# STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Protocol title:** | **Immunogenicity and Safety of High-Dose Quadrivalent Influenza Vaccine (SP0178) Administered by Intramuscular Route versus Standard-Dose Quadrivalent Influenza Vaccine by Subcutaneous Route in Subjects 60 Years of Age and Older in Japan** |
| **Protocol number:** | **QHD00010-EFC15150** |
| **Compound number (INN/Trademark):** | **SP0178** |
| **Study phase:** | **III** |
| **Short title:** | **Not Applicable** |
| **Statistician:** | [redacted] |
| **Statistical project leader:** | [redacted] |
| **Date of issue:** | **08-Jan-2021** |

**Regulatory agency identifier number(s):**

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| WHO universal trial number: | U1111-1225-1085 |
| ClinicalTrials.gov Identifier: | NCT04498832 |

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# VERSION HISTORY

This statistical analysis plan (SAP) for study QHD00010-EFC15150 is based on the protocol dated 24-Apr-2020. There are no major changes to the statistical analysis features in this SAP.

The first subject was randomized on 21-Oct-2020.

**Table 1 - Major changes in statistical analysis plan**

| SAP Version | Approval Date | Changes | Rationale |
|---|---|---|---|
| 1.0 | 08-Jan-2021 | Not Applicable | Original version |

# 1 INTRODUCTION

## 1.1 STUDY DESIGN

This will be a Phase III, randomized, modified double-blind, active-controlled, multi-center study to be conducted in approximately 2100 healthy adults 60 years of age and older to evaluate the immunogenicity and safety of the high-dose quadrivalent influenza vaccine (QIV-HD) administered by intramuscular (IM) route. A local standard-dose quadrivalent influenza vaccine (QIV-SD) administered by subcutaneous (SC) route will serve as a control arm.

Interactive response technology (IRT) will be used to randomly assign subjects to either of the 2 study groups (QIV-HD by IM route or QIV-SD by SC route) in a 1:1 ratio by block randomization, stratified according to age (i.e., 60 to 64, 65 to 74, and 75 years of age and older) and site, and to assign subject numbers in each of the groups.

Study primary analysis will be conducted after study completion.

## 1.2 OBJECTIVE AND ENDPOINTS

**Table 2 - Objectives and endpoints**

| | Objectives | Endpoints |
|---|---|---|
| **Primary** | **To demonstrate that QIV-HD induces an immune response (as assessed by hemagglutination inhibition [HAI] geometric mean titers [GMTs] and seroconversion rates) that is superior to responses induced by QIV-SD for the 4 virus strains at 28 days post-vaccination in all subjects** | • HAI antibody (Ab) titers obtained on Day (D) 28<br>• Seroconversion (titer <10 [1/dil] at D0 and post-injection titer ≥40 [1/dil] at D28, or titer ≥10 [1/dil] at D0 and a ≥4-fold increase in titer [1/dil] at D28) |
| **Secondary** | **Immunogenicity** | |
| | • To describe the immune response induced by QIV-HD and QIV-SD by HAI measurement method in all subjects | • HAI Ab titers obtained on D0 and D28<br>• Individual HAI titers ratio D28/D0<br>• Seroconversion (titer <10 [1/dil] at D0 and post-injection titer ≥40 [1/dil] at D28, or titer ≥10 [1/dil] at D0 and a ≥4-fold increase in titer [1/dil] at D28)<br>• Percentage of subjects with titers ≥40 (1/dil) at D0 and D28 |
| | **Safety** | |
| | • To describe the safety profile of all subjects in each study group | • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination. |

| Objectives | | Endpoints |
|---|---|---|
| | | • 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 case report book [CRB]) injection site reactions and systemic reactions occurring up to 7 days after vaccination.<br>• Occurrence, nature (MedDRA PT), time to onset, duration, intensity, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the study, of unsolicited AEs up to 28 days after vaccination.<br>• Occurrence, nature (MedDRA PT), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of serious adverse events (SAEs) throughout the study.<br>• Occurrence, nature (MedDRA PT), and relationship to vaccination of adverse events of special interest (AESIs) throughout the study. |
| **Tertiary/exploratory** | **Not Applicable** | |

# 2 SAMPLE SIZE DETERMINATION

A total of approximately 2100 adults 60 years of age and older will be enrolled. A sample size of 2100 is determined based on an overall power of 90% controlled with one-sided 0.025 type I error for demonstrating superiority in the primary objective for all 4 strains for both the HAI GMTs and seroconversion rates comparing QIV-HD versus QIV-SD groups. The superiority will be demonstrated if the lower bounds of confidence intervals (CIs) are greater than the thresholds defined as 1.0 for ratio of GMTs and 0 for difference in seroconversion rates. All the statistical assumptions used in the sample size calculation are presented in Table 3.

