



NCT03233217

## **STATISTICAL ANALYSIS PLAN**

**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**

**SP0178**

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Page 1

## TABLE OF CONTENTS

<b>STATISTICAL ANALYSIS PLAN .....</b>	<b>1</b>
<b>TABLE OF CONTENTS.....</b>	<b>2</b>
<b>LIST OF ABBREVIATIONS AND DEFINITION OF TERMS.....</b>	<b>5</b>
<b>1 OVERVIEW AND INVESTIGATIONAL PLAN .....</b>	<b>6</b>
1.1 STUDY DESIGN AND RANDOMIZATION .....	6
1.2 OBJECTIVES.....	7
1.3 DETERMINATION OF SAMPLE SIZE.....	7
1.4 STUDY PLAN.....	7
1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL.....	10
1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN .....	10
<b>2 STATISTICAL AND ANALYTICAL PROCEDURES .....</b>	<b>11</b>
2.1 ANALYSIS ENDPOINTS .....	11
2.1.1 Demographic and baseline characteristics .....	11
2.1.2 Prior or concomitant medications.....	12
2.1.3 Efficacy endpoints .....	13
2.1.4 Safety endpoints .....	13
2.1.4.1 Adverse events variables .....	14
2.1.4.2 Laboratory safety variables .....	22
2.1.4.3 Vital signs variables .....	22
2.1.4.4 Electrocardiogram variables .....	22
2.1.5 Immunogenicity endpoints .....	22
2.2 DISPOSITION OF PATIENTS .....	23
2.2.1 Randomization and drug dispensing irregularities.....	24
2.3 ANALYSIS SETS .....	25
2.3.1 Full analysis set.....	26
2.3.2 Per-protocol analysis set.....	26
2.3.3 Safety analysis set .....	26
2.4 STATISTICAL METHODS .....	27

2.4.1	Demographics and baseline characteristics .....	27
2.4.2	Prior or concomitant medications.....	27
2.4.3	Analyses of efficacy endpoints.....	27
2.4.4	Analyses of safety data.....	27
2.4.4.1	Analyses of adverse events .....	28
2.4.4.2	Deaths .....	30
2.4.4.3	Analyses of laboratory variables .....	30
2.4.4.4	Analyses of vital sign variables .....	30
2.4.4.5	Analyses of body stature variables .....	30
2.4.4.6	Analyses of electrocardiogram variables .....	31
2.4.5	Analyses of immunogenicity data .....	31
2.5	DATA HANDLING CONVENTIONS .....	33
2.5.1	General conventions .....	33
2.5.1.1	Duration of the study.....	33
2.5.1.2	Subject Duration.....	33
2.5.1.3	Time interval.....	34
2.5.1.4	Influenza vaccination during the previous influenza season .....	34
2.5.2	Data handling conventions for safety variables .....	34
2.5.2.1	Solicited reactions .....	34
2.5.2.2	Unsolicited non-serious AEs .....	37
2.5.2.3	Serious adverse events .....	38
2.5.2.4	Other safety endpoints.....	39
2.5.3	Data handling conventions for immunogenicity variables.....	40
2.5.3.1	Computed values for analysis.....	40
2.5.3.2	Seroprotection.....	40
2.5.3.3	Fold-rise .....	41
2.5.3.4	Seroconversion .....	41
2.5.4	Missing data .....	41
2.5.5	Windows for time points.....	42
2.5.6	Unscheduled visits .....	42
2.5.7	Pooling of centers for statistical analyses.....	43
2.5.8	Statistical technical issues .....	43
2.5.8.1	Confidence interval for the individual group GMT and GMT ratio .....	43
2.5.8.2	Confidence interval for the GMT ratio between 2 groups .....	43
2.5.8.3	Confidence interval for the single proportions .....	44
2.5.8.4	Confidence interval of the difference in proportions .....	44
<b>3</b>	<b>INTERIM ANALYSIS .....</b>	<b>45</b>
<b>4</b>	<b>DATABASE LOCK.....</b>	<b>46</b>
<b>5</b>	<b>SOFTWARE DOCUMENTATION .....</b>	<b>47</b>
<b>6</b>	<b>REFERENCES.....</b>	<b>48</b>

**7**      **LIST OF APPENDICES** ..... **49**

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AESI:	adverse events of special interest
AR:	adverse reaction
BL:	blood sample
BMI:	body mass index
CRB:	case report book
D:	Day
eCRF:	electronic case report form
EDC:	electronic data capture
FAS:	full analysis set
GMT:	geometric mean titer
GMTR:	geometric mean titer ratio
HA:	hemagglutination
HAI:	hemagglutination inhibition
ICH:	International Council for Harmonisation
IM:	intramuscular
IRT:	interactive response technology
LLOQ:	lower limit of quantitation
MedDRA:	Medical Dictionary for Regulatory Activities
NIID:	Japan National Institute of Infectious Diseases
NSAID:	non-steroidal anti-inflammatory drug
PPAS:	per-protocol analysis set
PT:	Preferred Term, preferred term
QIV-HD:	high-dose quadrivalent influenza vaccine
QIV-SD:	standard-dose quadrivalent influenza vaccine
RBC:	red blood cell
RCDC:	Reverse Cumulative Distribution Curve
SAE:	serious adverse event
SafAS:	safety analysis set
SAP:	statistical analysis plan
SC:	subcutaneous
SOC:	System Organ Class
UAR:	unexpected adverse reaction
ULOQ:	upper limit of quantitation
V:	Visit
VRBPAC:	Vaccines and Related Biological Products Advisory Committee
WHO:	World Health Organization

# 1 OVERVIEW AND INVESTIGATIONAL PLAN

## 1.1 STUDY DESIGN AND RANDOMIZATION

QHD00008-DFI15130 is a Phase I/II, randomized, modified double-blind, multi-center study to be 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 will serve as a control arm.

A total of 10 subjects will be randomized into 2 groups in Cohort 1, as shown below:

- QIV-HD by IM route: n = 5
- QIV-HD by SC route: n = 5

A total of 165 subjects will be randomized into 3 groups in Cohort 2, as shown below:

- Group 1 (QIV-HD by IM route): n = 55
- Group 2 (QIV-HD by SC route): n = 55
- Group 3 (QIV-SD by SC route): n = 55

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 will be randomized 1:1 to receive either QIV-HD by IM route or QIV-HD by SC route (Cohort 1). After review of the unblinded 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) will occur (see Section 5.1.6 of the protocol).

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

All subjects will provide a pre-vaccination (baseline) blood sample at Visit (V) 1 (D0) and a post-vaccination blood sample at V3 (D28 [+ 7 days]) for hemagglutination inhibition (HAI) testing.

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

Note: AESIs will have the same detailed information collected as SAEs. These include 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) will be 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 will be performed without stratification.

For Cohort 2, IRT will also be 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 will be stratified by value of age (<75, ≥75), sex (Male, Female), and sites.

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

## 1.2 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.

## 1.3 DETERMINATION OF SAMPLE SIZE

A total of 175 subjects are planned to be enrolled in the study.

A total of 10 subjects are planned to be enrolled and randomized into 2 groups in Cohort 1, as shown below:

- QIV-HD by IM route: n = 5
- QIV-HD by SC route: n = 5

A total of 165 subjects are planned to be enrolled and randomized into 3 groups in Cohort 2, as shown below:

- Group 1 (QIV-HD by IM route): n = 55
- Group 2 (QIV-HD by SC route): n = 55
- Group 3 (QIV-SD by SC route): n = 55

There is no statistical powered hypothesis test for sample size calculation.

## 1.4 STUDY PLAN

The study plan is summarized in [Table 1](#).

## **Vaccination**

All eligible subjects in Cohort 1 will be randomized to receive a single injection of either QIV-HD by IM route or QIV-HD by SC route at V1 (D0).

All eligible subjects in Cohort 2 will be randomized to receive a single injection of either QIV-HD by IM route, QIV-HD by SC route, or QIV-SD by SC route at V1 (D0).

## **Blood Sampling**

All subjects will provide a pre-vaccination blood sample at V1 (D0) and a post-vaccination blood sample at V3 (D28 [+ 7 days]).

## **Collection of Safety Data**

Subjects will be asked to notify the site immediately about any potential SAEs and AESIs at any time during the study.

All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time will be recorded as immediate unsolicited systemic AEs in the case report book (CRB).

