Objectives: Primary objective(s):

To demonstrate that QIV-ID 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 TIV-ID1 and TIV-ID2 for the 4 virus strains at 28 days post-vaccination.

Primary endpoint:

- HAI antibody (Ab) titers obtained on D0 and 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 increase in titer [1/dil] at D28).

Secondary objective(s):

Immunogenicity:

1) To demonstrate that each B strain in QIV-ID induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-ID that does not contain the corresponding B strain.
2) To describe the rate of post-vaccination seroprotection induced by QIV-ID and TIV-ID.
3) To describe post-vaccination immunogenicity stratified by age (18–49 years and 50–64 years), race, ethnicity, sex, previous vaccination status, and baseline seropositivity status.

Safety:

To describe the safety profile for subjects who receive QIV-ID and TIV-ID.

Secondary endpoint:

Immunogenicity

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

Safety

Safety will be 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 electronic Case Report Form [eCRF]) injection site reactions and systemic reactions occurring up to 7 days after vaccination.
- Occurrence, nature (MedDRA PT), time to onset, duration, intensity, action taken, 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, duration, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the trial, of SAEs (including adverse events of special interest [AESIs]) throughout the trial (D0 through D180).

Observational objectives:

Immunogenicity

To describe any leakage appearing at the injection site immediately after the vaccine injection.

Safety

1) To demonstrate non-inferiority of QIV-ID compared to TIV-ID in terms of all Grade 2 or Grade 3 solicited systemic reactions combined.
2) To demonstrate non-inferiority of QIV-ID compared to TIV-ID in terms of all Grade 3 solicited injection site reactions combined

Observational endpoint:

Immunogenicity: Leakage will be assessed as *yes* or *no*.

Safety

- All Grade 2 or Grade 3 solicited systemic reactions combined will be described.
- All Grade 3 solicited injection site reactions combined will be described.

Sample size:

Table S1: Sample size – all randomized subjects

	Number of Subjects					
	Immunogenicity Subset		**No Blood Sample**		**Total**	
Group (Vaccine)	**Planned**	**Actual**	**Planned**	**Actual**	**Planned**	**Actual**
Group 1 (QIV-ID)	1116	1119	558	557	1674	1676
Group 2 (TIV-ID1)	558	560	279	277	837	837
Group 3 (TIV-ID2)	558	570	279	277	837	847

Schedules of Vaccination and Specimen Collection and Duration of Participation in the Trial:

Vaccination

All eligible subjects were randomized to receive a single injection of either the QIV-ID or one of the TIV-IDs (TIV-ID1 or TIV-ID2) at D0.

The presence or absence of leakage at the injection site was observed and recorded immediately following vaccination.

Blood Sampling

A subset of 2/3 of subjects was randomly selected to provide a pre-vaccination blood sample at D0 and a post-vaccination blood sample at D28.

Collection of Safety Data

Subjects were asked to notify the site immediately about any potential SAEs at any time during the trial.

All subjects were to be observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time were recorded as immediate unsolicited systemic AEs in the eCRF.

Subjects were to record information about solicited reactions, unsolicited AEs, and SAEs (including AESIs) in a diary card from D0 to D7 after vaccination and were to continue to record information about unsolicited AEs and SAEs (including AESIs) from D8 to D28.

Using a standardized phone script, staff contacted subjects by phone on D8 post-vaccination to find out whether the subject experienced any SAEs not yet reported and reminded the subjects to bring their completed diary card with them to Visit 2.

At Visit 2, staff reviewed the D0 to D28 safety data (from diary card) with subjects and provided them with a memory aid to collect information on SAEs (including AESIs) from D28 to D180.

Subjects continued to collect information on SAEs (including AESIs) in memory aids (from D28 to D180). Using a standardized phone script, staff contacted subjects by telephone at 6 months (+14 days) post-vaccination to review the memory aid and to collect any SAEs that had not yet been reported.

The duration of each subject's participation was approximately 6 months (D0 through 6 month follow-up period).

Investigational Product:

Influenza Virus Vaccine Quadrivalent, (Zonal Purified Subvirion) 2012–2013 Formulation + B strain from the alternate (Victoria) lineage (QIV-ID)

Composition: Each 0.1 mL dose of QIV-ID contains:

A/California/7/2009 (H1N1)	9 µg HA
A/Victoria/361/2011 (H3N2)	9 µg HA
B/Texas/6/2011 (B strain from primary [Yamagata] lineage)	9 µg HA
B/Brisbane/60/2008 (B strain from alternate [Victoria] lineage)	9 µg HA
Buffered saline solution	q.s. 0.1 mL

This vaccine is thimerosal-free.

Form: Liquid

Route: ID, injected into the deltoid area

Batch number: [redacted]

Device: BD Soluvia™ Micro Injection System (BD Soluvia)

Control Product 1:

Influenza Virus Vaccine Trivalent Types A and B (Zonal Purified Subvirion) Fluzone® Intradermal 2012–2013 Formulation

Composition: Each 0.1 mL dose of TIV-ID1 contains:

A/California/7/2009 (H1N1)	9 µg HA
A/Victoria/361/2011 (H3N2)	9 µg HA
B/Texas/6/2011 (B strain from primary [Yamagata] lineage)	9 µg HA
Buffered saline solution	q.s. 0.1 mL

This vaccine is thimerosal-free.

Form: Liquid

Route: ID, injected into the deltoid area

Batch number: [redacted]

Device: BD Soluvia

Control Product 2:

Influenza Virus Vaccine Trivalent Types A and B (Zonal Purified Subvirion) Fluzone Intradermal Investigational Formulation (B strain from the alternate [Victoria] lineage)

Composition: Each 0.1 mL dose of TIV-ID2 contains:

A/California/7/2009 (H1N1)	9 µg HA
A/Victoria/361/2011 (H3N2)	9 µg HA
B/Brisbane/60/2008 (B strain from alternate [Victoria] lineage)	9 µg HA
Buffered saline solution	q.s. 0.1 mL

This vaccine is thimerosal-free.

Form: Liquid

Route: ID, injected into the deltoid area

Batch number: [redacted]

Device: BD Soluvia

Inclusion Criteria:

A potential subject had to meet *all* of the following criteria in order to be eligible for trial enrollment:

1) Aged 18 through 64 years on the day of inclusion
2) Informed consent form (ICF) has been signed and dated
3) Able to attend all scheduled visits and to comply with all trial procedures

Exclusion Criteria:

A potential subject meeting *any* of the following criteria was to be excluded from trial enrollment:

1) Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to vaccination and until at least 4 weeks after vaccination)

2) Participation at the time of trial enrollment (or in the 4 weeks preceding the trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
3) Receipt of any vaccine in the 4 weeks preceding the trial vaccination or planned receipt of any vaccine in the 4 weeks following trial vaccination
4) Vaccination against influenza in the past 6 months
5) Receipt of immune globulins, blood or blood-derived products in the past 3 months
6) Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)
7) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances
8) History of thrombocytopenia
9) Bleeding disorder or receipt of anticoagulants in the 3 weeks preceding inclusion
10) Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
11) Current alcohol abuse or drug addiction
12) Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion
13) Identified as an Investigator or employee of the Investigator or trial center with direct involvement in the proposed trial, or identified as an immediate family member (i.e., parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed trial
14) Personal or family history of Guillain-Barré syndrome
15) Neoplastic disease or any hematologic malignancy (except localized skin or prostate cancer that is stable at the time of vaccination in the absence of therapy, and subjects who have a history of neoplastic disease and who have been disease free for ≥ 5 years)

Temporary Contraindications

Moderate or severe acute illness/infection (according to investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective subject should not be included in the trial until the condition has resolved or the febrile event has subsided.