**Table 3 – Statistical Assumptions for the Sample Size Calculation**

| Statistical Criteria | Assumption |
|---|---|
| Allocation ratio | 1:1 between QIV-HD and QIV-SD |
| Overall power | >90% |
| Type I error | One-sided 0.025 on each strain for each endpoint |
| Expected GMT ratio | 1.6 for all strains |
| Standard deviation for the log titers (in log10 scale) | 0.7 for all strains |
| Expected seroconversion rates | 40% for 2 strains with an increase of 17% in the QIV-HD group and 50% for another 2 strains with an increase of 8% in the QIV-HD group |
| Attrition rate | 5% in the FAS |

# 3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

**Table 4 - Populations for analyses**

| Population | Description |
|---|---|
| Enrolled | Enrolled subjects are subjects for whom a case report form (CRF) has been created. |
| Randomized | Randomized subjects are subjects for whom an injection group has been allocated. |
| Full Analysis Set (FAS) | The FAS will include all randomized subjects who received at least one dose of the study vaccine and had a post-vaccination blood sample HAI result for at least one strain.<br>Subjects will be analyzed according to the vaccine group to which they were randomized. |
| Per-Protocol Analysis Set (PPAS) | The PPAS is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS:<br>• Subjects did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria<br>• Subject did not receive vaccine<br>• Subject received a vaccine other than the one that he / she was randomized to receive<br>• Preparation and / or administration of vaccine was not done as per-protocol<br>• Subject did not provide the post-dose serology sample at visit (V)02 in the proper time window (i.e., 28 to 35 days after vaccination) or a post-dose serology sample (V02) was not drawn<br>• Subject received a protocol-prohibited therapy / medication / vaccine (restricted therapies / medications / vaccine are indicated in "Concomitant medications" of Section 5.3)<br>• Subject had other protocol deviations that affected the subject's immune response, as determined by the clinical team before locking the database<br>In addition to the criteria listed above, subjects will also be excluded from the PPAS if their HAI serology sample at V02 did not produce a valid test result for all strains (i.e., results for all antigens are missing). In any case, the PPAS definition will be finalized before the database lock. |
| Safety Analysis Set (SafAS) | The SafAS is defined as those subjects who have received the study vaccine[a]. All subjects will have their safety analyzed according to the vaccine they actually received.<br>Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately). |

*a* For which safety data are scheduled to be collected.

The immunogenicity analysis set consists of the FAS and the PPAS. All subjects with data in the CRB will be taken into account in the description of the population (e.g., the disposition, the demographics, or baseline characteristics). The safety analyses will be performed on the SafAS.

The immunogenicity analyses will be performed on the FAS and PPAS, and the conclusion will be made based on the results of the FAS.

# 4 STATISTICAL ANALYSES

## 4.1 GENERAL CONSIDERATIONS

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).

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of subjects.

Clinical safety results will be presented using number and percentage of subjects with corresponding 95% CI. Number of events will be also added for unsolicited events.

For immunogenicity results, categorical data will be presented using number and percentage of subjects with their 95% CI. In order to provide results of continuous data (titer / data), 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 transformation will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

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

Rounding rules for descriptive statistics will follow the Sanofi Pasteur standard working instruction ("Conventions for the Presentation of Descriptive Statistics"). When presenting percentages (and 95% CI which are percentages), one digit after the decimal place will be used.

Each calculation of the CIs are detailed in Section 5.4.7.

Statistical analysis for immunogenicity will be performed using the results obtained from each strain used for HAI testing.

QIV-HD contains strains to be determined based on World Health Organization (WHO) / the United States (US) Vaccines and Related Biological Products Advisory Committee (VRBPAC) recommendations for the 2020-2021 Northern Hemisphere (NH) influenza season. QIV-SD contains strains to be determined by Ministry of Health, Labour and Welfare (MHLW) for the 2020-2021 NH influenza season.