Subjects will record information about solicited reactions (D0 to D7), unsolicited AEs (D0 to V3), SAEs (D0 to V3), and AESIs (D0 to V3) in a diary card.

Subjects will return to the site at V2 (D8 [+ 2 days]). Staff will review the recorded solicited reactions and unsolicited AEs, and determine whether the subject experienced any SAEs and AESIs not yet reported.

Staff will review the safety data (V2 to V3) with subjects at V3 (D28 [+ 7 days]).

**Table 1 – Study Procedures**

Phase I/II Study, 3 Visits, 1 Vaccination, 2 Blood Samples, 28 Days Duration per Subject

Visit/Contact	Visit 1 (V1)	Visit 2 (V2)	Visit 3 (V3)
<b>Study timelines (days)</b>	Day 0 (D0)	Day 8 (D8)	Day 28 (D28)
<b>Time windows (days)</b>	NA	[+ 2 days]	[+ 7 days]
Informed consent	X		
Inclusion/exclusion criteria	X		
Collection of demographic data	X		
Medical history	X		
History of seasonal influenza vaccination	X		
Reportable concomitant medications	X	X	X
Physical examination <sup>a</sup>	X		
Height	X		
Body weight	X		
Contacting interactive response technology	X		X
Randomization/allocation of subject number	X		
Blood sampling (BL), 10 mL	BL1 <sup>b</sup>		BL2
Vaccination	X		
Immediate surveillance (30 min)	X		
Diary card provided	X <sup>c</sup>	X <sup>d</sup>	
Recording of solicited injection site & systemic reactions	D0-D7		
Collection of unsolicited adverse events	D0-V3		
Diary card collected and reviewed		X <sup>e</sup>	X <sup>f</sup>
Study termination record			X
Collection of SAEs and AESIs <sup>g</sup>	To be reported at any time during the study		

AE = adverse event, AESI = adverse event of special interest, SAE = serious adverse event

<sup>a</sup> Targeted physical examination based on medical history will be performed at V1. Targeted physical examination may also be performed at V2 and V3, as necessary.

<sup>b</sup> Collection of the first blood sample (BL1) to occur before vaccination.

<sup>c</sup> Subjects will use this diary card to record information about solicited reactions from D0 to D7, unsolicited AEs, SAEs, and AESIs from D0 to V2 after vaccination.

<sup>d</sup> Subjects will use this diary card to record information about unsolicited AEs, SAEs, and AESIs from V2 to V3.

<sup>e</sup> Staff will collect the diary card at V2, and review the solicited reactions, unsolicited AEs, concomitant medications, SAEs, and AESIs.

<sup>f</sup> Staff will collect the diary card at V3, and review any solicited reactions ongoing after V2, unsolicited AEs, concomitant medications, SAEs, and AESIs.

<sup>g</sup> AESIs will have the same detailed information collected as SAEs. These include new onset of Guillain-Barré syndrome, encephalitis/myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis.

## **1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL**

There was no protocol amendment when this version 1.0 of statistical analysis plan (SAP) was published.

## **1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN**

Not applicable

## 2 STATISTICAL AND ANALYTICAL PROCEDURES

### 2.1 ANALYSIS ENDPOINTS

#### 2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value obtained at V1 (D0) before the vaccination.

All baseline safety and immunogenicity parameters are presented along with the summary statistics at pre-vaccination in the safety and immunogenicity sections ([Section 2.4.4](#) and [Section 2.4.5](#)).

##### *Demographic characteristics*

Demographic variables are sex (Male, Female), race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Unknown), age in years (quantitative and qualitative variable: 65-<75 and  $\geq 75$  years). Demographics data (Date of Birth, Sex and Race) are recorded at V1 (D0).

##### *Medical history*

At the time of enrollment, subjects will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document and the medical history module of the CRB.

Dates, medications, and body systems are not to be recorded, and if the information is collected, it will not be coded.

For each condition, the data collected will be limited to:

- Diagnosis (this is preferable to reporting signs and symptoms)
- Presence or absence of the condition at enrollment

##### *Disease characteristics at baseline*

No disease characteristics data at baseline will be obtained in the study.

##### *Influenza vaccination history*

History of seasonal influenza vaccination and any possible reactions to this vaccination in the previous year are recorded at V1 (D0).

### ***Body stature***

Body stature at baseline includes weight in kilograms (quantitative variable), and body mass index (BMI) in kilograms divided by the square of the body height in meters ( $\text{kg/m}^2$ ) (quantitative variable and qualitative variable:  $<18.5$ ,  $18.5-<25.0$  and  $25.0 \leq \text{kg/m}^2$ ). BMI is derived using weight and height measured at V1.

### ***Immunogenicity at baseline***

Approximately 10 mL of blood sample (BL) will be taken for the assessment of immunogenicity as a baseline value at V1 (D0).

Any technical details related to computation, dates, and imputations for missing dates are described in [Section 2.5](#).

## **2.1.2 Prior or concomitant medications**

### **Ongoing medication**

At the time of enrollment, ongoing medications including other therapies (e.g., blood products), should be recorded in the source document as well as new medications prescribed for new medical conditions/AEs during study participation.

Documentation in the CRB of concomitant medication will be limited to specific categories of medication of interest beginning on the day of vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRB from the day of vaccination to the end of the study (D28 [+ 7 days]).

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the antibody response to vaccination. Four standard categories of reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (e.g., antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs])
- Category 2: medications impacting or that may have an impact on the immune response (e.g., other vaccines, blood products, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors)
- Category 3: medications impacting or that may have an impact on both the safety and the immune response (e.g., steroids/corticosteroids)
- Category 4: the statin family of anti-hyperlipidemia medications (e.g., atorvastatin, rosuvastatin, simvastatin, pravastatin, and fluvastatin)

The information reported in the CRB for each reported medication will be limited to:

- Trade name or generic name

- Origin of prescription: prophylaxis Yes/No. Medication(s) prescribed for AE prophylaxis will be recorded in the Action Taken of the AE collection tables.
- Medication category
- Start and stop dates

Dosage and administration route will not be recorded.

Homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded.

Medication(s) given in response to an AE will be captured in the "Action Taken" Section of the AE CRF only. No details will be recorded on the concomitant medication(s) CRF unless the medication(s) received belongs to one of the prelisted categories. Medication(s) will not be coded.

### **Restricted treatments during the study period**

- Immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks)
- Immune globulins, blood or blood-derived products
- Any other vaccines

### **2.1.3 Efficacy endpoints**

No clinical efficacy data will be obtained in the study.

### **2.1.4 Safety endpoints**

The endpoints for the evaluation of safety are:

- 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 (D0 through D7) 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 (D0 through D28) 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)

#### **2.1.4.1 Adverse events variables**

##### **2.1.4.1.1 Safety Definitions**

The following definitions are taken from the ICH E2A Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

#### **Adverse Event (AE):**

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Therefore an AE may be:

- A new illness
- The worsening of a pre-existing condition
- An effect of the vaccination, including the comparator
- A combination of the above

All AEs include serious and non-serious AEs.

Surgical procedures are not AEs; they are the action taken to treat a medical condition. It is the condition leading to the action taken that is the AE (if it occurs during the study period).

Pre-existing medical conditions are not to be reported as AEs. However, if a pre-existing condition worsens in frequency or intensity, or if in the assessment of the treating physician there is a change in its clinical significance, this change should be reported as an AE (exacerbation). This applies equally to recurring episodes of pre-existing conditions (e.g., asthma) if the frequency or intensity increases post-vaccination.

#### **Serious Adverse Event (SAE):**

Serious and severe are not synonymous. The term severe is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as serious which is based on subject / event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening<sup>a</sup>
- Requires inpatient hospitalization or prolongation of existing hospitalization<sup>b</sup>
- Results in persistent or significant disability/incapacity<sup>c</sup>
- Is a congenital anomaly/birth defect
- Is an important medical event<sup>d</sup>

*a* The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

*b* All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of hospitalization planned before inclusion into the study or outpatient treatment with no hospitalization.

*c* "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

*d* Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse, new onset diabetes or autoimmune disease.

### **Adverse Reaction (AR):**

All noxious and unintended responses to a medicinal product related to any dose should be considered ARs.

(The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility)

### **Unexpected Adverse Reaction (UAR):**

An unexpected adverse reaction is an AR, the nature or severity of which is not consistent with the applicable product information (e.g., IB for an unapproved investigational medicinal product).