Statistical methods

The Per-Protocol Analysis Set (PPAS) was used for the main non-inferiority immunogenicity analysis, the Full Analysis Set (FAS) was used for the main superiority immunogenicity analysis, and the safety population was used for the safety analyses.

For the purposes of this statistical methods section, the B strains in the QIV-ID and the TIV-IDs are labeled as follows:

B strain from the primary (Yamagata) lineage = B1

B strain from the alternate (Victoria) lineage = B2

Primary Objective

Non-inferiority

The immunogenicity of QIV-ID was compared to that of TIV-ID. For each A strain, the comparison was made with the 2 pooled TIV-ID groups. For each B strain, the comparison was made with the TIV-ID 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 2-sided Type I error rate of 0.05 with the given individual hypotheses:

- $H_0^s : GMT^s_{QIV\text{-}ID} / GMT^s_{TIV\text{-}ID} \le 1/1.5 \Leftrightarrow \log_{10}(GMT^s_{QIV\text{-}ID}) - \log_{10}(GMT^s_{TIV\text{-}ID}) \le \log_{10}(1/1.5)$

  $H_1^s : GMT^s_{QIV\text{-}ID} / GMT^s_{TIV\text{-}ID} > 1/1.5 \Leftrightarrow \log_{10}(GMT^s_{QIV\text{-}ID}) - \log_{10}(GMT^s_{TIV\text{-}ID}) > \log_{10}(1/1.5)$

- $H_0^s : \pi_{\text{QIV-ID}}^s - \pi_{\text{TIV-ID}}^s \leq -0.1$

  $H_1^s : \pi_{\text{QIV-ID}}^s - \pi_{\text{TIV-ID}}^s > -0.1$

with:

- s, strain in {A/H1N1, A/H3N2, B1, and B2}
- TIV-ID1 corresponds to the licensed 2012–2013 TIV-ID1 group if s = B1
- TIV-ID2 corresponds to the investigational TIV-ID2 group if s = B2
- TIV-ID corresponds to the pooled TIV-ID1 and TIV-ID2 groups if s = {A/H1N1, A/H3N2}

Secondary Objectives

Immunogenicity

Superiority

The immunogenicity of QIV-ID was compared to that of TIV-ID as follows: for each B strain, the comparison was made with the TIV-ID group that does not contain the corresponding B strain.

A superiority approach was used to compare post-vaccination GMTs and seroconversion rates between groups with the following individual hypotheses:

- $H_0^s : GMT_{\text{QIV-ID}}^s / GMT_{\text{TIV-ID}}^s \leq 1.5 \Leftrightarrow \log_{10}(GMT_{\text{QIV-ID}}^s) - \log_{10}(GMT_{\text{TIV-ID}}^s) \leq \log_{10}(1.5)$

  $H_1^s : GMT_{\text{QIV-ID}}^s / GMT_{\text{TIV-ID}}^s > 1.5 \Leftrightarrow \log_{10}(GMT_{\text{QIV-ID}}^s) - \log_{10}(GMT_{\text{TIV-ID}}^s) > \log_{10}(1.5)$

- $H_0^s : \pi_{\text{QIV-ID}}^s - \pi_{\text{TIV-ID}}^s \leq 0.1$

  $H_1^s : \pi_{\text{QIV-ID}}^s - \pi_{\text{TIV-ID}}^s > 0.1$

for each B strain where TIV-ID corresponds to the licensed 2012–2013 TIV-ID1 group if s = B2 and TIV-ID corresponds to the investigational TIV-ID2 group if s = B1

Seroprotection

Descriptive statistics (i.e., proportions and their 95% confidence intervals [CIs] based on the Clopper-Pearson method) were used.

Safety

Descriptive safety

Safety results were described for subjects who received QIV-ID, TIV-ID1, TIV-ID2, and for pooled TIV-ID. The main parameters were described by 95% CI (based on the Clopper-Pearson method).

Observational Objectives

Immunogenicity

Presence or absence of leakage at the injection site was tabulated. Immunogenicity in terms of GMTs, seroconversion, and seroprotection rates for leakage at the injection site was summarized.

Safety

Non-inferiority

- The proportion of subjects with Grade 2 or Grade 3 solicited systemic reactions (all combined) was used to demonstrate that QIV-ID vaccine was at least as well tolerated as the 2 pooled TIV-ID reference vaccine groups. To demonstrate non-inferiority of the QIV-ID investigational vaccine versus the 2 pooled TIV-ID reference vaccine groups in terms of safety, the upper bound of the 2-sided 95% CI on the ratio of the proportions $\pi_{\text{QIV-ID}} / \pi_{\text{TIV-IDpooled}}$ should not exceed 3.
- The proportion of subjects with Grade 3 solicited injection site reactions (all combined) was used to demonstrate that QIV-ID vaccine was at least as well tolerated as the 2 pooled TIV-ID reference vaccine groups. To demonstrate non-inferiority of the QIV-ID investigational vaccine versus the 2 pooled TIV-ID reference vaccine groups in terms of safety, the upper bound of the 2-sided 95% CI on the ratio of the proportions $\pi_{\text{QIV-ID}} / \pi_{\text{TIV-IDpooled}}$ should not exceed 3.

Calculation of Sample Size

A total of 3348 adults 18 through 64 years of age were to be enrolled. This total sample size for the study was based on the observational solicited injection site reaction objective. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Results: ***Disposition***

A total of 3360 subjects were enrolled in the trial: 1676 subjects in the QIV-ID group and 1684 subjects in the pooled TIV-ID groups (837 and 847 subjects in the TIV-ID1 and TIV-ID2 groups, respectively).

A total of 2249/3360 (66.9%) of these subjects were randomized to the immunogenicity subset: 1119/1676 (66.8%) subjects in the QIV-ID group and 1130/1684 (67.1%) subjects in the pooled TIV-ID groups (560/837 [66.9%] and 570/847 [67.3%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively).

Most subjects (3313/3360 [98.6%]) completed the active phase of the study.

A total of 47/3360 (1.4%) subjects were withdrawn during the active phase of the study (i.e., between Visit 1 and 2): 20/1676 (1.2%) subjects in the QIV-ID group and 27/1684 (1.6%) subjects in the pooled TIV-ID groups (16/837 [1.9%] and 11/847 [1.3%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively).