The HAI testing will be performed using both the QIV-HD and QIV-SD strains as test antigens for all the subjects, irrespective of the vaccine received.

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

| | QIV-HD | QIV-SD |
|---|---|---|
| A/H1N1 | A/Guangdong-Maonan/SWL1536/2019 CNIC-1909 (H1N1) | A/Guangdong-Maonan/SWL1536/2019 (CNIC-1909) (H1N1) |
| A/H3N2 | A/Hong Kong/2671/2019 IVR-208 (H3N2) | A/Hong Kong/2671/2019 (NIB-121) (H3N2) |
| B(Victoria lineage) | B/Washington/02/2019 wt virus strain | B/Victoria/705/2018 (BVR-11) |
| B(Yamagata lineage) | B/Phuket/3073/2013 wt virus strain | B/Phuket/3073/2013 |

For the purpose of the immunogenicity statistical analysis, the 6 virus strains in the vaccine groups will be labeled as follow:

- A/Guangdong-Maonan/SWL1536/2019 CNIC-1909 (H1N1) : A/H1N1
- A/Hong Kong/2671/2019 IVR-208 (H3N2) : A/H3N2
- A/Hong Kong/2671/2019 (NIB-121) (H3N2) : A/H3N2-like
- B/Washington/02/2019 wt virus strain : B/Victoria
- B/Victoria/705/2018 (BVR-11) : B/Victoria-like
- B/Phuket/3073/2013 wt virus strain : B/Yamagata

### 4.2 PARTICIPANT DISPOSITIONS

Duration of the study will be presented using a summary table of Enrolled subjects.

The number (%) of randomized subjects will be summarized by center and randomized vaccine group.

A summary of inclusion and exclusion criteria will be presented by randomized vaccine group on randomized subjects.

Vaccine allocation, vaccine administration, and adherence to schedule will be summarized by randomized vaccine group giving the number (%) of randomized subjects. The following categories to summarize vaccine administration and adherence to schedule will be used.

- Vaccine administration
  - Administration as per the route provided by IRT
  - Administration as per the site defined by protocol
  - Side (left and right)
- Adherence to schedule

- Time interval from vaccination at V01 to blood sample at V02 (<28, 28 to 35, and >35 days)

The number (%) of subjects in the following categories will be provided on randomized subjects:

- Randomized subjects at V01
- Subjects present at V01
- Subjects who provided blood sample at V01
- Subjects injected at V01
- Subjects present at V02
- Subjects who provided blood sample at V02
- Subjects who completed the study
- Subjects who discontinued the study with following reasons of early termination
  - Adverse event
  - Protocol deviation
  - Lost to follow-up
  - Withdrawal by subject

The number (%) of randomized subjects will be summarized by site, following age category as randomization strata, and randomized vaccine group: 60 to 64 years, 65 to 74 years, and ≥75 years.

The number (%) of subjects included in immunogenicity analysis set (FAS and PPAS) and SafAS listed in Table 4 will be summarized.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized subjects.

## 4.3 PRIMARY ENDPOINT(S) ANALYSIS

### 4.3.1 Definition of endpoint(s)

The primary endpoints are as follows for the evaluation of immunogenicity:

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

The primary endpoints will be evaluated using the result from 4 strains to be determined by MHLW contained in the QIV-SD used for the HAI testing.

### 4.3.2 Main analytical approach

A superiority approach will be used to compare post-vaccination GMTs and seroconversion rates between QIV-HD and QIV-SD groups for each strain using a 1-sided test with Type I error rate of 0.025 following the individual hypotheses. The definitions of superiority correspond to statistical superiority where 1.0 is used as the threshold for the ratio of GMTs and 0 is used as the threshold for difference of seroconversion rates. Superiority as defined in the primary objective is based on following individual hypothesis:

$$H_0^s: \frac{GMT_{QIV-HD}^s}{GMT_{QIV-SD}^s} \leq 1 \Leftrightarrow \log_{10}\left(GMT_{QIV-HD}^2\right) - \log_{10}\left(GMT_{QIV-SD}^s\right) \leq \log_{10}(1) = 0$$