The following additional definitions are used by the Sponsor:

### **Solicited Reaction:**

A solicited reaction is an event that is prelisted in the CRB. The assessment of these AEs post-vaccination is mandatory. A solicited event is defined by a combination of:

- Symptom and
- Onset post-vaccination

e.g., injection site pain between D0 and D7 post-vaccination, or headache between D0 and D7.

A solicited reaction is therefore an AR observed and reported under the conditions (symptom and onset) prelisted (i.e., solicited) in the CRB and considered as related to the product administered.

### **Unsolicited AE/AR:**

An unsolicited AE is an observed AE that does not fulfill the conditions prelisted in the CRB in terms of symptom and/or onset post-vaccination, i.e., excluding solicited reactions, e.g., if headache between D0 and D7 is a solicited reaction (i.e., prelisted in the CRB), then a headache starting on D7 is a solicited reaction, whereas headache starting on D8 post-vaccination is an unsolicited AE. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

### **Injection Site Reaction:**

An injection site reaction is an AR at and around the injection site. Injection site reactions are commonly inflammatory reactions. They are considered to be related to the product administered.

### **Systemic AE:**

Systemic AEs are all AEs that are not injection site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination site, e.g., erythema that is localized but that is not at the injection site.

### **Adverse Events of Special Interest (AESIs):**

An AESI is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (e.g., regulators) might also be warranted.

#### **2.1.4.1.2 Safety assessment methods**

At V1, the Investigator or a delegate will perform a targeted physical examination based on medical history.

At V2 and V3, the Investigator or a delegate may perform a targeted physical examination, as necessary, and will ask the subject about any solicited reactions and unsolicited AEs recorded in the diary card, as well as about any other AEs that may have occurred since the previous visit.

All relevant data will be transcribed into the CRB according to the instructions provided by the Sponsor.

##### **2.1.4.1.2.1 Immediate post-vaccination surveillance period**

Subjects will be kept under observation for 30 minutes after vaccination to ensure their safety. The post-vaccination surveillance should be documented in the source document. Any AE that

occurs during this period will be noted on the source document and recorded in the CRB, as follows:

- Unsolicited systemic AEs will be recorded as immediate AEs in the CRB (presence marked as “yes” and details collected).
- Solicited and unsolicited injection site reactions and solicited systemic reactions will be recorded and analyzed as starting on the day of vaccination.
- Any SAE occurred during the first 30 minutes post-vaccination will be reported in the same way as any other SAE and to the Sponsor, according to the procedures described in Section 10 of the protocol.

#### 2.1.4.1.2.2 Reactogenicity (Solicited reactions from Day 0 to Day 7 after vaccination)

After vaccination, subjects will be provided with a safety diary card, a digital thermometer, and a flexible ruler, and will be instructed how to use them. The following items will be recorded by the subjects in the diary card on the day of vaccination and for the next 7 days (i.e., D0 to D7) until resolution:

- Daily temperature, with the route by which it was taken
- Daily measurement or intensity grade of all other solicited injection site and systemic reactions
- Action taken for each event (e.g., medication)
- The action(s) taken by the subject to treat and/or manage any solicited reactions will be classified in the CRB using the following list (all applicable items should be checked):
  - None
  - Medication
  - Health care provider contact
  - Hospitalized

Table 2 and Table 3 present, respectively, the solicited injection site reactions and solicited systemic reactions that are prelisted in the diary cards and CRB, together with the intensity scales.

**Table 2 - Solicited Injection Site Reactions: Terminology, Definitions, and Intensity Scales**

CRB term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	Injection site bruising
Data analysis term (MedDRA preferred term [PT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	injection site bruising
Diary card term	Pain	Redness	Swelling	Hardening	Bruising
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized.	Presence of a redness including the approximate point of needle entry.	Swelling at or near the injection site. Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling.	Hardening at or near the injection site. Hardening is caused by a slow diffusion of the product in the tissue leading to a thick or hard area to touch at or near the injection site and thus can be best described by looking at the size of the hardening.	Bruising is the result of the diffusion of blood in the skin from ruptured blood vessels that forms a purple or black and blue spot on the skin. It can be best described by looking at its size.
Intensity scale <sup>a</sup>	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: ≥25 to ≤50 mm Grade 2: ≥51 to ≤100 mm Grade 3: >100 mm	Grade 1: ≥25 to ≤50 mm Grade 2: ≥51 to ≤100 mm Grade 3: >100 mm	Grade 1: ≥25 to ≤50 mm Grade 2: ≥51 to ≤100 mm Grade 3: >100 mm	Grade 1: ≥25 to ≤50 mm Grade 2: ≥51 to ≤100 mm Grade 3: >100 mm

<sup>a</sup> For the subjective reaction of pain, subjects will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness, swelling, hardening and bruising, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis.

**Table 3 - Solicited Systemic Reactions: Terminology, Definitions, and Intensity Scales**

CRB term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Shivering
Data analysis term (MedDRA preferred term [PT])	Pyrexia	Headache	Malaise	Myalgia	Chills
Diary Card term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Chills
Definition	Fever is defined by a temperature of $\geq 38.0^{\circ}\text{C}$ ( $\geq 100.4^{\circ}\text{F}$ ).	A headache is pain or discomfort in the head, or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons).  Does not apply to muscle pain at the injection site which should be reported as injection site pain.	Cold feeling.
Intensity scale <sup>a</sup>	Grade 1: $\geq 38.0^{\circ}\text{C}$ to $\leq 38.4^{\circ}\text{C}$ , or $\geq 100.4^{\circ}\text{F}$ to $\leq 101.1^{\circ}\text{F}$ Grade 2: $\geq 38.5^{\circ}\text{C}$ to $\leq 38.9^{\circ}\text{C}$ , or $\geq 101.2^{\circ}\text{F}$ to $\leq 102.0^{\circ}\text{F}$ Grade 3: $\geq 39.0^{\circ}\text{C}$ , or $\geq 102.1^{\circ}\text{F}$	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

<sup>a</sup> For all reactions but fever, subjects will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

### **Important notes for the accurate assessment of temperature:**

Subjects are to measure body temperature once per day (in degrees Celsius), preferably always at the same time. The optimal time for measurement is the evening, when body temperature is highest. Temperature is also to be measured at the time of any apparent fever. The highest observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the CRB. The preferred route for this study is oral. Pre-vaccination temperature is also systematically collected by the investigator on the source document. Tympanic and temporal artery thermometers must not be used.

#### **2.1.4.1.2.3 Unsolicited Adverse Events**

In addition to recording solicited reactions, subjects will be instructed to record any other medical events that may occur during the 28-day period after vaccination. Space will be provided in the diary card for this purpose.

Information on SAEs will be collected and assessed throughout the study, from inclusion until 28 (+ 7) days after vaccination. Any SAE occurring at any time during the study will be reported by the Investigator in the CRB according to the completion instructions provided by the Sponsor; this includes checking the “Serious” box on the AE CRF and completing the appropriate Death/Safety Complementary Information CRFs. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (e.g., outcome, medical history, results of investigations, copy of hospitalization reports). See Section 10 of the protocol for further details on SAE reporting.

For each unsolicited AE (whether serious or non-serious), the following information is to be recorded:

- Start and stop dates<sup>1</sup>
- Intensity of the event

For measurable unsolicited AEs that are part of the list of solicited reactions, the size of the AE as well as the temperature for fever will be collected and analyzed based on the corresponding scale used for solicited reactions (see [Table 2](#) and [Table 3](#)).

All other unsolicited AEs will be classified according to the following intensity scale:

- Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

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<sup>1</sup> The stop date of all related AEs will be actively solicited. For other events, the investigator will provide the stop date when it becomes available. AEs for which no stop date was obtained during the course of the study will be considered as ongoing at the end of the study.

