NCT04537234

Immunogenicity and Safety of a High-Dose Quadrivalent Influenza Vaccine in Subjects 65 Years of Age and Older in Taiwan

Phase III, randomized, modified double-blind, active-controlled, multi-center study describing the immunogenicity and safety of high-dose quadrivalent influenza vaccine (QIV-HD) and standard--dose quadrivalent influenza vaccine (QIV-SD) administered by the intramuscular route in subjects 65 years of age and older in Taiwan

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	QHD00023
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur 14 Espace Henry Vallée, 69007 Lyon, France
Investigational Product:	Quadrivalent Influenza Vaccine (split virion, inactivated) High-Dose (QIV-HD)
Form / Route:	Suspension for injection in pre-filled syringe / Intramuscular
Indication For This Study:	Active immunization in adults 65 years of age and older for the prevention of influenza disease
Version and Date of the SAP core body part:	Version 2.0 dated 30 April 2021

Table of Contents

List of Tables

List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CDE	Center for Drug Evaluation
CI	confidence interval
CRB	case report book
CSR	clinical study report
D	day
dil	dilution
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
GBS	Guillain-Barré syndrome
GM	geometric mean
GMT	geometric mean titer
GMTR	geometric mean titer ratio
HA	hemagglutinin
HAI	hemagglutination inhibition
IM	intramuscular
IRB	institutional review board
IRT	interactive response technology
LLOQ	lower limit of quantitation
MD	missing data
µg	microgram
mL	milliliters
NM	non-measurable
PPAS	per-protocol analysis set
PT	preferred term
QIV-HD	high-dose quadrivalent influenza vaccine
QIV-SD	standard-dose quadrivalent influenza vaccine
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan

SOC	system organ class
TFDA	Taiwan Food and Drug Administration
TIV-HD	high-dose trivalent influenza vaccine
TIV-SD	standard-dose trivalent influenza vaccine
ULOQ	upper limit of quantitation
V	visit
WHO	World Health Organization

1 Introduction

Influenza is a contagious, acute viral respiratory disease caused by influenza type A and type B viruses. Individuals in high-risk groups (eg, adults 65 years of age and older and persons with underlying medical conditions) are at high risk of influenza and its complications.

Influenza outbreaks are a serious public health threat in Taiwan. The Western Pacific region has one of the highest burdens of influenza related deaths, and a mortality rate of 9% has been reported in Taiwan. These outbreaks are costly and strain public services. Furthermore, Taiwan has one of the most rapidly aging populations in the world. The population of adults 65 years of age and older in Taiwan in 2017 was estimated at 13.3% of the country's population and is expected to grow to at least 20% over the next decade. In 2017, adults 65 years of age and older accounted for 33.1% and 35.4%, for men and women, respectively, of the Taiwan National Health Insurance expenditures and approximately 44% of hospitalization costs. Despite influenza vaccine coverage rates in Taiwanese adults 65 years of age and older ranging from 40.79-49.2% between 2012 and 2017, this population and its burden of influenza disease and complications has a significant impact on Taiwan's health care system.

Since adults 65 years of age and older are at significantly increased risk of influenza infection and related complications, Taiwan's national mass vaccination campaign has designated this population as a priority group since 2001 and began to cover all adults over the age of 50 in 2016. With a growing population of adults 65 years of age and older, an influenza vaccine that can better prevent influenza infection and its complications would have a significant public health impact.

Vaccination remains the most effective means of preventing influenza infection and complications associated with the disease. The World Health Organization (WHO) recommends annual vaccination against influenza because it has been shown to be effective in reducing influenza-associated morbidity and mortality. However, the effectiveness of the influenza vaccine in preventing or attenuating illness depends in part on the age, underlying conditions, and immune competence of the vaccine recipient and on the similarity between the virus strains present in the vaccine and the strains circulating in the community. The immune response to standard-dose influenza vaccines (15 µg hemagglutinin ([HA)] per strain) is sub-optimal in adults 65 years of age and older compared to healthy young adults. One strategy to combat the observed decreased immune response to influenza vaccination in adults 65 years of age and older is to increase the antigen dose in the vaccine. Therefore, Sanofi Pasteur developed the high-dose quadrivalent influenza vaccine (QIV-HD) containing 60 µg HA of each of 4 virus strains for a total of 240 µg of HA antigen per dose for licensure in adults aged 65 years and older and thus eliminating the issue of having to choose a strain from only one B lineage for the seasonal high-dose trivalent influenza vaccine (TIV-HD) and the resulting risk posed by the potential widespread circulation of a strain from the alternate B lineage.