$$H_A^s: \frac{GMT_{QIV-HD}^s}{GMT_{QIV-SD}^s} > 1 \Leftrightarrow \log_{10}\left(GMT_{QIV-HD}^s\right) - \log_{10}\left(GMT_{QIV-SD}^s\right) > \log_{10}(1) = 0$$

$$H_0^s: \pi_{QIV-HD}^s - \pi_{QIV-SD}^s \leq 0$$
$$H_A^s: \pi_{QIV-HD}^s - \pi_{QIV-SD}^s > 0$$

where

- $s$: strain
- $\pi$: the seroconversion rate

the statistical methodology will be based on the use of the lower bound of the 2-sided 95% CIs of the ratio of post-vaccination GMTs and difference in seroconversion rates between the QIV-HD group and QIV-SD group. The 95% CIs will be calculated by normal approximation of log-transformed titers for GMTs and by the Wilson score method without continuity correction, quoted by Newcombe, for seroconversion rates (2). The superiority will be demonstrated if the lower bounds of CIs are greater than the thresholds defined as 1.0 for ratio of GMTs and 0 for differences in seroconversion rates. The graphical presentations by GMTs and seroconversion rates will also be provided with their 95% CIs.

The superiority objective will be achieved if the superiority is demonstrated for all of the 4 strains for both GMTs and seroconversion rates. For the objective, it is planned to use the HAI assay results using both the QIV-HD and QIV-SD strains as test antigens for all the subjects irrespective of the vaccine received. The FAS will be used for the immunogenicity analyses.

### 4.3.3 Sensitivity analysis

Sensitivity analyses will be also performed according to the following analyses for the ratios of post-vaccination GMTs and the differences in the seroconversion rates in the FAS:

- Analysis of covariance (ANCOVA) with treatment group and age group (60 to 64, 65 to 74, and 75 years of age and older) of the stratification factor as fixed effects, and pre-vaccination value (V01) as a covariate for ratio of GMTs.
- Cochran-Mantel-Haentzel method stratified on age group (60 to 64, 65 to 74, and 75 years of age and older) of the stratification factor for difference in seroconversion rates.

#### 4.3.4 Supplementary analyses

The GMTs and seroconversion rates will be analyzed using similar main analytical approach as described in Section 4.3.2 on the PPAS to compared the endpoints between the QIV-HD and QIV-SD groups.

#### 4.3.5 Subgroup analyses

Subgroup analyses will be performed on the primary endpoint on the FAS across the following subgroups:

- Age group (60 to 64 years, 65 to 74 years, and ≥75 years; 60 to 64 years and ≥65 years)

The ratios of post-vaccination GMTs between the QIV-HD and QIV-SD groups and the differences in seroconversion rates with the corresponding 95% CIs will be presented. No statistical testing will be conducted for the subgroup analyses.

### 4.4 SECONDARY ENDPOINT(S) ANALYSIS

#### 4.4.1 Key/Confirmatory secondary endpoint(s)

##### *4.4.1.1 Definition of endpoint(s)*

The secondary endpoints for the evaluation of immunogenicity are:

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

The statistical analyses for secondary endpoints will be performed on the FAS using all 6 strains tested.

##### *4.4.1.2 Main analytical approach*

For descriptive purposes, following statistics with their corresponding 95% CI will be displayed:

- HAI GMTs and the ratios of the GMTs between the QIV-HD and QIV-SD groups at V02

- GMs of HAI titers
  - Pre-dose (V01) and post-dose (V02)
  - Post-dose response based on pre-dose (individual titer ratio V02/V01)
- Seroconversion rates and the difference between the QIV-HD and QIV-SD at V02
- Number and percentage of subjects with HAI titers ≥40 (1/dil) at each time point
- Distribution of HAI titers at each time point

Graphical presentations will be provided with their 95% CIs by:

- HAI GMTs at V02
- GMs of individual titer ratio V02/V01
- Seroconversion rates at V02

Reverse cumulative distribution curves (RCDCs) against each strain will be performed for pre-dose (V01) and post-dose immunogenicity (V02).

As a summary of hemagglutinin (HA) antibody response antigen, the following parameters will be displayed:

- Pre-dose (V01) and Post-dose (V02)
  - Geometric mean
  - Number and percentage of subjects with HAI titer ≥1:10
  - Number and percentage of subjects with HAI titer <1:10
  - Number and percentage of subjects with HAI titer ≥1:40
- Post-dose response based on pre-dose
  - Geometric mean (of individual ratio)
  - Seroconversion rate

More detailed summaries of the HA antibody response will also be provided by strain, adding median, Q1, Q3, minimum, maximum, mean and SD of Log10 transformed value for continuous data of titers.