- Grade 2: A type of AE that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
- Whether the AE was related to the investigational product (for unsolicited systemic AEs)
- The Investigator will assess the causal relationship between the AE and the investigational product as either "Not related" or "Related", as described in Section 9.1.3.5 of the protocol.
- Action taken for each event (e.g., medication)

The action(s) taken by the subject to treat and/or manage any unsolicited AEs will be classified in the CRB using the following list (all applicable items should be checked):

- None
- Medication
- Health care provider contact
- Hospitalized
- Whether the AE was serious

For each SAE, the investigator will complete all seriousness criteria that apply (outcome and elapsed time)

- Whether the AE was AESI
- Whether the AE caused study discontinuation

#### 2.1.4.1.2.4 Adverse Events of Special Interest

AESIs will have the same detailed information collected as SAEs (collected throughout the study). These include (1):

- new onset of Guillain-Barré syndrome
- encephalitis/myelitis (including transverse myelitis)
- Bell's palsy
- optic neuritis
- brachial neuritis

#### 2.1.4.1.2.5 Assessment of Causality

The Investigator will assess the causal relationship between each unsolicited systemic AE and the product administered as either not related or related, based on the following definitions<sup>2</sup>:

Not related – The AE is clearly/most probably caused by other etiologies such as subject’s underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the vaccination (screening phase, if applicable).

Related – There is a “reasonable possibility” that the AE was caused by the product administered, meaning that there is evidence or arguments to suggest a causal relationship.

Note: By convention, all injection site AEs (solicited and unsolicited) and all solicited systemic reactions are considered to be related to the administered product and therefore are referred to as reactions and do not require the Investigator’s opinion on relatedness.

AEs likely to be related to the product, whether serious or not, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the subject’s condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of “chronicity” establishment.

#### **2.1.4.2 Laboratory safety variables**

No laboratory safety data will be obtained in the study.

#### **2.1.4.3 Vital signs variables**

No vital sign data will be obtained in the study.

#### **2.1.4.4 Electrocardiogram variables**

No electrocardiogram data will be obtained in the study.

#### **2.1.5 Immunogenicity endpoints**

The endpoints for the evaluation of immunogenicity are:

- GMT of HAI at D0 and D28
- Individual Geometric Mean Titer Ratio (GMTR) of HAI at D28/D0
- Seroconversion rate (percentage of subjects with HAI titer <10 [1/dil] at D0 and post-injection titer  $\geq$ 40 [1/dil] at D28, or HAI titer  $\geq$ 10 [1/dil] at D0 and a  $\geq$ 4-fold increase in HAI titer [1/dil] at D28)

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<sup>2</sup> ICH Guidelines, Clinical Safety Data Management E2A

- Seroprotection rate (percentage of subjects with HAI titer  $\geq 40$  [1/dil]) at D0 and D28

### **Anti-Influenza Virus Antibody Titration by Inhibition of Hemagglutination**

Assays will be performed by the Sanofi Pasteur laboratory (GCI, Swiftwater, PA, USA) or at an external testing laboratory under GCI responsibility. The address is provided in the sample handling procedures.

Test serum samples and quality control sera (sheep, ferret, and/or human sera) are incubated with Sigma Type III neuraminidase from *Vibrio cholerae* to eliminate non-specific inhibitors. Adsorption of spontaneous anti-species agglutinins is then performed by incubating the test serum samples and quality control sera with a red blood cell (RBC) suspension. Following this, the mixtures are centrifuged and the supernatants containing the treated test sera are collected for testing. Ten two-fold dilutions (starting at 1:10) of the treated test serum samples and quality control sera are incubated with a previously titrated influenza antigen at a concentration of 4 hemagglutination unit (HAU)/25  $\mu$ L. Influenza antigen is not added to the serum control wells containing only serum and RBCs. The mixture is then incubated and a RBC suspension is added. Following incubation, the results are read. The endpoint of the assay is the highest serum dilution in which complete inhibition of hemagglutination occurred. Each serum sample is titrated in two independent assay runs, and the 2 values, which cannot differ by more than 1 two-fold dilution, are reported. The HAI GMT between the 2 values is calculated at the time of statistical analysis. The lower limit of quantitation (LLOQ) is set at the lowest dilution used in the assay, 1:10. If the first/lowest serum dilution exhibits hemagglutination, the serum antibody titer is reported as  $<10$  (1/dil). If the last/highest serum dilution exhibits complete inhibition of hemagglutination, the serum antibody titer is reported as  $\geq 10$  240 (1/dil).

In this study, QIV-HD will be compared to a local QIV-SD, and it is possible that the two vaccines contain different strains based on comparison of strains between Sanofi Pasteur QIV-HD (based on WHO / VRBPAC recommendations) and a local QIV-SD (based on NIID). Sanofi Pasteur plans on performing the HAI testing using both the QIV-HD and QIV-SD strains as test antigens for all the subjects, irrespective of the vaccine received. For example, if QIV-HD is comprised of a, b, c and d strains and QIV-SD is comprised of a, b, c and “d-like” strains (3 common and 1 “-like strain”), the proposed testing strategy would require HAI testing of sera from all subjects (irrespective of the vaccine received) with a, b, c, d and “d-like” strain test antigens in order to evaluate the comparability between the “-like strains” in this study.

## **2.2 DISPOSITION OF PATIENTS**

This section describes patient disposition for both patient study status and the patient analysis populations.

Enrolled subjects are defined as subjects who signed the informed consent and met the inclusion criteria and did not meet any of the exclusion criteria, i.e., CRB have been created for them.

Randomized subjects consist of all enrolled subjects who have a vaccine dose number allocated and recorded in the IRT database, regardless of whether the vaccine dose kit was used.

Duration of the study in each cohort and the summary of inclusion and exclusion criteria by randomized groups will be presented using a summary table.

Randomized subjects will be summarized by sites and vaccine groups for each cohort.

For subjects' study status, the total number of subjects in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Enrolled subjects
- Randomized subjects
- Randomized and not vaccinated subjects
- Randomized and vaccinated subjects
- Subjects who did not complete the study
- Subjects who completed the study

For all categories of subjects (except for the enrolled category), percentages will be calculated using the number of randomized subjects as the denominator. Reasons for study discontinuation will be supplied in tables giving numbers and percentages by study groups.

The subjects who discontinued the study and subjects who completed the study will be listed separately. The subjects with at least one inclusion criterion not met or at least one exclusion criterion met will also be listed.

Randomization strata, vaccine allocation, vaccine administration, and adherence to schedule will be summarized in tables giving numbers and percentages by study groups on randomized subjects. Subjects randomized in a group but who received an unallocated study vaccine will be listed.

All critical or major deviations potentially impacting immunogenicity analyses, randomization and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by study groups.

Additionally, the analysis sets for safety and immunogenicity will be summarized in a table by number of subjects on the randomized subjects.

- Safety analysis set (SafAS)
- Immunogenicity analysis set: full analysis set (FAS) /per-protocol analysis set (PPAS)

Subjects (observations) excluded from the immunogenicity analyses will be listed.

### **2.2.1 Randomization and drug dispensing irregularities**

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible subject is randomized, b) a subject is randomized based on an incorrect stratum, c) a subject is randomized twice, or d) in a dynamic randomization

scheme the treatment assignment is, in fact, not random, due to a computer program error.

OR

2. A subject is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a subject at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized subject is treated with IMP reserved for randomized subject.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized subjects (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

<b>Randomization and drug allocation irregularities</b>
<i>IMP administered but not as per protocol</i>
<i>IMP given outside Randomization procedure</i>
<i>IMP intake is prior to Randomization</i>
<i>Randomization procedure not performed in the correct sequence as specified in the protocol</i>
<i>Subject randomized twice</i>
<i>IMP number actually administered to the subject is different from the IMP number allocated according to the Randomization list</i>
<i>Same kit number used for several subjects</i>
<i>Wrong stratum of randomization</i>
<i>Kit not available</i>
<i>Randomization by error</i>
<i>Subject switched to another site</i>

### 2.3 ANALYSIS SETS

Subjects vaccinated without being randomized will not be considered randomized and will not be included in any analysis sets performing immunogenicity analyses.

The randomized subject includes any subject who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any subjects randomized more than once, only the data associated with the first randomization will be used in any analysis set. The safety experience associated with any later randomization will be assessed separately.

### **2.3.1 Full analysis set**

The full analysis set (FAS) will include all randomized subjects who received the study vaccine and had a post-vaccination blood sample HAI result for at least one strain. Subjects will be analyzed according to the vaccine group to which they were randomized.

### **2.3.2 Per-protocol analysis set**

The per-protocol analysis set (PPAS) is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from PPAS.