The most frequently reported reason for withdrawal was lost to follow-up, with reports for a total of 24/3360 (0.7%) subjects. Other reported reasons were voluntary withdrawal not due to an AE (19/3360 [0.6%] subjects) and non-compliance with the protocol (3/3360 [0.1%] subjects). One subject [redacted] in the TIV-ID2 group was withdrawn due to an SAE (pneumonia).

Deviations

A total of 98/1676 (5.8%) subjects in the QIV-ID group and 73/1684 (4.3%) subjects in the pooled TIV-ID groups (29/837 [3.5%] and 44/847 [5.2%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively) had at least one protocol deviation.

For each study group, the most frequently reported deviation was planned pre-or post-vaccination blood sample was not drawn: 28/1119 (2.5%) subjects in the QIV-ID group and 34/1130 (3.0%) subjects in the pooled TIV-ID groups (12/560 [2.1%] and 22/570 [3.9%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively).

A total of 3 (0.2%) subjects in the QIV-ID group and 2 (0.1%) subjects in the TIV-ID2 group did not receive any vaccine. Therefore, these subjects were not included in the SafAS.

One subject was randomized to the QIV-ID group but received the investigational TIV-ID2 vaccine. For the safety analyses, this subject was analyzed according to vaccine received (TIV-ID2 group). This subject was not randomized to the immunogenicity subset.

At Site [redacted], a total of 10/1676 (0.6%) subjects in the QIV-ID and 10/1684 (0.6%) subjects in the pooled TIV-ID groups (4/837 [0.5%] subjects in the TIV-ID1 group and 6/847 [0.7%] in the TIV-ID2 group) received vaccine that had a cold chain break; this temperature deviation was considered a transient change recorded by one of 3 temperature monitoring devices. Vaccine was considered not to be damaged by the Investigator. The IRB was notified and also determined there were no safety concerns regarding administration of the vaccines to these subjects. Follow-up requirements as specified in the protocol continued to be followed. These subjects were included in the SafAS. The subjects assessed for immunogenicity (N=15) were included in the FAS but were not included in the PPAS.

Data Sets Analyzed

Of subjects randomized to the immunogenicity subset, a total of 1092/1119 (97.6%) subjects in the QIV-ID group and 1102/1130 (97.5%) subjects in the pooled TIV-ID groups (548/560 [97.9%] and 554/570 [97.2%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively) were included in the FAS.

Of subjects randomized to the immunogenicity subset, a total of 1041/1119 (93.0%) subjects in the QIV-ID group and 1072/1130 (94.9%) subjects in the pooled TIV-ID groups (539/560 [96.3%] and 533/570 [93.5%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively) were included in the PPAS. A total of 1672 subjects in the QIV-ID group and 1683 subjects in the pooled TIV-ID groups (837 subjects in the TIV-ID1 group and 846 subjects in the TIV-ID2 group) were included in the SafAS.

Demographic and Baseline Characteristics

Overall, the demographics were similar across all trial groups. There were more females than males in the trial, with a total of 2055/3355 (61.3%) female subjects (range across groups: 60.3% to 62.4%) and 1300/3355 (38.7%) male subjects (range across groups: 37.6% to 39.7%).

The mean age was similar among all trial groups (41.6 and 41.5 years for the QIV-ID and pooled TIV-ID groups, respectively). There were more subjects in the younger (18 to 49 years) adult group (2233/3355 [66.6%]; range across groups: 66.4% to 66.8%) than in the older (50 to 64 years) adult group (1122/3355 [33.4%]; range across groups: 33.2% to 33.6%) as planned.

The majority of subjects in the trial were White (2848/3355 [84.9%] subjects), followed by Black or African American (400/3355 [11.9%] subjects). Subjects with other racial origins were ≤ 1.4% of the trial population. There was a total of 2789/3355 (83.1%) non-Hispanic or Latino subjects (range across groups: 83.0% to 83.3%) and 566/3355 (16.9%) Hispanic or Latino subjects (range across groups: 16.7% to 17.0%).

Immunogenicity

Primary Immunogenicity Objective

Non-inferiority

QIV-ID induced an immune response (as assessed by HAI GMTs and seroconversion rates) that was non-inferior to responses induced by TIV-ID1 and TIV-ID2 for the 4 virus strains at 28 days post-vaccination.

The non-inferiority of QIV-ID to TIV-ID in terms of GMTs was demonstrated. For each strain, the lower limit of the 2-sided 95% CI for the ratio of GMTs was > 2/3 (see **Table S2**).

The non-inferiority of QIV-ID to TIV-ID in terms of seroconversion rates was demonstrated. For each strain, the lower limit of the 2-sided 95% CI for the difference between the seroconversion rates was > -10% (see **Table S3**).

Table S2: Non-inferiority using GMTs at 28 days after vaccination - Per-protocol analysis set

	QIV-ID			TIV-ID*			QIV-ID / TIV-ID*		
Antigen/strain	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**GMT Ratio**	**(95% CI)**	**Non inferiority****
A/California/07/2009 (A/H1N1)†	1041	589	(546; 636)	1072	680	(629; 734)	0.866	(0.777; 0.966)	Yes
A/Victoria/361/2011 (A/H3N2)†	1041	368	(342; 397)	1071	430	(397; 464)	0.857	(0.770; 0.955)	Yes
B/Texas/6/2011 (B1)‡	1041	105	(99.1; 112)	539	93.5	(85.9; 102)	1.13	(1.02; 1.25)	Yes
B/Brisbane/60/2008 (B2)§	1041	136	(128; 145)	533	130	(118; 143)	1.05	(0.939; 1.16)	Yes

M: number of subjects with available data for the considered endpoint
2-sided 95% CI is based on the Student t-distribution.
* According to the strain, this column contains either one of the TIV-ID groups or the pooled TIV-ID groups.
† QIV-ID group is compared with pooled Licensed and Investigational TIV-ID1 and TIV-ID2 groups.
‡QIV-ID group is compared with Licensed TIV-ID1 group.
§ QIV-ID group is compared with investigational TIV-ID2 group.
** Non-inferiority concluded if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups is > 2/3 for each strain.

Table S3: Non-inferiority using seroconversion rates at 28 days after vaccination – Per protocol analysis set

	QIV-ID			TIV-ID*			QIV-ID minus TIV-ID*		
Antigen/strain	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**Difference**	**(95% CI)**	**Non-inferiority****
A/California/ 07/2009 (A/H1N1)†	600/1041	57.6	(54.6; 60.7)	647/1072	60.4	(57.4; 63.3)	-2.72	(-6.90; 1.47)	Yes
A/Victoria/ 361/2011 (A/H3N2)†	608/1040	58.5	(55.4; 61.5)	640/1071	59.8	(56.8; 62.7)	-1.30	(-5.48; 2.89)	Yes
B/Texas/ 6/2011 (B1)‡	580/1041	55.7	(52.6; 58.8)	253/539	46.9	(42.7; 51.3)	8.78	(3.58; 13.9)	Yes
B/Brisbane/ 60/2008 (B2)§	525/1041	50.4	(47.3; 53.5)	235/533	44.1	(39.8; 48.4)	6.34	(1.13; 11.5)	Yes

M: number of subjects with available data for the considered endpoint

2-sided 95% CI for the single proportion is based on the Clopper-Pearson method. 2-sided 95% CI for the difference is based on the Wilson score method.