Results of QHD00023 will allow the registration of QIV-HD by the Taiwan Food and Drug Administration (TFDA) for use in adults 65 years of age and older. The design of this study was agreed by the Center for Drug Evaluation (CDE) during a formal consultation meeting on 22 August 2019.

2 Trial Objectives

2.1 Study Objectives

Immunogenicity

To describe the immune response induced by QIV-HD and AdimFlu-S (QIS) by hemagglutination inhibition (HAI) measurement method in all subjects.

Safety

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

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

QHD00023 will be a Phase III, randomized, modified double-blind, active-controlled, multi-center study. The study will be conducted during the 2020-2021 Northern Hemisphere influenza season in 200 adults 65 years of age and older in Taiwan. The objective of this study is to describe the immunogenicity and safety of QIV-HD administered by intramuscular (IM) route. A locally licensed standard-dose quadrivalent influenza vaccine (QIV-SD) (AdimFlu-S (QIS)) administered by intramuscular (IM) route will serve as a control arm. AdimFlu-S (QIS) was approved for use by the TFDA in 2017. AdimFlu-S (QIS) is a split vaccine and contains 15 µg HA of each of 4 virus strains (A/H1N1, A/H3N2, and one B strain from each of the Victoria and the Yamagata lineages) for a total of 60 µg of HA antigen per 0.5 mL dose. Starting in 2019, Taiwan's mass vaccination campaign will switch from a standard-dose trivalent influenza vaccine (TIV-SD) to a QIV-SD vaccine.

Eligible subjects will be randomized in a 1:1 ratio to receive a single IM injection of either QIV-HD or QIV-SD at Day (D)0.

Interactive response technology (IRT) will be used to randomly assign subjects to one of the 2 study groups and to assign subject numbers in each of the groups. Electronic data capture (EDC) will be used for the collection of data.

3.2 Trial Plan

The study plan is summarized in the Table of Study Procedures below (Table 3.1).

Vaccination

All eligible subjects will be randomized to receive a single injection of either the QIV-HD or QIV-SD vaccine at Visit (V) 01 (D0).

Blood Sampling

All subjects will provide a pre-vaccination blood sample at V01 (D0) and a post-vaccination blood sample at V02 (D28 [+ 7 days]).

Collection of Safety Data

Subjects will be asked to notify the site immediately about any potential serious adverse events (SAEs) (including adverse events of special interest [AESIs]) at any time during the study.

All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic adverse events (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-D7), unsolicited AEs (D0-V02), SAEs (D0-V02), and AESIs (D0-V02) in a diary card. Staff will review the D0 to V02 safety data with subjects at V02.

Table 3.1: Study procedures

Phase III Study, 2 Visits, 1 Vaccination, 2 Blood Samples, 28 Days Duration per Subject

Visit/Contact	**Visit 1**	**Visit 2**
Study timelines (days)	D0	D28
Time windows (days)	NA	[+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
Physical examination*	X	
Contact IRT system for randomization, subject number, and unique dose number allocation	X	
Blood sampling (BL), 10 mL	BL0001†	BL0002
Vaccination	X	
Immediate surveillance (30 minutes)	X	
Diary card provided‡	X	
Recording of solicited injection site & systemic reactions	D0-D7	
Collection of unsolicited adverse events	D0-D28	
Diary card collected and reviewed		X
Study termination record		X
Collection of SAEs (including AESIs)**	To be reported at any time during the study	

Abbreviations: AE, adverse event; AESI, adverse event of special interest; D, Day; SAE, serious adverse event.

§Previous influenza vaccination history should be collected for the previous year

* Clinical or medically-driven physical examination based on medical history will be performed at V01. Clinical or medically-driven physical examination may also be performed at V02, as necessary.

† Collection of the first blood sample (BL1) to occur before vaccination.

‡ Subjects will use this diary card to record information about solicited reactions from D0 to D7, as well as unsolicited AEs, SAEs, and AESIs from D0 to D28 after vaccination.

** 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.

4 Endpoints and Assessment Methods

4.1 Endpoints and Assessment Methods

See Section 9 of the protocol.

For measured safety events, two different scales will be used for classification at the time of statistical analysis:

- Sponsor standard intensity scales will be used to assess safety as part of study objective and described in the final study report.
- National Medical Products Administration (NMPA) intensity scale will also be used at the time of analysis for exploratory purpose only and thus described in Appendix 15.

  Solicited reactions or unsolicited AEs that meet Chinese grading criteria guideline for Grade 4 (at least potentially life-threatening) will be considered as SAEs with life-threatening seriousness, which will be reported specifically at the time of statistical analysis. This allows complying with Chinese Guideline for "Adverse Reaction of Prophylactic Vaccines in Clinical Trial" (published by NMPA on 31 December 2019).