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specific exclusion criteria
- Subject did not receive vaccine
- Subject received a vaccine other than the one that he/she was randomized to receive
- Preparation and/or administration of vaccine was not done as per-protocol
- Subject did not provide the post-dose serology sample at V3 in the proper time window (i.e., 28 to 35 days after vaccination) or a post-dose serology sample (V3) was not drawn
- Subject received a protocol-restricted therapy / medication / vaccine (prohibited therapies / medications / vaccines should have been indicated in Section 6.7 of the protocol).

In addition to the criteria listed above, subjects will also be excluded from the PPAS if their HAI serology sample at V3 did not produce a valid test result for all strains.

The PPAS definition will be finalized before the database lock.

### **2.3.3 Safety analysis set**

The safety analysis set (SafAS) is defined as those subjects who have received the study vaccine<sup>3</sup>. All subjects will have their safety analyzed according to the vaccine they actually received.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

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<sup>3</sup> For which safety data are scheduled to be collected

## **2.4 STATISTICAL METHODS**

### **2.4.1 Demographics and baseline characteristics**

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum for each vaccine group. Categorical and ordinal data will be summarized using the number and percentage of subjects in each vaccine group.

Parameters will be summarized on the safety analysis set analyzed in the vaccine group to which they were randomized. Demographic characteristics will also be summarized on the randomized subjects, full analysis set and per-protocol analysis set for each vaccine group.

Parameters described in [Section 2.1.1](#) will be summarized by vaccine group and overall using descriptive statistics.

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

No specific description of the immunogenicity parameters will be provided at baseline. If relevant, the baseline values will be described along with each immunogenicity analysis.

In addition, demographic data will also be presented in the listings.

### **2.4.2 Prior or concomitant medications**

Reportable medications will be presented for the safety analysis set by vaccine groups. Reportable medications will be also summarized by category and the presence of prophylactic medication.

### **2.4.3 Analyses of efficacy endpoints**

Not applicable

### **2.4.4 Analyses of safety data**

The summary of safety results will be presented by vaccine groups. The safety data in Cohort 1 will be summarized and reviewed by the Sponsor at a planned Safety Management Team meeting as Early Safety Data Review.

#### ***General common rules***

All safety analyses will be performed in Cohort 2 and all subjects, combining both Cohort 1 and Cohort 2 (hereafter, Cohort 1+Cohort 2), for the SafAS defined in [Section 2.3.3](#), unless otherwise specified, using the following common rules:

- Safety data from subjects who do not belong to the safety analysis set will be listed separately

- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned. The main parameters will be described using the number and percentage of subjects with 95% CIs (Clopper-Pearson method) (2) in each vaccine group.

#### **2.4.4.1 Analyses of adverse events**

##### ***Generalities***

Summary tables of each solicited reaction will be presented with number of subjects who reported each solicited reactions occurring within 7 days after the day of injection (D0 to D7). The intensity, the time to onset and number of days of occurrence of each solicited reaction will be summarized. When more than 1 intensity level is reported within a time period, the highest intensity will be used.

Unsolicited AEs will be collected and coded by System Organ Class (SOC) and Preferred Term (PT), using the MedDRA currently in effect at Sanofi at the time of database lock. For each type of unsolicited AE, the number of subjects with at least one instance of that event will be reported. Unsolicited AEs will also be tabulated by relationship to the vaccine group and intensity.

Adverse event incidence tables will present the terms (LLT) prelisted in the CRB for solicited reactions, the SOC and PT for unsolicited AEs, and the number (n) and percentage (%) of subjects experiencing an AE. Multiple occurrences of the same event in the same subject during the study period will be counted only once in the tables.

Sorting within tables ensures the same presentation for the set of all AEs within the observation period. For that purpose, the table of all solicited reactions presented using the terms (LLT) prelisted in the CRB will be sorted by order in the CRB for all similar tables unless otherwise specified. The table of unsolicited AEs presented using primary SOC and PT will be sorted by SOC internationally agreed order and PT sorted by decreasing frequency according to all unsolicited AE summary for all other similar tables unless otherwise specified. In case of equal frequencies of PTs within a SOC, the alphabetic order will be applied.

##### ***Safety overview***

The following AEs within 28 days after vaccination will be summarized.

- Immediate unsolicited systemic AE and AR
- Solicited reaction
- Solicited injection site reaction
- Solicited systemic reaction
- Unsolicited AE and AR
- Unsolicited non-serious AE and AR
- Unsolicited non-serious injection site AR
- Unsolicited non-serious systemic AE and AR

- AE leading to study discontinuation
- SAE
  - Death
- AE of special interest

This safety overview will also be summarized by the following subgroups:

- Age: 65-<75 and  $\geq 75$  years
- Sex: Male and Female
- Previous influenza vaccination status: Yes and No
- Baseline seropositivity status:  $<10$  [1/dil] and  $\geq 10$  [1/dil]

### ***Solicited reactions***

The following solicited reaction summaries will be presented using the terms prelisted in CRB.

- Summary of solicited reactions (Solicited injection site reactions and Solicited systemic reactions) within 7 days after vaccine injection by intensity (Grade 2, Grade 3, and Grade 2 or 3)
- Solicited injection site reactions (injection site pain, injection site erythema, injection site swelling, injection site induration, and injection site bruising) and solicited systemic reactions (fever, headache, malaise, myalgia, and shivering) within 7 days after vaccine injection:
  - By maximum intensity
  - By time of onset
  - By number of days of occurrence during the solicited period
  - By overall number of days of occurrence

Listings of solicited reactions (solicited injection site reactions and solicited systemic reactions) will be presented. Action taken and whether the reaction led to early termination from the study will be displayed in the listings. Solicited reactions not included in the safety analysis will be also presented in listings.

### ***Unsolicited non-serious AEs***

- Summary of unsolicited non-serious AEs and ARs within 28 days after vaccine injection
  - By maximum intensity (Grade 1, Grade 2, Grade 3, and Missing)
  - By time of onset
  - By duration
- Unsolicited AEs and ARs within 28 days after vaccine injection by SOC and PT
- All and related AEs leading to study discontinuation within 28 days after vaccine injection

Listings of unsolicited non-serious AEs will be presented. Unsolicited non-serious AEs not included in the safety analysis will be also presented in listings.

### ***Serious adverse events (SAEs)***

- Summary of SAEs after vaccination:
  - Within 7 days after vaccine injection
  - Within 28 days after vaccine injection
  - After vaccine injection during the whole study
- All and related SAEs by seriousness criterion
  - Within 28 days after vaccine injection
  - After vaccine injection during the whole study
- All and related SAEs by SOC and PT
  - Within 28 days after vaccine injection
  - After vaccine injection during the whole study
- All and related SAEs by outcome
  - Within 28 days after vaccine injection
  - After vaccine injection during the whole study

Listings of serious adverse events/reactions will be presented. SAEs not included in the safety analysis will be also presented in listings.

### ***AEs of Special Interest (AESIs)***

AESIs will be listed by each AESI as shown in [Table 7](#) separately.

#### **2.4.4.2 Deaths**

Listing of death will be presented.

#### **2.4.4.3 Analyses of laboratory variables**

Not applicable

#### **2.4.4.4 Analyses of vital sign variables**

Not applicable

#### **2.4.4.5 Analyses of body stature variables**

The summary statistics of all body statures variable at V1 will be presented as the result of demographics and baseline characteristics described in [Section 2.1.1](#) and [Section 2.4.1](#).

#### 2.4.4.6 Analyses of electrocardiogram variables

Not applicable

#### 2.4.5 Analyses of immunogenicity data

QIV-HD vaccine and QIV-SD vaccine contain the following strains:

	QIV-HD	QIV-SD
H1N1	A/Michigan/45/2015(H1N1)	A/Singapore/GP1908/2015(IVR-180)(H1N1)pdm09
H3N2	A/Hong Kong/4801/2014(X-263B)(H3N2)	A/Hong Kong/4801/2014(X-263)(H3N2)
B (Yamagata lineage)	B/Phuket/3073/2013	B/Phuket/3073/2013
B (Victoria lineage)	B/Brisbane/60/2008	B/Texas/2/2013

For the purposes of this section, the 7 virus strains in the vaccine groups will be labeled as follow:

- A/Michigan/45/2015(H1N1) A1
- A/Singapore/GP1908/2015(IVR-180)(H1N1)pdm09 A1-like
- A/Hong Kong/4801/2014(X-263B)(H3N2) A2
- A/Hong Kong/4801/2014(X-263)(H3N2) A2-like
- B/Phuket/3073/2013 B1
- B/Brisbane/60/2008 B2
- B/Texas/2/2013 B2-like

The immunogenicity analyses will be performed on the PPAS and the FAS. The main immunogenicity analyses will be conducted on Cohort 2 for the PPAS. Similar analyses with the main immunogenicity analyses will also be conducted on Cohort 2 for the FAS and Cohort 1+Cohort 2 for PPAS and FAS, unless otherwise specified.