* According to the strain, this column contains either one of the TIV-ID groups or the pooled TIV-ID groups.

† QIV-ID group is compared with pooled Licensed and Investigational TIV-ID1 and TIV-ID2 groups.

‡QIV-ID group is compared with Licensed TIV-ID1 group.

§ QIV-ID group is compared with investigational TIV-ID2 group.
** Non-inferiority concluded if the lower limit of the 2-sided 95% CI of the difference of seroconversion rates between groups is > -10% for each strain.

Secondary Immunogenicity Objectives

Superiority

QIV-ID induced an immune response to each B strain (as assessed by HAI GMTs and seroconversion rates) that was superior to the response induced by the TIV-ID that did not contain the corresponding B strain at 28 days post-vaccination.

The superiority of QIV-ID to TIV-ID in terms of GMTs was demonstrated. For each B strain, the lower limit of the 2-sided 95% CI for the ratio of GMTs was > 1.5 (see **Table S4)**.

The superiority of QIV-ID to TIV-ID in terms of seroconversion rates was demonstrated. For each B strain, the lower limit of the 2-sided 95% CI for the difference between the seroconversion rates was > 10% (see **Table S5**).

Table S4: Superiority using GMTs at 28 days after vaccination - Full analysis set

	QIV-ID			TIV-ID*			QIV-ID / TIV-ID*		
Antigen/strain	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**GMT Ratio**	**(95% CI)**	**Superiority****
B/Texas/6/2011 (B1)†	1092	104	(97.9; 110)	554	54.6	(49.8; 59.7)	1.90	(1.71; 2.11)	Yes
B/Brisbane/60/2008 (B2)‡	1091	135	(127; 143)	547	66.2	(60.6; 72.4)	2.04	(1.84; 2.26)	Yes

M: number of subjects with available data for the considered endpoint

2-sided 95% CI is based on the Student t-distribution.

* For each B strain, QIV-ID is compared to the results of the TIV-ID which does not contain this strain

† QIV-ID group is compared with Investigational TIV-ID2 group

‡ QIV-ID group is compared with Licensed TIV-ID1 group

** Superiority concluded if the lower limit of the 2-sided 95% CI of the ratio of GMTs between groups is > 1.5 for each strain

Table S5: Superiority using seroconversion rates at 28 days after vaccination - Full analysis set

	QIV-ID			TIV-ID*			QIV-ID minus TIV-ID*		
Antigen/strain	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**Difference**	**(95% CI)**	**Superiority****
B/Texas/6/2011 (B1)†	606/1085	55.9	(52.8; 58.8)	136/548	24.8	(21.3; 28.7)	31.0	(26.2; 35.5)	Yes
B/Brisbane/60/2008 (B2)‡	545/1085	50.2	(47.2; 53.2)	120/546	22.0	(18.6; 25.7)	28.3	(23.5; 32.7)	Yes

M: number of subjects with available data for the considered endpoint

2-sided 95% CI for the single proportion is based on the Clopper-Pearson method. 2-sided 95% CI for the difference is based on the Wilson score method.

* For each B strain, QIV-ID is compared to the results of the TIV-ID which does not contain this strain

† QIV-ID group is compared with Investigational TIV-ID2 group

‡ QIV-ID group is compared with Licensed TIV-ID1 group

** Superiority concluded if the lower limit of the 2-sided 95% CI of the difference of seroconversion rates between groups is > 10% for each strain.

Post-vaccination Seroprotection

On D28, the numbers and percentages of subjects who were seroprotected against:

Strain A/H1N1 were 1014/1041 (97.4%), 537/539 (99.6%), 524/533 (98.3%), and 1061/1072 (99.0%) in the QIV-ID, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively.

Strain A/H3N2 were 1008/1041 (96.8%), 526/538 (97.8%), 519/533 (97.4%), and 1045/1071 (97.6%) in the QIV-ID, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively.

Strain B1were 923/1041 (88.7%), 464/539 (86.1%), and 351/533 (65.9%) in the QIV-ID, TIV-ID1, and TIV-ID2 groups, respectively. TIV-ID2 does not contain strain B1.

Strain B2 were 976/1041 (93.8%), 403/538 (74.9%), and 477/533 (89.5%), in the QIV-ID, TIV-ID1, and TIV-ID2 groups, respectively. TIV-ID1 does not contain strain B2.

Immunogenicity

Subjects with Titers ≥ 1:80, ≥ 1:160, and ≥ 1:320

Combined Seropositive and Seronegative Status at Baseline

Titers ≥ 1:80

On D28, the percentages of subjects achieving post-vaccination antibody titers of ≥ 1:80 against strains A/H1N1 and AH3N2 in the QIV-ID group were similar to those in the TIV-ID groups and were > 90% in all groups, with an overall range from 91.4% (492/538) to 96.5% (520/539). The percentage of subjects achieving post-vaccination antibody titers of ≥ 1:80 against strain B1 in the QIV-ID group (69.9% [728/1041]) was similar to the percentage in the TIV-ID1 group (65.3% [352/539]), and higher than the percentage in the TIV-ID2 group (40.0% [213/533]). The percentage of subjects achieving post-vaccination antibody titers of ≥ 1:80 against strain B2 in the QIV-ID group (77.8% [810/1041]) was higher than the percentage in the TIV-ID1 group (53.9% [290/539]), and similar to the percentage in the TIV-ID2 group (73.7% [393/533]).

Titers ≥ 1:160

On D28 post-vaccination, the percentages of subjects achieving antibody titers of ≥ 1:160 against strains A/H1N1 and AH3N2 in the QIV-ID group were similar to those in the TIV-ID groups and were ≥ 80% in all groups with a range from 84.6% (389/460) to 91.6% (779/850). The percentage of subjects achieving post-vaccination antibody titers of ≥ 1:160 against strain B1 in the QIV-ID group (45.8% [376/821]) was similar to the percentage in the TIV-ID1 group (41.2% [180/437]), and higher than the percentage in the TIV-ID2 group (22.9% [100/437]). The percentage of subjects achieving post-vaccination antibody titers of ≥ 1:160 against strain B2 in the QIV-ID group (50.2% [414/824]) was higher than the percentage in the TIV-ID1 group (28.6% [127/444]), and similar to the percentage in the TIV-ID2 group (44.6% [184/413]).

Titers ≥ 1:320

Results were similar across the groups for each strain for the percentages of subjects achieving antibody titers ≥ 1:320; overall percentages were lower than for titers ≥ 1:160

Ethnicity

GMTs: On D28, GMTs for Hispanic or Latino subjects were generally similar to or higher than the GMTs for subjects who were not Hispanic or Latino.