#### *4.4.1.3 Subgroup analyses*

GMTs at V02, seroconversion rates at V02, and percentages of subjects with titers ≥40 (1/dil) and their corresponding 95% CIs will be presented on the FAS by following subgroups:

- Age group (60 to 64 years, 65 to 74 years, and ≥75 years; 60 to 64 years and ≥65 years)
- Sex (Male, Female)
- Previous influenza vaccination status (Yes, No)

- Baseline seropositivity status (Seronegative[<1:10], Seropositive[≥1:10])

#### 4.4.2 Supportive secondary endpoint(s)

Not applicable

### 4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

#### 4.5.1 Definition of endpoint(s)

Not applicable

#### 4.5.2 Main analytical approach

Not applicable

### 4.6 MULTIPLICITY ISSUES

It is required to demonstrate superiority on the FAS in all 4 strains determined by the MHLW to be contained in the QIV-SD for both GMTs and seroconversion rates. Therefore, no multiplicity issues are to be considered.

### 4.7 SAFETY ANALYSES

All safety analyses will be performed on the SafAS as defined in Section 3, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned. However, the 95% CI (Clopper-Pearson method) will be provided.
- Safety data in subjects who do not belong to the SafAS will be provided (in the listings of Appendix).

#### 4.7.1 Extent of exposure

Not applicable

#### 4.7.2 Adverse events

**General common rules for adverse events**

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), and associated primary system organ class (SOC) using the MedDRA version currently in effect at Sanofi at the time of database lock.

The AE tables will be sorted as indicated in Table 5.

**Table 5 - Sorting of AE tables**

| AE presentation | Sorting rules |
|---|---|
| SOC and PT | By the primary SOC and PT alphabetical order |

## Analysis of all adverse events

The safety overview after injection with the details below will be generated:

- Within 28 days after vaccine injection
  - Immediate unsolicited AE and adverse reaction (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
  - Serious adverse event (SAE)
  - Death
  - AE of special interest (AESI)
- During the study
  - SAE
  - Death
  - AESI

## Solicited reactions

The following summaries of solicited reactions within 7 days after vaccine injection will be presented using the terms prelisted in CRB:

- All and Grade 2 or 3 solicited reaction, solicited injection site reaction, and solicited systemic reaction
- Solicited reaction, each solicited injection site reaction (injection site pain, injection site erythema, injection site swelling, injection site induration, and injection site bruising), and solicited systemic reaction (fever, headache, malaise, myalgia, and shivering)

- 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) by following category:
  - By maximum intensity
  - By time of onset period
  - By range of number of days of occurrence during the solicited period (for any solicited reaction and Grade 3 solicited reactions)
  - By range of overall number of days of occurrence for the reactions still ongoing at D8 after vaccine injection
  - By action taken

**Unsolicited AEs**

The summary of unsolicited AEs within 7 days after vaccine injection with the details below will be generated:

- Immediate unsolicited AE and AR (any and Grade 3)
- Unsolicited AE and AR
- Unsolicited non-serious AE and AR (any and Grade 3)
- Unsolicited non-serious injection site AR (any and Grade 3)
- Unsolicited non-serious systemic AE and AR (any and Grade 3)
- SAE
- AESI

The summary of unsolicited AEs within 28 days after vaccine injection will also be generated.

The unsolicited non-serious AEs and ARs within 28 days after vaccine injection will also be summarized by maximum intensity, time of onset, and duration.

The AE summaries after vaccine injection of Table 6 will be generated with number (%) of subjects experiencing at least one event. In the summaries, the 95% CI of proportion and number of AE/ARs will also be presented.

The all and related SAEs within 28 days after vaccine injection and during the study will also be summarized by seriousness criterion and outcome.