For descriptive purposes, no hypothesis will be tested.

Assuming that  $\log_{10}$  transformation of the titers/data follows a normal distribution, at first, the mean and the 95% CI will be calculated on  $\log_{10}$  (titers/data) using the usual calculation for normal distribution (using Student's  $t$  distribution with  $n-1$  degree of freedom) as described in [Section 2.5.8.1](#) and [Section 2.5.8.2](#), then antilog transformations will be applied to the results of calculations, in order to provide GMs and their 95% CI.

For categorical data such as seroprotection and seroconversion, the percentage of subjects achieving the endpoint and the corresponding 95% CIs (Clopper-Pearson method) (2) will be performed for pre-vaccination (V1) and post-vaccination immunogenicity (V3) (See the detail in [Section 2.5.8.3](#)). The 95% CI of the difference in percentage between time points and vaccine

group will be computed using the Wilson score method without continuity correction, quoted by Newcombe (3) (See the detail in [Section 2.5.8.4](#)).

For GMTs of HAI, the following will be analyzed by vaccine groups and strains.

- GMTs of HAI for QIV-HDs and QIV-SD, and the ratio of GMTs of HAI for each QIV-HD/QIV-SD at V3 after vaccination
- GMTs of HAI for QIV-HDs and QIV-SD using strains selected for each vaccine, and the ratio of GMTs of HAI for each QIV-HD/QIV-SD at V3 after vaccination
- Ratio of GMTs of HAI for QIV-HDs between the 2 different administration routes at V3 after vaccination

GMTs of HAI for each vaccine group at V1 and V3 after vaccination and the corresponding ratio of GMT will be summarized by strains.

For seroconversion rates, the following will be analyzed by vaccine groups and strains.

- Seroconversion rates and the difference of each QIV-HD and QIV-SD (QIV-HD – QIV-SD) at V3 after vaccination
- Seroconversion rates using strains selected for each vaccine and the difference of each QIV-HD and QIV-SD (QIV-HD – QIV-SD) at V3 after vaccination
- Seroconversion rates and the difference of QIV-HDs between the 2 different administration routes at V3 after vaccination

For seroprotection rate, the following will be analyzed by vaccine groups and strains

- Seroprotection rates of HAI for QIV-HDs and QIV-SD at V3 after vaccination
- Seroprotection rates of HAI for each vaccine group at V1 and V3 after vaccination

Immunogenicity data will be analyzed using GMTs, seroconversion rate, and seroprotection rate at each time point by following subgroups:

- Age: 65-<75 and  $\geq 75$  years
- Sex: Male and Female
- Previous influenza vaccination status: Yes and No
- Baseline seropositivity status:  $<10$  [1/dil] and  $\geq 10$  [1/dil]

For comparison between groups in terms of GMTs, the exploratory analyses will be performed if necessary.

The followings will be presented as the summary of HA antibody response for each antigen:

- The number of subjects with HAI titer  $<10$  [1/dil] and  $\geq 10$  [1/dil], the number of subjects with seroprotection ( $\geq 40$  [1/dil]), and summary of titers [1/dil] (using geometric mean and the corresponding 95% CI, median, minimum and maximum value of antilog transformed value, and mean and standard deviation calculated on  $\log_{10}$  (titers/data)) at V1 and V3

- GMTR of the individual titers (using geometric mean and the corresponding 95% CI, median, minimum and maximum of antilog transformed value, and mean and standard deviation calculated on  $\log_{10}$  (titers/data)) at V3 over V1, and the number of subjects with seroconversion at V3

In addition, Reverse Cumulative Distribution Curve (RCDC) by vaccine groups and timepoints (V1 and V3) will be presented in a graph for each strain in Cohort 2 for the PPAS and FAS.

Individual diagram of titers will be also presented for each strain by vaccine groups in Cohort 2 for the PPAS.

To assess the immunogenicity of -like strains, the following results will be presented for corresponding strains by vaccine groups:

- GMTs of HAI at V1, V3 and GMTR of HAI for V3/V1 with the corresponding 95% CI
- Seroconversion rate
- Seroprotection rates at V1 and V3

Using the titer including all of the 3 vaccine groups and all of the 2 time points for a pair of -like strains, scatter plots with the titers of 2 -like strains will be presented, and the Pearson product-moment correlation coefficient  $r$  between -like strains will be calculated using  $\log_{10}$  transformed values of the titers in Cohort 2 for the PPAS and FAS. Also a regression line will be drawn and the coefficient of determination  $R^2$  will be calculated through a simple regression model using  $\log_{10}$  transformed values of the titers.

Individual immunogenicity data will be presented in listings.

## **2.5 DATA HANDLING CONVENTIONS**

### **2.5.1 General conventions**

The following formulas will be used for computation of parameters.

#### **2.5.1.1 Duration of the study**

The duration of the study is computed in days as follows:

$$\text{Maximum (Visit dates, Termination date)} - \text{minimum (Date of V1)} + 1$$

#### **2.5.1.2 Subject Duration**

The duration of a subject participation in the trial is computed as follows:

$$\text{Maximum (Date of visits, termination date)} - \text{Date of V1} + 1$$

### **2.5.1.3 Time interval**

The time interval between two visits/vaccinations/blood samples is computed as follows:

Later date – earlier date.

### **2.5.1.4 Influenza vaccination during the previous influenza season**

This information will be used as collected. No derivation or imputation will be done.

## **2.5.2 Data handling conventions for safety variables**

### **2.5.2.1 Solicited reactions**

#### **Daily intensity:**

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing. The category of Unknown will be considered Missing if Unknown is recorded.

For measurable injection site reactions (Erythema/Swelling/Induration/Bruising):

- Grade 1:  $\geq 25$  to  $\leq 50$  mm
- Grade 2:  $\geq 51$  to  $\leq 100$  mm
- Grade 3:  $> 100$  mm

For measurable systemic reactions (Fever):

- Grade 1:  $\geq 38.0$  to  $\leq 38.4$  °C, or  $\geq 100.4$  to  $\leq 101.1$  °F
- Grade 2:  $\geq 38.5$  to  $\leq 38.9$  °C, or  $\geq 101.2$  to  $\leq 102.0$  °F
- Grade 3:  $\geq 39.0$  °C, or  $\geq 102.1$  °F

For the derivation of daily intensities the following sequential steps will be applied:

For solicited reactions (except Fever/Pyrexia) with an investigator presence recorded as “No” and with all daily records missing, all daily intensities will be derived as “None”.

For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, “NM”) is Grade 3. Note that the intensity could be considered as “None” (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement  $> 0$  mm but  $< 25$  mm in adults).

Note: The maximum intensity during the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

**Maximum intensity:**

Maximum intensity is derived from the daily intensities computed as described in above “Daily intensity” and is calculated as the maximum of the daily intensities over the period considered. The Grade of intensity is applied following the rules described in Section 9.1.3.2 of the protocol.

**Presence:**

Presence is derived from the maximum intensity of the period considered:

- No presence : None
- Presence : Grade 1, Grade 2 or Grade 3
- Unknown or Missing presence : Missing

Subjects with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

**Time of onset:**

Time of onset is derived from the daily intensities computed as described above in “Daily intensity”. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

**Table 4 – Categories for time of onset**

<b>Injection Site Reactions (D0-D7)</b>	<b>Systemic Reactions (D0-D7)</b>
D0-D3	D0-D3
D4-D7	D4-D7

**Number of days of occurrence:**

Number of days of occurrence over the period considered is derived from the daily intensities computed as described above in “Daily intensity”. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

**Table 5 – Categories for number of days of occurrence during the solicited period**

<b>Injection Site Reactions (D0-D7)</b>	<b>Systemic Reactions (D0-D7)</b>
1-3 days	1-3 days
4-7 days	4-7 days
8 days	8 days

**Overall number of days of occurrence:**

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence is derived from the daily intensities and the stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

$$\begin{aligned}
 & (\text{stop date} - \text{vaccination date}) \\
 & + (\text{number of days of occurrence within the solicited period}) \\
 & - \text{length of the solicited period} + 1
 \end{aligned}$$

If the stop date is missing or incomplete (containing missing data [MD]), the overall number of days of occurrence will be considered as Missing.