Seroconversion: The percentages subjects who seroconverted were generally similar for subjects who were Hispanic or Latino and for subjects who were not Hispanic or Latino, in all trial groups for all strains. The differences in seroconversion rates (QIV-ID minus TIV-ID) were similar for subjects of either ethnicity for all strains.

Seroprotection: The seroprotection rates at 28 days after vaccination were similar for both ethnicities in all groups for all strains. The differences in seroprotection rates (QIV-ID minus TIV-ID) were similar for both ethnicities for all strains.

Sex

GMTs: On Day 28, GMTs for males were generally similar to or higher than the GMTS for females. The GMT ratios (QIV-ID / TIV-ID) were similar for both sexes for all strains.

Seroconversion: The seroconversion rates for females and males were similar for all trial groups and all 4 strains. The differences in seroconversion rates (QIV-ID minus TIV-ID) were similar for females and males for all strains.

Seroprotection: Seroprotection rates were similar for females and males on D0 and on D28 after vaccination, in all trial groups and for all strains. The differences in seroprotection rates (QIV-ID minus TIV-ID) were similar for males and females for all strains.

Baseline Seropositivity Status

GMTs: On D28, GMTs were generally higher for subjects who were seropositive at baseline compared to subjects who were seronegative at baseline.

Seroconversion: The percentages of subjects who seroconverted were higher for subjects who were baseline seronegative than those who were baseline seropositive for all trial groups and all strains. The differences in seroconversion rates (QIV-ID minus TIV-ID) were similar for subjects who were baseline seronegative and those who were baseline seropositive for all 4 strains.

Seroprotection: On D28, seroprotection rates of subjects who were seropositive at baseline were generally higher than or similar to those of subjects who were seronegative at baseline. The differences in seroprotection rates (QIV-ID minus TIV-ID) were higher for subjects who were seropositive at baseline for all strains except strain A/H3N2.

Observational Immunogenicity Objective

Injection Site Leakage

The presence of leakage during injection was observed in 46/1041 subjects in the QIV-ID group and in 38/1072 subjects in the pooled TIV-ID group (18/539 and 20/533 subjects in the TIV-ID1 and the TIV-ID2 groups, respectively) for the PPAS. Similar incidences of injection site leakage were observed in the FAS.

GMTs: On D28, GMTs were generally similar for subjects with or without injection site leakage in all trial groups for all strains. The GMT ratios (QIV-ID / TIV-ID) were similar for subjects with or without injection site leakage for all strains.

Seroconversion: Seroconversion rates on D28 after vaccination were generally similar for subjects with or without injection site leakage in all trial groups for all strains. The differences in seroconversion rates (QIV-ID minus TIV-ID) were similar for subjects with or without injection site leakage for all strains.

Seroprotection: On D28, seroprotection rates of subjects with injection site leakage were generally similar to those of subjects without injection site leakage. The differences in seroprotection rates (QIV-ID minus TIV-ID) were similar for subjects with or without injection site leakage for all strains.

Safety

Secondary Safety Objective

Solicited Injection Site Reactions

Within 7 days after vaccine injection, 1266/1656 (76.4%) subjects in the QIV-ID group and 1207/1658 (72.8%) subjects in the pooled TIV-ID groups (605/820 [73.8%] and 602/838 [71.8%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively) experienced at least one solicited injection site reaction.

Pain and pruritus after vaccine injection were the most frequently reported solicited injection site reactions. Pain was reported by 883/1656 (53.3%) subjects in the QIV-ID group and 815/1658 (49.2%) subjects in the pooled TIV-ID groups (395/820 [48.2%] and 420/838 [50.1%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). Pruritus was reported by 862/1656 (52.1%) subjects in the QIV-ID group and 746/1658 (45.0%) subjects in the pooled TIV-ID groups (372/820 [45.4%] and 374/838 [44.6%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). Erythema was reported less frequently, by between 32.1% and 36.7% of subjects in the vaccine groups. Swelling and induration were reported less frequently, but by slightly more subjects in the QIV-ID group (322/1655 [19.5%] and 282/1656 [17.0%], respectively) than by subjects in the pooled TIV-ID groups (244/1658 [14.7%] and 205/1657 [12.4%], respectively). Ecchymosis was reported by 43/1656 (2.6%) subjects in the QIV-ID group and 30/1658 (1.8%) subjects in the pooled TIV-ID groups.

Most solicited injection site reactions after vaccine injection were Grade 1 in intensity and started within 3 days of vaccine injection. Most occurred for 1 to 3 days and required no action to be taken.

Reports of Grade 3 reactions after vaccine injection were comparable across the trial groups, with Grade 3 pruritus reported most frequently. The percentage of subjects with Grade 3 pruritus in the QIV-ID group (2.8% [47/1656]) was similar to the percentage in the pooled TIV-ID groups (2.1% [34/1658]) (1.8% [15/820] and 19/838 [2.3%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). Other Grade 3 solicited injection site reactions were reported by ≤ 1.4% of subjects.

Medication and/or any medical intervention (health care provider contact, health care provider contact and medication, and hospitalization) were used infrequently to treat solicited injection site reactions. Medication to treat pain was used more frequently than for other solicited injection site reactions: 15/883 (1.7%) subjects in the QIV-ID group and 10/815 (1.2%) subjects in the pooled TIV-ID groups.

Grade 3 solicited injection site reactions which required health care provider contact (with or without medication) occurred rarely. A health care provider was contacted and medication administered for Grade 3 pain for 2/24 (8.3%) subjects in the QIV-ID group. A health care provider was contacted and medication administered for Grade 3 pruritus for 1/47 (2.1%) subject in the QIV-ID group. A health care provider was contacted for Grade 3 pain for 1/22 (4.5%) subject in the TIV-ID1 group. Only non-narcotic medication was used to treat solicited injection site reactions. No subjects were hospitalized for treatment of solicited injection site reactions in either trial group

Solicited Injections Site Reaction - Observational Safety Objectives (Non-inferiority)

The non-inferiority of QIV-ID to TIV-ID was demonstrated. The percentages of subjects experiencing at least 1 Grade 3 solicited injection site reaction were 4.0% (66/1656) and 3.1% (51/1658) for the QIV-ID and pooled TIV-ID groups, respectively. The upper bound of the 2-sided 95% CI on the ratio of the proportions was < 3. QIV-ID was at least as well tolerated as the 2 pooled TIV-ID reference vaccine groups.

Table S6: Comparison between QIV-ID and TIV-ID pooled groups in terms of all Grade 3 solicited injection site reactions combined during the solicited period - Safety analysis set

	QIV-ID (N=1672)			TIV-ID Pooled (N=1683)			Ratio of proportions QIV-ID/ TIV-ID pooled	95% CI For ratio	Non-inferiority (upper confidence level of ratio<3)
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**			
All Grade 3 solicited injection site reactions combined	66/1656	4.0	(3.1; 5.0)	51/1658	3.1	(2.3; 4.0)	1.30	(0.90; 1.86)	Yes

n: number of subjects experiencing the endpoint listed in the first column

M: number of subjects with available data for the relevant endpoint

The solicited injection site reactions include Ecchymosis, Erythema, Induration, Pain, Pruritus, and Swelling.