**Table 6 - Analyses of adverse events**

| Type of AE | MedDRA levels |
|---|---|
| All unsolicited AE within 28 days | Primary SOC and PT |
| All unsolicited AR within 28 days | Primary SOC and PT |

| Type of AE | MedDRA levels |
|---|---|
| Unsolicited AEs within 28 days occurring in >1% of subjects | Primary SOC and PT |
| Unsolicited non-serious AE within 28 days | Primary SOC and PT |
| Unsolicited non-serious AR within 28 days | Primary SOC and PT |
| All and related AE leading to study discontinuation within 28 days | Primary SOC and PT |
| SAE | Overview[a] |
| | Primary SOC and PT |

*a* Will include the following AE categories: all SAEs and related SAEs within 7 days after vaccine injection, within 28 days after vaccine injection, and during the study

## Analysis of deaths

The summary of death will be presented above in safety overview.

## Analysis of adverse events of special interest (AESIs)

AESIs will be selected for analyses as indicated in Table 7. Number (%) of subjects experiencing at least one event within 28 days after vaccine injection and during the study will be provided for each event of interest. Tables will be sorted by SOC and PT as indicated in Table 5.

**Table 7 - Selections for AESIs**

| AESIs | Selection (PT) |
|---|---|
| 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 Standardised MedDRA Query (SMQ) term "Noninfectious encephalitis" (MedDRA Version 23.1) |
| 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 |

### 4.7.3 Additional safety assessments

#### *4.7.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)*

Not applicable

## 4.8 OTHER ANALYSES

### 4.8.1 Assessment of impact of COVID-19 pandemic

In order to assess an impact of Coronavirus Disease 2019 (COVID-19) pandemic on study conduct, the number (%) of subjects in the following categories will be also summarized on enrolled subjects.

- Subjects with a CRF
- Subjects impacted by COVID-19 pandemic situation
- Subjects with at least one major/critical protocol deviation due to COVID-19 pandemic situation, and each detailed deviation
- Subjects who discontinued the trial with following reasons of early termination due to COVID-19
  - Adverse event
  - Protocol deviation
  - Lost to follow-up
  - Withdrawal by subject
- Visit disposition at each visit (Visit 1 and Visit 2)
  - COVID-19 Visit not done
  - COVID-19 Visit partially done: blood sample not performed, vaccination not performed, and no solicited safety data available
  - COVID-19 At least one procedure out of time window: blood sample out of time window, vaccination out of time window, and visit date out of time window
  - COVID-19 No procedure done on site
  - COVID-19 At least one procedure done by phone
  - COVID-19 At least one procedure done at home

## 4.9 INTERIM ANALYSES

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

# 5 SUPPORTING DOCUMENTATION

## 5.1 APPENDIX 1 LIST OF ABBREVIATIONS

| | |
|---|---|
| Ab: | antibody |
| AE: | adverse event |
| AESI: | adverse event of special interest |
| ANCOVA: | analysis of covariance |
| AR: | adverse reaction |
| CI: | confidence interval |
| COVID-19: | Coronavirus Disease 2019 |
| CRB: | case report book (all the case report forms for a subject) |
| CRF: | case report form |
| CSR: | clinical study report |
| D: | Day |
| FAS: | Full Analysis Set |
| GBS: | Guillain-Barré syndrome |
| GM: | geometric mean |
| GMT: | geometric mean titer |
| GMTR: | geometric mean of individual titer ratio |
| HA: | hemagglutinin |
| HAI: | hemagglutination inhibition |
| IM: | intramuscular |
| IRT: | interactive response technology |
| LLOQ: | lower limit of quantification |
| LLT: | lower-level term |
| MCAR: | missing completely at random |
| MD: | missing data |
| MedDRA: | Medical Dictionary for Regulatory Activities |
| MHLW: | Ministry of Health, Labour and Welfare |
| NH: | Northern Hemisphere |
| NM: | non-measurable |
| NSAIDs: | non-steroidal anti-inflammatory drugs |
| PPAS: | Per-Protocol Analysis Set |
| PT: | preferred term |
| Q1: | first quartile |
| Q3: | third quartile |
| 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 |

| | |
|---|---|
| SC: | subcutaneous |
| SD: | standard deviation |
| SMQ: | Standardised MeDRA Query |
| SOC: | system organ class |
| ULOQ: | upper limit of quantification |
| US: | United States |
| V: | visit |
| VRBPAC: | Vaccines and Related Biological Products Advisory Committee |
| WHO: | World Health Organization |
| WHO-DD: | World Health Organization-drug dictionary |

## 5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

**Table 8 - Major statistical changes in protocol amendment(s)**

| Amendment Number | Approval Date | Changes | Rationale |
|---|---|---|---|
| 1 | 24-Apr-2020 | No changes in protocol amendment | |

## 5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

***Demographics, baseline characteristics, medical surgical history***

The following demographics and baseline characteristics, and medical history will be summarized using descriptive statistics in the randomized population. The demographics and baseline characteristics will also be summarized in the FAS, PPAS, and SafAS.