4.2 Derived Endpoints: Calculation Methods

4.2.1 Immunogenicity

4.2.1.1 Computed Values for Analysis

In order to appropriately manage extreme values (< lower limit of quantitation [LLOQ] and ≥ upper limit of quantitation [ULOQ]) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each BL drawn:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is ≥ LLOQ and < ULOQ (or ≤ ULOQ), then use the value
- If a value is ≥ ULOQ (or > ULOQ), then use the computed value ULOQ

Duplicate records (per subject, antigen, and method) are recorded for the hemagglutination inhibition (HAI) assay. A geometric mean of duplicate will be applied in order to obtain a unique value for the statistical analysis.

4.2.1.2 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-vaccination computed values which are computed as described in Section 4.2.1.1. The computed value for fold-rise is:

- Computed value = Post-vaccination computed value / Baseline computed value.

For HAI assay, if the computed value is ≥ 4-fold rise, then the derived 4-fold rise indicator will be "Yes" for that test, otherwise the corresponding indicators will be "No".

Note: If baseline or post-vaccination is missing, then the fold-rise is missing.

4.2.1.3 Seroconversion

Seroconversion is defined for HAI assay as either

- A computed value < 10 [1/dil] at D0 and post-vaccination computed value ≥ 40 [1/dil] at D28,

or

- A computed value ≥ 10 [1/dil] at D0 and a ≥ 4-fold rise in computed titer values [1/dil] at D28 as described in Section 4.2.1.1.

4.2.2 Efficacy

Not applicable.

4.2.3 Safety

4.2.3.1 Solicited Reactions

4.2.3.1.1 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.

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

- Grade 1: ≥ 25 to ≤ 50 mm
- Grade 2: ≥ 51 to ≤ 100 mm
- Grade 3: > 100 mm

For measurable systemic reactions (Fever):

- Grade 1: ≥ 38.0°C to ≤ 38.4°C, or ≥ 100.4°F to ≤ 101.1°F
- Grade 2: ≥ 38.5°C to ≤ 38.9°C, or ≥ 101.2°F to ≤ 102.0°F
- Grade 3: ≥ 39.0°C or ≥ 102.1°F

NMPA scale:

For measurable injection site reactions

- Grade 1: ≥ 25 to < 50 mm
- Grade 2: ≥ 50 to < 100 mm
- Grade 3: ≥ 100 mm
- Any solicited reactions at least life-threatening (that meet Chinese grading criteria guideline for Grade 4) will also be considered as SAEs with life-threatening seriousness, which will be reported specifically at the time of the statistical analysis.

For fever by axillary route

- Grade 1: ≥ 37.3°C to < 38.0°C,

- Grade 2: ≥ 38.0°C to < 38.5°C,
- Grade 3: ≥ 38.5°C to < 39.5°C, or >=39.5°C lasting <=3 days,
- Grade 4: ≥ 39.5°C, lasting for more than 3 days

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

Solicited reactions (except Fever/Pyrexia) with an investigator occurrence recorded as "No" and with all daily records missing then 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 the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (eg, swelling measurement > 0 millimeter (mm) but < 25 mm in adults).

Note: The maximum intensity on 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.

4.2.3.1.2 Maximum Intensity

Maximum intensity is derived from the daily intensities computed as described in Section 4.2.3.1.1 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 the Section 9.1.2.3.2 of the protocol.

4.2.3.1.3 Occurrence

Occurrence is derived from the maximum intensity on the period considered:

- None: No occurrence
- Grade 1, Grade 2, Grade 3 or Grade 4: Occurrence
- Missing: Missing occurrence

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

4.2.3.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.3.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, Grade3 or Grade 4.

Note: If a reaction is not continuous (ie, reaction occurs over 2 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 4.1: Categories for time of onset

Injection Site Reactions (D0-D7)	Systemic Reactions (D0-D7)
D0-D3	D0-D3
D4-D7	D4-D7

4.2.3.1.5 Number of Days of Occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.2.3.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, Grade 3 or Grade 4. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

Table 4.2: Categories for number of days of occurrence during the solicited period

Injection Site Reactions (D0-D7)	Systemic Reactions (D0-D7)
1-3 days	1-3 days
4-7 days	4-7 days
8 days	8 days

4.2.3.1.6 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:

- (stop date - vaccination date) + (number of days of occurrence within the solicited period) − length of the solicited period + 1.