Exact 2-sided 95%CI for the single proportion is based on the Clopper-Pearson method.
The asymptotic 2-sided 95% CI for the ratio of proportions (relative risk) is based on the normal distribution

Solicited Systemic Reactions

The frequency of solicited systemic reactions was similar across the trial groups; there were 848/1656 (51.2%) subjects in the QIV-ID group and 823/1658 (49.6%) subjects in the pooled TIV-ID groups (395/820 [48.2%] and 428/838 [51.1%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively) who experienced at least 1 solicited systemic reaction.

The most common solicited systemic reactions reported in all trial groups were myalgia, headache, and malaise and the numbers and percentages of subjects were similar for the trial groups. For myalgia, the percentages were 34.1%, 29.0%, 31.1%, and 30.1% of subjects; for headache, the percentages were 33.1%, 31.3%, 33.2%, and 32.3% of subjects; for malaise, the percentages were 27.7%, 26.3%, 30.4%, and 28.4% of subjects in the QIV-ID, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively.

Reports of fever were low in all trial groups: 13/1649 (0.8%) subjects in the QIV-ID group and 10/1655 (0.6%) subjects in the TIV-ID pooled groups (6/819 [0.7%] and 4/836 [0.5%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). Grade 3 fever within the solicited period was reported by 3/1649 (0.2%) subjects in the QIV-ID group and 1/819 (0.1%) subject in the TIV-ID1.

Most of the solicited systemic reactions were Grade 1 in intensity and started within 3 days of vaccine injection. Most solicited systemic reactions occurred for 1 to 3 days, and no action was taken.

The percentages of subjects who reported Grade 3 reactions were low in all groups. The percentages reported for Grade 3 myalgia, headache, and malaise in the QIV-ID group (2.6%, 3.2%, and 3.0%, respectively) were similar to the percentages in the pooled TIV-ID groups (2.0%, 2.1%, and 2.2%, respectively).

Medication and any medical intervention (health care provider contact, health care provider contact and medication, and hospitalization) were used infrequently to treat solicited systemic reactions. Malaise was the solicited systemic reaction most frequently treated with any medical intervention: 6/459 (1.3%) subjects in the QIV-ID group and

4/471 (0.8%) subjects in the pooled TIV-ID groups (1/216 [0.5%] and 3/255 [1.2%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). Non-narcotic medication was most often used to treat headache and fever. Narcotic medication was not used to treat systemic reactions in the QIV-ID group, and was used infrequently in the pooled TIV-ID groups (2/34 [5.9%], 3/110 [2.7%], 2/16 [12.5%], and 2/5 [40.0%], for myalgia, headache, malaise, and shivering, respectively).

Any medical intervention administered for Grade 3 solicited systemic reactions is summarized below:

- In subjects with Grade 3 myalgia, health care provider was contacted and medication was administered for 3/43 (7.0%) subjects in the QIV-ID groups and for 1/33 (3.0%) subject in the pooled TIV-ID groups (1/12 [8.3%] subject in the TIV-ID1 group).
- In subjects with Grade 3 headache, health care provider was contacted and medication was administered for 2/53 (3.8%) subjects in the QIV-ID group and for 1/35 (2.9%) subject in the pooled TIV-ID groups (1/20 [5.0%] subject in the TIV-ID1 group). Subject 003-10066 in the QIV-ID group (1/53 [1.9%]) was hospitalized for treatment of a Grade 3 headache (see Section 9, Table 9.92 and Appendix 16, Listing 7.3).
- In subjects with Grade 3 malaise, health care provider was contacted and medication was administered for 6/49 (12.2%) subjects in the QIV-ID group and for 4/36 (11.1%) of subjects in the pooled TIV-ID groups (1/15 [6.7%] and 3/21 [14.3%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively).
- In subjects with Grade 3 shivering, health care provider was contacted for 1/24 (4.2%) subject and medication was administered for 3/24 (12.5%) subjects in the QIV-ID group.
- In subjects with Grade 3 fever, there was no medical intervention.

***Solicited Systemic Reactions - Non-inferiority (Observational Objective*)**

The non-inferiority of QIV-ID to TIV-ID was demonstrated. The percentages of subjects experiencing at least 1 Grade 2 or 3 solicited systemic reaction were 21.2% (351/1656) and 20.2% (335/1658) for the QIV-ID and pooled TIV-ID groups, respectively. The upper bound of the 2-sided 95% CI on the ratio of the proportions was < 3. QIV-ID was at least as well tolerated as the 2 pooled TIV-ID reference vaccine groups in terms of all Grade 2 or 3 solicited systemic reactions.

Table S7: Grade 2 or 3 solicited systemic reactions combined during the solicited period - Safety analysis set

Subjects experiencing at least one:	QIV-ID (N=1672)			TIV-ID Pooled (N=1683)			Ratio of proportions QIV-ID/TIV-ID pooled	95% CI For ratio	Non-inferiority (upper confidence level of ratio<3)
	n/M	%	(95% CI)	n/M	%	(95% CI)			
Grade 2 or 3 Solicited Systemic Reaction	351/1656	21.2	(19.2; 23.2)	335/1658	20.2	(18.3; 22.2)	1.05	(0.92; 1.20)	Yes

n: number of subjects experiencing the endpoint listed in the first column

M: number of subjects with available data for the relevant endpoint

The solicited systemic reactions include Fever, Headache, Malaise, Myalgia, and Shivering.

Exact 2-sided 95%CI for the single proportion is based on the Clopper-Pearson method.

The asymptotic 2-sided 95% CI for the ratio of proportions (relative risk) is based on the normal distribution.

Immediate Unsolicited AEs

The number and percentage of subjects reporting immediate unsolicited AEs were similar for the trial groups: 7/1672 (0.4%) subjects in the QIV-ID group and 6/1683 (0.4%) subjects in the pooled TIV-ID groups (2/837 [0.2%] and 4/846 [0.5%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively).

Most of these immediate unsolicited AEs were considered related to vaccination. Immediate unsolicited ARs were reported in 6/1672 (0.4%) subjects in the QIV-ID group and 5/1683 (0.3%) subjects in the pooled TIV-ID groups (2/837 [0.2%] and 3/846 [0.4%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively).

Unsolicited Injection Site Reactions

Unsolicited non-serious injection site reactions were reported by 27/1672 (1.6%) subjects in the QIV-ID group and by 15/1683 (0.9%) subjects in the pooled TIV-ID groups (4/837 [0.5%] and 11/846 [1.3%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively).