Demographic and baseline characteristics

- age in years as quantitative variable and in categories (60 to <65, ≥65, 65 to <75, ≥75)
- gender (Male, Female) and the ratio
- race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Multiple, Not reported, and Unknown)
- weight in kilograms
- BMI (body mass index) as quantitative variable and in categories (<18.5, 18.5 to 24.9, ≥25.0)

Medical history includes conditions/illness for which the subject is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an

SAE or to a repetitive outpatient care will be collected in the case report book (CRB). The medical history will not be coded using the MedDRA.

Influenza disease history during 2019 through 2020 season, and history of influenza vaccination during 2019 through 2020 season, pneumococcal vaccination and shingles vaccination will also be collected.

***Concomitant medications***

All reportable medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

Documentation in the CRB of ongoing concomitant medication(s) will be limited to specific categories of medication(s) 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 Ab 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 and immune globulins, immune-suppressors, immune-modulators with immunosuppressive properties, antiproliferative 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)

Following treatments are the protocol-restricted 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

The reportable medications will be summarized for the randomized subjects. The summary will be presented based on the use of any medication and each category, and the medication considered by the sponsor as prophylactic, protocol-restricted treatment, and ongoing at study termination.

**Protocol-prohibited therapy, medication or vaccines**

In general, the "prohibited" variable is not derived. All concomitant medications are reviewed by the clinical team and the value of "prohibited" variable is determined before database lock by the clinical team according to the treatments defined above as "protocol-restricted."

If the above protocol-restricted therapy, medication or vaccines are received during study participation, it may impact the corresponding immunogenicity analyses.

## 5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

### 5.4.1 General conventions

***Duration of the study***

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

Maximum (Visit dates, Termination date) – minimum (Date of Visit 1) + 1.

***Subject duration***

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

Maximum (Date of visits, termination date) – Date of Visit 1 + 1.

***Time interval***

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

Last date – earlier date.

### 5.4.2 Data handling conventions for safety variables

#### *5.4.2.1 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 reaction (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 to ≤38.4 °C, or ≥100.4 to ≤101.1 °C
- Grade 2: ≥38.5 to ≤38.9 °C, or ≥101.2 to ≤102.0 °C
- Grade 3: ≥39.0 °C, or ≥102.1 °C

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 overall intensity***

Maximum intensity is derived from the daily intensities computed as described above in "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 the Section 9.2.2.3.2 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 period 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 9 – Categories for time of onset**

| Injection Site Reactions (D0-D7) | Systemic Reactions (D0-D7) |
|---|---|
| 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 10 – 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 |

### *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 11 – 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 |

***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 in adults). 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.

#### *5.4.2.2 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 and is not a Grade 0 intensity event.

Grade 0 events are not included in safety analysis but are included in separate listings.

***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 of 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 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.

***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 the 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
- ≥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
- ≥15 days
- Missing

#### *5.4.2.3 SAEs*

***Time of onset***

Time of onset will be computed using the same methodology than for unsolicited non-serious AEs described in Section 5.4.2.2.

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

- Within 28 days after vaccine injection
- During the 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, and will be included in these tables.

Note: SAEs that occurred before vaccination (negative time of onset) will not be included in analysis but will be listed separately.

***Duration***

Duration will be computed using the same methodology than for unsolicited non-serious AEs described in Section 5.4.2.2.

***Intensity***

The intensity for SAE will be computed using the same methodology than for unsolicited non-serious AEs described in Section 5.4.2.2.

#### *5.4.2.4 Other Safety Endpoints*

***Action taken***

This information will be summarized as collected, including missing observation. 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 5.4.4.

***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 "Caused Study 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" checked that is at least Grade 1 and is within the time period indicated.