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 4.3: Categories for overall number of days of occurrence

Injection Site Reactions	Systemic Reactions
1-3 days	1-3 days
4-7 days	4-7 days
≥ 8 days	≥ 8 days
Missing	Missing

4.2.3.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.3.1.1 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 (eg, when the maximum measurement after D7 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.

4.2.3.2 Unsolicited AEs

4.2.3.2.1 Occurrence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event. Grade 0 events should be included in the listing "Unsolicited (non-serious) adverse events not included in the safety analysis".

4.2.3.2.2 Intensity

Intensity for unsolicited AEs will be derived according to the following classification:
None, Grade 1, Grade 2, Grade 3, Grade 4 or Missing.

If the unsolicited 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 than the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (eg, swelling measurement > 0 mm but < 25 mm in adults). 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.

4.2.3.2.3 Time of Onset

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

- Start date of the unsolicited 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 AEs 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
- ≥ D15
- Missing

Serious adverse events (SAEs) will be analyzed during post-dose period (ie, within 28 days after the injection).
An SAE 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.

4.2.3.2.4 Duration

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

- Stop date of unsolicited AE - start date of unsolicited AE + 1.

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

Duration will be displayed by period as following:

- 1-3 days
- 4-7 days

- 8-14 days
- ≥ 15 days
- Missing

4.2.3.2.5 Seriousness (SAE)

No derivation or imputation will be done. This information will be at least listed and eventually could be summarized as collected.

4.2.3.2.6 Outcome (SAE)

No derivation or imputation will be done. This information will be at least listed and eventually could be summarized as collected.

4.2.3.3 Other Safety Endpoints

4.2.3.3.1 Action Taken

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

4.2.3.3.2 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 5.3.1.2.

4.2.3.3.3 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.

4.2.3.3.4 AEs of Special Interest (AESIs)

AESIs will be captured as SAEs. These include:

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

4.2.4 Derived Other Variables

4.2.4.1 Age for Demographics

The age of a subject in the study is the calendar age in years at the time of inclusion. The age calendar is the age computed automatically in the eCRF, and presented as an integer.

4.2.4.2 Duration of the Study

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

- Maximum (Visit dates, Termination date, safety follow-up date) – minimum (V01 date) +1

4.2.4.3 Subject Duration

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

Maximum (V02 dates, termination date) – V01 date + 1

4.2.4.4 Time Interval

The time interval between 2 study timepoints (visits/vaccination/blood samples) is computed as follows:

Later date – earlier date.

4.2.4.5 Influenza Vaccination Received the Year Preceding the Enrollment in the Study

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

5 Statistical Methods and Determination of Sample Size

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 software or later.

The results of the statistical analysis will be available in the final clinical study report (CSR).

For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% confidence intervals [CIs]) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
Immunogenicity results	**Categorical data (seroconversion, cutoff)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer / data)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

The confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (1), ie, using the inverse of the beta integral with SAS®).

For immunogenicity results, assuming that Log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

The impact of COVID-19 pandemic situation on study conduct will be summarized through impact on visit procedures, study completion and major/critical protocol deviations due to COVID-19. The subjects impacted by COVID-19 pandemic situation will be defined as the subjects with at least one major/critical protocol deviation due to COVID-19 or who did not complete the study due to COVID-19. If more than 20% of subjects are impacted as per this definition and still evaluable for immunogenicity/safety at primary timepoints, the main immunogenicity and safety endpoints will also be summarized in these subjects to assess the impact of COVID-19 situation on study outcome.

5.1 Statistical Methods

For the purposes of the statistical methods section, the 4 virus strains in the QIV-HD study groups and the QIV-SD study groups will be labeled as follows:

- A/(H1N1)-like strain A/H1N1
- A/(H3N2)-like strain A/H3N2
- B/(Victoria Lineage)-like strain B1
- B/(Yamagata Lineage)-like strain B2

5.1.1 Hypotheses and Statistical Methods for Objectives

5.1.1.1 Immunogenicity

5.1.1.1.1 Hypotheses

No hypotheses will be tested.