**Table 6 – Categories for overall number of days of occurrence**

<b>Injection Site Reactions</b>	<b>Systemic Reactions</b>
1-3 days	1-3 days
4-7 days	4-7 days
≥8 days	≥8 days
Missing	Missing

**Ongoing:**

Ongoing is derived from the last daily intensity of the solicited period computed as described above in “Daily intensity” and the maximum intensity on the ongoing period. The investigator’s ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

Note: a reaction could be derived as not ongoing for the analysis despite being considered as ongoing by the investigator (e.g. when the maximum measurement after D7 for adults aged ≥65 years is >0 mm but <25 mm). If the last daily intensity of the solicited period is at least Grade 1 and maximum intensity on the ongoing period is also at least Grade 1, then the reaction is considered ongoing. In any other cases the reaction will not be considered as ongoing.

### **2.5.2.2 Unsolicited non-serious AEs**

Unsolicited AEs include non-serious unsolicited AEs and SAEs. This subsection only covers the endpoints for unsolicited non-serious AEs.

#### **Presence:**

An observation will be considered an event if it has at least a verbatim term.

#### **Intensity:**

Intensity for unsolicited non-serious AE will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited non-serious AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule as the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

Note that the intensity could be considered as “None” (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement >0 mm but <25 mm). Intensity for the other unsolicited non-serious AEs will correspond to the value reported in the electronic case report form (eCRF).

The maximum intensity corresponds to the highest intensity for a unique term.

#### **Time of onset:**

Time of onset is derived from the start date of the unsolicited non-serious AE provided in the clinical database and the date of last vaccination:

Start date of the unsolicited non-serious AE – date of vaccination.

The time of onset should be considered as missing only if one or both of the dates are missing or partially missing.

The unsolicited non-serious AEs will be analyzed “Within 28 days”, which corresponds to AEs with a time of onset between 0 and 28 days after vaccination or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: Unsolicited non-serious AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above (>28 days) will not be included in analysis, but will be listed separately.

Time of onset will be displayed as follows:

- D0-D3
- D4-D7

- D8-D14
- $\geq$ D15
- Missing

**Duration:**

Duration is derived from the start and stop dates of the unsolicited non-serious AE provided in the clinical database:

Stop date of unsolicited non-serious AE – start date of unsolicited non-serious AE + 1.

The duration should be considered as missing only if one or both of the start and stop dates of the unsolicited non-serious AE is missing or partially missing.

Duration will be displayed by period as following:

- 1-3 days
- 4-7 days
- 8-14 days
- $\geq$ 15 days
- Missing

**2.5.2.3 Serious adverse events**

**Time of onset:**

Time of onset will be computed using the same methodology than for unsolicited non-serious AEs described in [Section 2.5.2.2](#).

SAEs will be analyzed throughout the study using the following periods:

- Within 28 days after vaccine injection
- During the whole study (i.e., all SAEs occurred during the study)

An SAE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, but will be listed separately.

**Duration:**

Duration will be computed using the same methodology than for unsolicited non-serious AEs described in [Section 2.5.2.2](#).

**Intensity:**

The intensity for SAE will be computed using the same methodology than for unsolicited non-serious AEs described in [Section 2.5.2.2](#).

#### **2.5.2.4 Other safety endpoints**

##### **Action taken:**

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

##### **Seriousness:**

This information will be summarized as collected for SAE. No derivation or imputation will be done.

##### **Outcome:**

This information will be summarized as collected. No derivation or imputation will be done.

##### **Causality:**

This information will be summarized as collected. An adverse reaction (AR) is defined as an unsolicited non-serious AE or an SAE with causality to the vaccine. Missing causality (relationship) will be handled as described in [Section 2.5.4](#).

##### **AEs leading to study discontinuation:**

A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- Disposition table: A subject who has, on the termination form, the reason for early termination “adverse event” is checked.
- Safety overview table: A subject who has either on the termination form, the reason for early termination “adverse event” is checked or lists an AE on an AE page (solicited, unsolicited, or SAE) that has “Reaction Leading to Termination” or “Event Leading to Termination” or “Serious Adverse Event Leading to Termination” checked that is at least Grade 1 and is within the time period indicated. Note: If the Grade is below 1, the AE will be excluded from the list of AEs leading to study discontinuation.
- System organ class (SOC)/Preferred term (PT) table: An event (solicited, unsolicited, or SAE) that has “Cause Study Termination” or “Caused Study Discontinuation” checked that is at least Grade 1 and is within the time period indicated.

##### **AEs of special interest (AESIs):**

AESIs will be collected throughout the study (D0 through V3). AESIs will have the same detailed information collected as SAEs. Each AESI will be retrieved using the following (as shown in [Table 7](#)):

**Table 7 – AESI PTs**

<b>AESI</b>	<b>PT</b>
Guillain-Barré syndrome (GBS)	Chronic inflammatory demyelinating polyradiculoneuropathy Demyelinating polyneuropathy Guillain-Barre syndrome Miller Fisher syndrome
encephalitis/myelitis (including transverse myelitis)	Myelitis Myelitis transverse Encephalitis is using the narrow SMQ term “Noninfectious encephalitis” (Medical Dictionary for Regulatory Activities [MedDRA] Version 20.1)
Bell’s palsy	Facial palsy Facial paralysis Facial paresis Bell’s palsy
optic neuritis	Optic neuritis Optic neuropathy
brachial neuritis	Brachial neuritis Brachial plexopathy Neuralgic amyotrophy Parsonage Turner Syndrome

### 2.5.3 Data handling conventions for immunogenicity variables

#### 2.5.3.1 Computed values for analysis

In order to appropriately manage replicate values for analysis purpose, the individual GMT of all values will be computed for each blood sample after managing extreme values as described. The computed value is then considered the titer for that particular blood sample.

- If a titer is <LLOQ, then the computed value, LLOQ/2, will be used
- If a titer is  $\geq$ LLOQ and <ULOQ (or  $\leq$ ULOQ), then the titer itself will be used
- If a titer is  $\geq$ ULOQ (or >ULOQ), then computed value, ULOQ, will be used.

No test or search for outliers will be performed.

#### 2.5.3.2 Seroprotection

If the computed value of HAI titer  $\geq$ 40 [1/dil], then the derived seroprotection indicator will be “Yes” for that test, otherwise seroprotection will be “No”.

Note: If the computed value is missing, seroprotection indicator will be missing.

### **2.5.3.3 Fold-rise**

The derived endpoint fold-rise is driven by both baseline and post-vaccination computed values which are computed as described in [Section 2.5.3.1](#). The computed value for fold-rise is:

$$\text{Computed value} = \text{Post-vaccination computed value} / \text{Baseline computed value.}$$

For HAI assay, if the computed value is  $\geq 4$ -fold rise, then the derived 4-fold rise indicator will be “Yes” for that test, otherwise the corresponding indicators will be “No”. If baseline or post-vaccination value is missing, then the fold-rise is missing.

### **2.5.3.4 Seroconversion**

Seroconversion is defined for HAI assay as either

- A computed value of HAI titer  $< 10$  [1/dil] at D0 and post-injection titer  $\geq 40$  [1/dil] at D28
- A computed value of HAI titer  $\geq 10$  [1/dil] at D0 and a  $\geq 4$ -fold increase in HAI titer [1/dil] at D28

## **2.5.4 Missing data**

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

### ***Handling of safety data***

In general, no replacement will be done.

Nevertheless, missing relationship will be considered as related at the time of statistical analysis. No search for outliers will be performed. In all subject listings, partial and missing data will be clearly indicated as missing.

### ***Handling of medication missing/partial dates***

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

### ***Handling of adverse events with missing or partial date/time of onset***

Missing or partial missing start dates for unsolicited AEs will remain missing and not be imputed. If either the start or stop date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless unsolicited AEs with missing time of onset will be included in analyses according to the visit collected.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

#### ***Handling of immediate field for adverse events with missing***

For unsolicited non-serious systemic AEs, a missing response to the “Immediate” field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

For SAEs, missing or partially missing elapsed time from last vaccination recorded if within 24 hours will remain missing and not be imputed. Such SAEs will not be considered as immediate.