### 5.4.3 Data handling conventions for immunogenicity variables

***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 <lower limit of quantification (LLOQ), then the computed value, LLOQ/2, will be used
- If a titer is ≥LLOQ and <upper limit of quantification (ULOQ) (or ≤ULOQ), then the titer itself will be used
- If a titer is ≥ULOP (or >ULOQ), then computed value, ULOQ, will be used.

No test or search for outliers will be performed.

***Fold-rise***

The derived endpoint fold-rise is driven by both baseline and post-vaccination computed values which are computed as described above. 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." If baseline or post-vaccination value is missing, the fold-rise is missing.

***Seroconversion***

Seroconversion is defined for HAI assay as either

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

### 5.4.4 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.

#### *5.4.4.1 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.

***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 vaccination recorded if within 24 hours will remain missing and not be imputed. Such SAEs will not be considered as immediate.

***Causality***

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

***Measurements***

Partially missing temperatures will be handled as described in "Daily intensity" of Section 5.4.2.1.

***Intensity***

For solicited reactions, missing intensities will be handled as described in "Daily intensity" of Section 5.4.2.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

***Start Date and Stop Date***

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.

***Action taken***

Missing actions taken will remain missing and not be imputed.

#### *5.4.4.2 Immunogenicity*

LLOQ and ULOQ management will be performed as described in "Computed values for analysis" of Section 5.4.3. No test or search for outliers will be performed.

No replacement will be done for missing values. Based on the previous TIV-HD, QIV-HD, and QIV-SD studies in this population, the amount of missing immunogenicity data is expected to be ≤5 % in this study. Usually in vaccine studies, it seems generally reasonable to assume missing immunogenicity data are missing completely at random (MCAR) (3). Indeed, it is highly unexpected that the dropout (or any other reaction for missing data) could be linked to the immune response of the subject.

### 5.4.5 Windows for time points

***Analysis windows for time points***

A measurement at each visit will be used for immunogenicity according to following table defined in the protocol. Solicited reactions and unsolicited (non-serious/serious) AEs observed at time of onset mentioned in Section 5.4.2 will be analyzed for safety analyses.

**Table 12 – Study procedure window definition**

| Visit / Contac | Visit 1 (V01) | Visit 2 (V02) |
|---|---|---|
| Study timelines (days) | 0 | 28 |
| Time windows (days) | NA | [+7 days] |

### 5.4.6 Pooling of centers for statistical analyses

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

### 5.4.7 Statistical technical issues

***Confidence interval for the individual group GMT and GMTR***

The 2-sided 95% CI for the individual group GMT and GM of individual titer ratio (GMTR) will be computed using the normal approximation as follows:

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

where $10^{(\bar{x})}$ is the GMT, $\bar{x} = \sum \log_{10}(x)/N$, $\log_{10}(x)$ 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 $\bar{x}$, $\alpha = 0.05$, and $t_{n-1,\alpha/2}$ is the $100(1-\alpha/2)$ percentile of the central *t*-distribution with *n*-1 degree of freedom.

***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 $\log_{10}$ (titer) is normally distributed, the 95% CI for the difference in $\log_{10}$ (GMT) between group $i$ and group $j$ will be in the form:

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

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

$S^2 = \left[(n_i - 1)S_i^2 + (n_j - 1)S_j^2\right] / (n_i + n_j - 2)$ 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)= $n_i + n_j - 2$.

***Confidence interval for the single proportion***

The 2-sided 95% CI for the single proportions will be constructed using the exact binomial method (Clopper-Pearson's method, quoted by Newcombe (1), i.e., using the inverse of the beta integral with SAS®):

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

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

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

***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 (2) 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:

$$\frac{\left(2n_1p_A + Z_{0.025}^2 \pm Z_{0.025}\sqrt{\left(Z_{0.025}^2 + 4n_1p_A(1-p_A)\right)}\right)}{2(n_1 + Z_{0.025}^2)},$$

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

$$\frac{\left(2n_2p_B + Z_{0.025}^2 \pm Z_{0.025}\sqrt{\left(Z_{0.025}^2 + 4n_2p_B(1-p_B)\right)}\right)}{2(n_2 + Z_{0.025}^2)},$$

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

# 6 REFERENCES

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

2. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998;17(8):873-90.

3. Li X, Wang WWB, Liu GF, Chan ISF. Handling missing data in vaccine clinical trials for immunogenicity and safety evaluation. J Biopharm Stat. 2011;21(2):294-310.

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