5.1.1.1.2 Statistical Methods

For descriptive purposes, the statistics presented in Table 5.1 will be produced. Immunogenicity endpoints will be summarized by vaccine group with 95% CIs. Assuming that $\log_{10}$ transformation of the data follows a normal distribution, the $\log_{10}$ (data) will be used for the statistical analysis, then antilog transformations will be applied to the results of calculations, in order to provide the results in terms of GMs. The following descriptive statistics will be displayed:

- Geometric mean titers (GMTs) for each strain at D0 and D28
- The geometric mean titer ratios (GMTRs): geometric mean of the post-vaccination/pre-vaccination ratios for each strain
- Ratios of GMTs between vaccine groups at D28
- Seroconversion rates at D28 from baseline titers at D0
- Proportion of subjects with titers ≥ 10 (1/dilution [dil]) for each strain at D0 and D28
- Proportion of subjects with titers ≥ 40 (1/dilution [dil]) for each strain at D0 and D28
- Reverse Cumulative Distribution of titers for each strain at D0 and D28 (eg, Reverse Cumulative Distribution Curves (RCDCs) of the titers)

In addition, immunogenicity data will be displayed using GMTs and seroconversion rates by subgroups of age (65 to 74 years and ≥75 years, sex , previous influenza vaccination status (received a seasonal influenza vaccine in the previous influenza season or not), and baseline

seropositivity status (seropositive and seronegative are defined as baseline antibody titer ≥ 1:10 or < 1:10).

5.1.1.2 Safety

5.1.1.2.1 Hypotheses

No hypotheses will be tested.

5.1.1.2.2 Statistical Methods

Safety endpoints will be summarized by vaccine group. Solicited reactions (solicited injection site and systemic reactions), unsolicited AEs, SAEs, and AESIs will be summarized. The main parameters will be described with 95% CIs (Clopper-Pearson method) (1).

In addition, safety overview will be described by subgroups of age, sex and previous influenza vaccination status.

5.2 Analysis Sets

Three main analysis sets will be used: the per-protocol analysis set (PPAS), the full analysis set (FAS), and the Safety Analysis Set (SafAS).

5.2.1 Full Analysis Set

The FAS is defined as the subset of randomized subjects who received one of the study vaccines and had a post-vaccination blood sample. Subjects will be analyzed according to the vaccine group to which they were randomized.

5.2.2 Per-Protocol Analysis Set

The PPAS is a subset of the FAS. The subjects presenting with at least one of the following criteria will be excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified 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 V02 in the proper time window (ie, 28 to 35 days after vaccination) or a post-dose serology sample was not drawn at V02
- Subject received protocol-prohibited* medication or vaccine.
- Subjects with no post-vaccination HAI results for the 4 strains

* Protocol prohibited medication is category 2 and 3 concomitant medication taken before visit 2 and flagged as prohibited in the database

The definition may be complemented with additional criteria for exclusion after the review of protocol deviations reported on site. During the review, such deviations will be marked with exclusion from analysis set for programming purpose.

5.2.3 Safety Analysis Set

The SafAS is defined as those subjects who have received one of the study vaccines and have any safety data available. 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).

5.2.4 Other Analysis Sets

Enrolled Subjects

Enrolled subjects are subjects for whom a CRB has been created.

Randomized Subjects

A randomized subject is a subject for whom a vaccine group has been allocated.

5.2.5 Populations Used in Analyses

All randomized subjects with data in the CRB will be taken into account in the description of the population (eg, the disposition, the demographic, or baseline characteristics).

The immunogenicity analyses from the HAI assay will be performed on the PPAS and on the FAS.

The safety analyses will be performed on the SafAS.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

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

5.3.1.1 Immediate

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.

5.3.1.2 Causality

Missing causality (relationship) for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

5.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 4.2.3.1.1.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.3.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and will 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 will not be imputed.

5.3.1.6 Action Taken

Missing actions taken will remain missing and will not be imputed.

5.3.2 Immunogenicity

LLOQ and ULOQ management will be performed as described in Section 4.2.1. No test or search for outliers will be performed.

No replacement will be done for missing values.

5.4 Interim / Preliminary Analysis

No interim analyses are planned.

5.5 Determination of Sample Size and Power Calculation

The sample size is not based on any hypothesis testing.

The number of subjects is designed to provide supportive immunogenicity and safety data on the study vaccine when administered in adults 65 years of age and older in Taiwan. During the meeting with TFDA in Aug 2019, Sanofi Pasteur proposed a sample size of 200 subjects (100 subjects in each group) and TFDA agreed, but there was no specific sample size requirement.

There was no power assessment as the analyses will be descriptive.

Data Review for Statistical Purposes

This study will not include an early review of safety data (ie, no early safety review of preliminary data occurring at pre-determined milestones defined in the protocol with pause in enrollment). However, it may be interrupted at any time if new data about the investigational product become available, and/or on advice of the Sponsor, the institutional review boards (IRBs), or the governing regulatory authorities in the country where the study is taking place.

A blind review of the data is anticipated through the data review process led by Data Management before database lock. This review of the data will include a statistical review.

5.6 Changes in the Conduct of the Trial or Planned Analyses

Not applicable.

6 References List

1 Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.