#### ***Handling of missing assessment of relationship of adverse events to investigational medicinal product***

Missing causality (relationship) for unsolicited non-serious AEs and SAEs will be considered at the time of analyses as related to vaccination, but no imputation should be done at the data level.

#### ***Handling of missing measurements of adverse events***

Partially missing temperatures will be handled as described in “Daily intensity” of [Section 2.5.2.1](#).

#### ***Handling of missing intensity adverse events***

For solicited reactions, missing intensities will be handled as described in “Daily intensity” of [Section 2.5.2.1](#). For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

#### ***Handling of potentially clinically significant abnormalities***

Not applicable.

#### ***Handling of immunogenicity data***

LLOQ and ULOQ management will be performed as described in [Section 2.5.3.1](#). No test or search for outliers will be performed. No replacement will be done for missing values.

### **2.5.5 Windows for time points**

Refer to [Table 1](#) for the allowance at each visit.

### **2.5.6 Unscheduled visits**

Unscheduled visit measurements of immunogenicity out of the allowance described in [Section 2.5.5](#) will not be analyzed.

## 2.5.7 Pooling of centers for statistical analyses

All data from each center will be pooled and analyzed as Enrolled subjects, Randomized subjects, PPAS, FAS and SafAS.

## 2.5.8 Statistical technical issues

### 2.5.8.1 Confidence interval for the individual group GMT and GMT ratio

The 2-sided 95% CI for the individual group GMT and GMTRs will be computed using the normal approximation as follows:

$$10^{(\bar{x} \pm t_{n-1, \alpha/2} \sqrt{v(\bar{x})})}$$

where  $10^{(\bar{x})}$  is the GMT,  $\bar{x} = \frac{1}{N} \sum \log_{10}(x)$ ,  $\log_{10}(x)$  is the log base 10 of the observed titer,  $N$  is the total observations in each vaccination group,  $\sqrt{v(\bar{x})}$  is the estimated standard deviation of  $\bar{x}$ ,  $\alpha = 0.05$ ,  $t_{n-1, \alpha/2}$  is the  $100(1 - \alpha/2)$  percentile of the central  $t$ -distribution with  $n-1$  degree of freedom.

### 2.5.8.2 Confidence interval for the GMT ratio between 2 groups

The calculations of the 95% CI for the GMT ratio between 2 groups are as following:

Logarithmic transformation of the individual titers will be calculated first. Assuming that individual  $\log_{10}(\text{titer})$  is normally distributed, the 95% CI for the difference in  $\log_{10}(\text{GMT})$  between group  $i$  and group  $j$  will be in the form:

$$\bar{X}_i - \bar{X}_j \pm t(1 - \alpha/2, n_i + n_j - 2) \cdot S \sqrt{1/n_i + 1/n_j}$$

where  $\bar{X}_i = \log_{10}(\text{GMT})$  is the mean of  $\log_{10}(\text{titer})$  of group  $i$ ,

$S^2 = [(n_i - 1)S_i^2 + (n_j - 1)S_j^2] / (n_i + n_j - 2)$  is the pooled sample variance,

$n_i$  and  $S_i^2$  are the sample size and sample variance of group  $i$ ,

$t(1 - \alpha/2, n_i + n_j - 2)$  is the  $100(1 - \alpha/2)$  percentile of the  $t$ -distribution with degrees of freedom (df) =  $n_i + n_j - 2$ .

### 2.5.8.3 Confidence interval for the single proportions

The 2-sided 95% CI for the single proportions will be constructed using the exact binomial method (Clopper-Pearson's method, quoted by Newcombe (2), i.e., using the inverse of the beta integral with SAS®):

$$\text{Lower bound: } 1 - \text{Beta}(1 - \alpha / 2, n - r + 1, r) \text{ and}$$

$$\text{Upper bound: } \text{Beta}(1 - \alpha / 2, r + 1, n - r),$$

where  $\alpha = 0.05$ , and  $r$  is the observed number of events/responders in  $n$  observations.

### 2.5.8.4 Confidence interval of the difference in proportions

The 2-sided 95% CI of the difference in proportions will be computed using the Wilson Score method without continuity correction, quoted by Newcombe (3) as follows:

Let  $\hat{\theta} = \pi_A - \pi_B$ , then if  $L = \hat{\theta} - \delta$  and  $U = \hat{\theta} + \varepsilon$  are respectively the lower and the upper limits of the CI, where:

$$\delta = Z_{0.025} \sqrt{\left\{ \frac{l_1(1-l_1)}{n_1} + \frac{u_2(1-u_2)}{n_2} \right\}}$$

$$\varepsilon = Z_{0.025} \sqrt{\left\{ \frac{l_2(1-l_2)}{n_2} + \frac{u_1(1-u_1)}{n_1} \right\}},$$

$l_1$  and  $u_1$  are calculated from the CI of the single proportion in group A given by:

$$\frac{\left( 2n_1 p_A + Z_{0.025}^2 \pm Z_{0.025} \sqrt{\left( Z_{0.025}^2 + 4n_1 p_A (1 - p_A) \right)} \right)}{2(n_1 + Z_{0.025}^2)},$$

$l_2$  and  $u_2$  are calculated from the CI of the single proportion in group B given by:

$$\frac{\left( 2n_2 p_B + Z_{0.025}^2 \pm Z_{0.025} \sqrt{\left( Z_{0.025}^2 + 4n_2 p_B (1 - p_B) \right)} \right)}{2(n_2 + Z_{0.025}^2)},$$

where  $Z_{0.025}$  is the upper 97.5th percentile of the standard normal distribution.

### **3 INTERIM ANALYSIS**

No interim analyses are planned. There will be 1 statistical analysis conducted after the end of the study (D28).

## 4 DATABASE LOCK

To keep the blinding of the vaccination (dose, route and site) information during the eCRF data review and immunogenicity assay, a 2-step database lock is planned as follows:

- Before 1st DBL:
  - SDV for blinded data, data review and deviation review need to be completed
  - Ongoing data lock for eCRF data (each CRF page)
- **1st DBL for eCRF data and Deviation**  
(except for Vaccination page and deviation related to vaccination, validity in immunogenicity and randomization anomalies by IRT system)
  - Actual vaccination information is still blinded at this time.
- After 1st DBL:
  - SDV for Unblinded Vaccination data (Consistency check between Unblinded source document and Blinded source document)  
If any data entry error is found, eCRF vaccination page (blinded data) will be updated. If it has impact on the deviation conclusion, DEVIAT file (blinded data) will be updated. (e.g., If the answer to “Administered as per Route provided by IRT?” at Vaccination page is changed to “No”, it impacts the DEVIAT file.)
  - Immunogenicity data release from GCI
- **2nd DBL for Immunogenicity data and eCRF Vaccination page** (also for DEVIAT if it is updated after 1st DBL)
- After 2nd DBL:
  - Key code release from Biostatistics & Programming
  - RANDO data release from IRT provider
  - “Unblinded TRTNO” data release from IRT provider  
“Unblinded TRTNO” includes detailed vaccination deviation/anomaly information. (e.g., the allocated route was IM, but the vaccine was actually administered by SC mistakenly.)

## **5 SOFTWARE DOCUMENTATION**

All summaries and statistical analyses will be generated using the SAS software, at least version 9.4 (SAS Institute, Cary, North Carolina, USA).

## 6 REFERENCES

1. Brighton Collaboration Website. <https://brightoncollaboration.org/public/what-we-do/setting-standards/case-definitions.html>. Accessed 30 March 2015.
2. Newcombe R.G. Two-sided confidence intervals for the single proportion: comparison of seven methods. *Stat Med.* 1998;17(8):857-72.
3. Newcombe R.G. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med.* 1998;17(8):873-90.

## **7 LIST OF APPENDICES**

Not applicable

# DFI15130-QHD00008 Appendix 10 Statistical Analysis Plan

## ELECTRONIC SIGNATURES

<b>Signed by</b>	<b>Meaning of Signature</b>	<b>Server Date (dd-MMM-yyyy HH:mm)</b>
[REDACTED]	Clinical Approval	13-Sep-2017 04:19 GMT+0200
[REDACTED]	Clinical Approval	13-Sep-2017 11:05 GMT+0200