The most frequently reported unsolicited injection site reactions were injection site hemorrhage and injection site warmth. Injection site hemorrhage was reported in 3/1672 (0.2%) subjects in the QIV-ID group and in 6/1683 (0.4%) subjects in the pooled TIV-ID groups (2/837 [0.2%] and 4/846 [0.5%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). Injection site warmth was reported in 7/1672 (0.4%) subjects in the QIV-ID group and in 2/1683 (0.1%) subjects in the pooled TIV-ID groups (2/846 [0.2%] subjects were in the TIV-ID2 group).Most unsolicited injection site reactions were Grade 1 started within 3 days of vaccine injection, occurred for 1 to 3 days, and required no action to be taken. There were no Grade 3 unsolicited non-serious injection site ARs reported within 28 days after vaccine injection.

Unsolicited Systemic AEs

Unsolicited non-serious systemic AEs were reported by 364/1672 (21.8%) subjects in the QIV-ID group and 372/1683 (22.1%) subjects in the pooled TIV-ID groups (166/837 [19.8%] and 206/846 [24.3%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). The most common unsolicited systemic AE within 28 days after vaccine injection was cough, in the SOC of Respiratory, Thoracic and Mediastinal Disorders: 62/1672 (3.7%) subjects in the QIV-ID group and 57/1683 (3.4%) subjects in the pooled TIV-ID groups (27/837 [3.2%] and 30/846 [3.5%] in the TIV-ID1 and TIV-ID2 groups, respectively). Headache (SOC of Nervous System Disorders) and oropharyngeal pain (SOC of Respiratory, Thoracic and Mediastinal Disorders) were also frequently reported. The percentages of subjects with Grade 3 unsolicited non-serious systemic AEs were comparable between the trial groups. Grade 3 unsolicited non-serious systemic AEs were reported by 59/1672 (3.5%) subjects in the QIV-ID group and 76/1683 (4.5%) subjects in the pooled TIV-ID groups (32/837 [3.8%] and 44/846 [5.2%] in the TIV-ID1 and TIV-ID2 groups, respectively).

Unsolicited Systemic ARs

Unsolicited non-serious systemic ARs were reported by 49/1672 (2.9%) subjects in the QIV-ID group and 46/1683 (2.7%) subjects in the pooled TIV-ID groups (18/837 [2.2%] and 28/846 [3.3%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). The majority of the unsolicited non-serious systemic ARs were of Grade 1 or Grade 2 intensity. Grade 3 unsolicited non-serious systemic ARs were reported infrequently in the trial groups, by 7/1672 (0.4%) subjects in the QIV-ID group and 5/1683 (0.3%) subjects in the pooled TIV-ID groups (1/837 [0.1%] and 4/846 [0.5%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively).

The ARs of Grade 3 intensity included cough, dyspepsia, insomnia, migraine, muscle weakness, muscular spasms, lymphadenopathy, diarrhea, vomiting, muscular stiffness (neck and shoulder blades), neck pain, pain in extremity (fingers), and influenza.

AEs Leading to Withdrawal from the Study (from D0 through D28)

Pneumonia (in the SOC of Infections and Infestations) that led to study discontinuation was reported for Subject [redacted] in the TIV-ID2 group within 28 days after vaccine injection. [redacted] The SAE of pneumonia began on D24 and lasted for 17 days; the subject was hospitalized. The SAE was considered not related to the vaccine injection by the Investigator. During the hospitalization, this subject also experienced an SAE of hypercapnic respiratory failure. Three additional SAEs were collected for this subject subsequent to his discontinuation from the trial: dehydration, hypotension, and post-procedure respiratory distress. These other SAEs were also considered not related to the vaccine injection by the Investigator.

AEs of Medical Interest (AEMIs)

Immediate Unsolicited Non-serious AEMIs

The number and percentage of subjects experiencing at least 1 immediate unsolicited non-serious AEMI was 3/1672 (0.2%) subjects in the QIV-ID group and 1/1683 (< 0.1%) subject in the pooled TIV-ID groups (1 subject [0.1%] in the TIV-ID1 group). These immediate AEMIs were neurological events, and were considered related to the vaccine. The AEMIs included presyncope and dizziness. There were no Grade 3 immediate unsolicited non-serious AEMIs reported in the trial.

Unsolicited Non-serious Injection Site AEMIs

The numbers and percentages of subjects that experienced at least 1 unsolicited non-serious injection site AEMI were 10/1672 (0.6%) subjects in the QIV-ID group and 8/1683 (0.5%) subjects in the pooled TIV-ID groups (3/837 [0.4%] and /846 [0.6%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively).

Injection site hemorrhage (category of injection site trauma), was the most frequently reported unsolicited non-serious injection site AEMI, reported by 3/1672 (0.2%) subjects in the QIV-ID group and 6/1683 (0.4%) subjects in the pooled TIV-ID groups (2/837 [0.2%] and 4/846 [0.5%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). Injection site rash, injection site urticaria, mechanical urticaria, paresthesia, and rash (category of allergic skin disorder at the injection site), were each reported by 1/1672 (< 0.1%) subject in the QIV-ID group, but were not reported by any subject in the TIV-ID groups. There were no Grade 3 unsolicited non-serious injection site ARMIs reported in the trial

Non-serious Systemic AEMIs

The numbers and percentages of subjects that experienced at least 1 unsolicited non-serious systemic AEMI were 17/1672 (1.0%) subjects in the QIV-ID group and 16/1683 (1.0%) subjects in the pooled TIV-ID groups (7/837 [0.8%] and 9/846 [1.1%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). Neurological events were reported in 12/1672 (0.7%) subjects in the QIV-ID group and 11/1683 (0.7%) subjects in the pooled TIV-ID groups (5/837 [0.6%] and 6/846 [0.7%] subjects in the TIV-ID1 and TIVID2 groups, respectively). Dizziness was the neurological event reported most frequently. Allergic events were reported as AEMIs by similar percentages of subjects in the trial groups. Allergic events were reported by 5 (0.3%) subjects in both the QIV-ID and pooled TIV-ID groups. Urticaria was the allergic event reported most frequently.

Non-serious Systemic ARs of Medical Interest (ARMIs)

The numbers and percentages of subjects that experienced at least 1 unsolicited non-serious systemic ARMI were 10/1672 (0.6%) subjects in the QIV-ID group and 7/1683 (0.4%) subjects in the pooled TIV-ID groups (3/837 [0.4%] and 4/846 [0.5%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). Neurological events were reported as ARMIs most frequently, by 9/1672 (0.5%) subjects in the QIV-ID group and 6/1683 (0.4%) subjects in the pooled TIV-ID groups (3 [0.4%] subjects each in the TIV-ID1 and TIVID2 groups). The most frequently reported neurological event was dizziness, reported by 5/1672 (0.3%) of subjects in the QIV-ID group and by 3/1683 (0.2%) subjects in the pooled TIV-ID groups (1/837 [0.1%] and 2/846 [0.2%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively). Paresthesia and presyncope were each reported by 2/1672 (0.1%) subjects in the QIV-ID group and by 1/837 (0.1%) subject in the TIV-ID1 group. Hypersensitivity and vertigo were each reported by 1/846 (0.1%) subject in the TIV-ID2 group. Rash generalized and hypoesthesia were each reported by 1/1672 (<0.1%) subject in the QIV-ID group.

Deaths

D0 Through D28

No deaths occurred within 28 days after vaccine injection.

6-Month Follow-up Period

There was 1 death reported for a subject in the QIV-ID group. Subject [redacted] died of acute coronary myocardial infarction symptoms 177 days after study vaccine; this death was considered not related to the study vaccine by the Investigator.

SAEs Other than Deaths

D0 Through D28

There were 6/1672 (0.4%) subjects who reported 6 SAEs in the QIV-ID group and 5/1683 (0.3%) subjects who reported 5 SAEs in the pooled TIV-ID groups (2/837 [0.2%] and 3/846 [0.4%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively) between D0 and D28 after vaccine injection. All SAEs required or prolonged inpatient hospitalization and were considered not related to the vaccine injection by the Investigator.

6-Month Follow-up Period

There were 13/1672 (0.8%) subjects who reported 15 SAEs in the QIV-ID group and 21/1683 (1.2%) subjects who reported 25 SAEs in the pooled TIV-ID groups (12/837 [1.4%] and 9/846 [1.1%] subjects in the TIV-ID1 and TIV-ID2 groups, respectively) from D29 until the end of the trial. All SAEs required or prolonged inpatient hospitalization and were considered unrelated to the vaccine injection by the Investigator.

Safety by Covariate Factors

Age

Solicited Injection Site Reactions

Injection site pain was reported more frequently for subjects 18 to < 49 years old than subjects 50 to < 64 years old in all trial groups. The numbers and percentages of injection site pain for subjects 18 to < 49 years old were 620/1099 (56.4%), 283/543 (52.1%), 309/555 (55.7%), and 592/1098 (53.9%) for the QIV-ID, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively. The proportions of injection site pain for subjects 50 to < 64 years old were 263/557 (47.2%), 112/277 (40.4%), 111/283 (39.2%), and 223/560 (39.8%) for the QIV-ID, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively. Injection site pruritus was reported more frequently in subjects 18 to < 49 years old (600/1099 [54.6%]) than in subjects 50 to < 64 years old (262/557 [47.0%]) in the QIV-ID group.

Sex

Solicited Injection Site Reactions

Injection site pain was reported by more females (625/1019 [61.3%], 289/496 [58.3%], 302/523 [57.7%], and 591/1019 [58.0%]) than males (258/637 [40.5%], 106/324 [32.7%], 118/315 [37.5%], and 224/639 [35.1%]) in the QIV-ID, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively.

Injection site pruritus was reported by more females (584/1019 [57.3%], 248/496 [50.0%], 248/523 [47.4%], and 496/1019 [48.7%]) than males (278/637 [43.6%], 124/324 [38.3%], 126/315 [40.0%], and 250/639 [39.1%]) in the QIV-ID, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively.

Erythema was generally reported by more females (410/1019 [40.2%], 179/496 [36.1%], 180/523 [34.4.%], and 359/1019 [35.2%]) than males (197/637 [30.9%], 100/324 [30.9%], 89/315 [28.3%], and 189/639 [29.6%]) in the QIV-ID1, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively.

Induration was reported by more females (213/1019 [20.9%], 81/496 [16.3%], 64/523 [12.2%], and 145/1019 [14.2%]) than males (69/637 [10.8%], 30/324 [9.3%], 30/314 [9.6%], and 60/638 [9.4%]), in the QIV-ID, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively.

Solicited Systemic Reactions

Headache was reported by more females (387/1019 [38.0%], 182/496 [36.7%], 197/523 [37.7%], and 379/1019 [37.2%]) than in males (161/637 [25.3%], 75/324 [23.1%], 81/315 [25.7%], and 156/639 [24.4%]) in the QIV-ID, TIV-ID1, TIV-ID2 and pooled TIV-ID groups, respectively.

Myalgia was reported by more females (381/1019 [37.4%]. 161/496 [32.5%]), 171/523 [32.7%], and 332/1019 [32.6%]) than males (183/637 [28.7%], 77/324 [23.8%], 90/315 [28.6%], and 167/639 [26.1%]) in the QIV-ID, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively.

Malaise was reported by more females (316/1019 [31.0%], 146/496 [29.4%], 178/523 [34.0%], and 324/1019 [31.8%]) than males (143/637 [22.4%], 70/324 [21.6%], 77/315 [24.4%], and 147/639 [23.0%]) in the QIV-ID, TIV-ID1, TIV-ID2, and pooled TIV-ID groups, respectively.

Pregnancy

There were 15 reported pregnancies. Of these, 7 were reported in the QIV-ID group and 8 were reported in the TIV-ID groups.

The pregnancy outcome was reported for 4 of the 7 subjects that were administered QIV-ID (1 outcome was reported prior to database lock, 3 outcomes were reported after database lock). Subject [redacted] gave birth to a healthy baby, Subject [redacted] voluntarily terminated her pregnancy (this subject had no complication of pregnancy), and 2 subjects had premature delivery:

- Subject [redacted], age 34 with a history of secondary amenorrhea, asthma, hypertension, and type II diabetes, experienced an SAE of incompetent cervix. She delivered her baby prematurely [redacted] while enrolled in the study. The birth outcome was normal. The event of incompetent cervix was reported by the Investigator as unrelated to the investigational vaccine.
- Subject [redacted] age 35 with a medical history of a spontaneous abortion, gastric bypass surgery, and ongoing anemia, had a non-serious AE of gestational diabetes. [redacted] She received the vaccine 10 weeks before pregnancy. The birth outcome was live birth with congenital abnormality specified as severe stenosis with endocardial fibroelastosis. Follow up information on the baby has been requested.

Among the 8 pregnancies reported in subjects after any TIV-ID administration, the outcomes were documented in 5 subjects after database lock. Subjects [redacted] (in the TIV-ID2 group) delivered healthy babies. The outcome for the remaining 3 pregnancy cases is not available.

Conclusions:

- QIV-ID induced statistically non-inferior GMTs and seroconversion rates for each A strain (H1N1 and H3N2) and each B lineage strain (Texas and Brisbane) compared with the control TIV-ID containing the respective strains.
- QIV-ID induced an immune response to each B strain, as assessed by GMTs and seroconversion rates, that is superior to the response induced by the TIV-ID that does not contain the corresponding B strain.
- Safety profiles of QIV-ID and TIV-ID did not differ, as assessed by rates of solicited injection-site and systemic reactions, unsolicited AEs, and SAEs. All 52 SAEs were reported as unrelated to vaccination and no AESI were identified.
- QIV-ID was non-inferior to pooled TIV-ID in terms of all Grade 2 or 3 solicited systemic reactions (21.2% vs. 20.2%).
- QIV-ID was non-inferior to pooled TIV-ID in terms of all Grade 3 solicited injection site reactions combined (4% vs. 3.1%).
- QIV-ID was as immunogenic and as well-tolerated as TIV-ID in a healthy adult population. By providing immunogenicity to a second B strain and thereby avoiding the problem of mismatched B strains, over time, QIV-ID may provide improved protection against influenza.

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