NCT04137887

Relative Effectiveness of a High-Dose Quadrivalent Influenza Vaccine versus a Standard-Dose Quadrivalent Influenza Vaccine in Subjects 65 Years of Age and Older

Phase IIIb/IV, randomized, modified double-blind, active-controlled, single center pragmatic study evaluating the effectiveness of high-dose quadrivalent influenza vaccine (QIV-HD) compared to a standard-dose quadrivalent influenza vaccine (QIV-SD) in subjects 65 years of age and older

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	QHD00012
Study Phase:	Phase IIIb/IV
Sponsor:	Sanofi Pasteur, Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product(s):	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 as well as complications like cardiovascular and respiratory related hospitalizations
Version and Date of the SAP core body part:	Version 1.0 dated 02Jun2022

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List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
ARC	Adjudication review committee
AVOHILMO	Register of Primary Health Care Visits
CI	confidence interval
CSR	clinical study report
COVID-19	Coronavirus disease 19
DTA	data transfer agreement
ECDC	European Centre for Disease Control and Prevention
eCRF	(electronic) case report form
GBS	Guillain-Barré syndrome
HA	hemagglutinin
HD	high-dose
HCC	health care centers
HCP	health care professional
HILMO	Care Register for Health Care
HS	health stations
ICD-10	International Classification of Diseases, tenth revision
ICF	informed consent form
ICPC-2	International Classification of Primary Care 2nd edition
IM	intramuscular
KELA	The Social Insurance Institution of Finland
KM	Kaplan-Meier
MACE	major acute cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NA	not applicable
NC	not computed
NH	Northern Hemisphere
NIDR	National Infectious Disease Register
PCR	polymerase chain reaction
PIC	personal identity code
PT	preferred term
QIV	quadrivalent influenza vaccine

QIV-HD	high-dose quadrivalent influenza vaccine
QIV-SD	standard-dose quadrivalent influenza vaccine
rVE	relative vaccine effectiveness
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	standard-dose
SOC	(primary) system organ class
THL	Finnish Institute for Health and Welfare
TIV	trivalent influenza vaccine
Vac+14d	vaccination plus 14 days
WHO	World Health Organization

1 Introduction

This study QHD00012 evaluates the vaccine effectiveness of high-dose quadrivalent influenza vaccine (QIV-HD) relative to standard-dose quadrivalent influenza vaccine (QIV-SD) in persons 65 years of age and older.

Influenza is a contagious, acute viral respiratory disease which affects persons of all ages during annual epidemics and represents a substantial public health burden, causing significant morbidity and mortality. The World Health Organization (WHO) estimates that the global disease burden from influenza is 1 billion individuals infected, 3 to 5 million cases of severe disease, and 300 000 to 650 000 deaths annually, mostly from respiratory complications.

The WHO and numerous national immunization technical advisory groups, such as the Advisory Committee on Immunization Practice and the European Centre for Disease Control and Prevention (ECDC), recommend annual vaccination against influenza because vaccines have been shown to be effective in reducing influenza-associated morbidity and mortality.

Traditional trivalent and quadrivalent inactivated influenza vaccines (TIV and QIV) administered by the intramuscular (IM) route contain a standard-dose (SD) of 15 µg hemagglutinin (HA) of each of the virus strains (one A/H1N1 strain, one A/H3N2 strain and one B strain for TIV and two B strains [B Yamagata lineage and B Victoria lineage for QIV]) with a total of 45 µg and 60 µg of HA antigen per dose, respectively.

As with most vaccines for active immunization, the mechanism of action of influenza vaccines consists of the induction of immune responses against the antigens contained in the vaccine.

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 SD influenza vaccines (15 µg HA per strain) is sub-optimal in adults 65 years of age and older compared to healthy young adults.

Consequently, people 65 years of age and older may not have sufficient protection against influenza. Therefore, even if vaccination rates could be high in a few countries in older adults, this age group is at high risk of developing influenza illness and its complications and a significant burden of influenza disease remains.

QIV-HD has been developed based on the experience gained with Sanofi Pasteur's high-dose trivalent influenza vaccine (TIV-HD) containing 60 µg HA of each of 3 virus strains manufactured in the US. QIV-HD is produced using the same drug substance process as the licensed TIV-HD; for the drug product, the TIV-HD manufacturing process was modified slightly to increase the fill volume (0.7 mL for QIV-HD versus 0.5 mL for TIV-HD) in order to include the 2nd influenza B strain at the same HA content as the other 3 strains (60 µg HA/strain/dose).

Results of clinical studies conducted in subjects 65 years of age and older have shown that TIV-HD resulted in superior immune responses and superior vaccine efficacy compared to

standard-dose trivalent influenza vaccine (TIV-SD) containing 15 µg HA of each of the virus strains. These data were confirmed by real world evidence in more than 20 million people.

TIV-HD provides better protection against influenza disease: 24.2% more effective in preventing laboratory-confirmed influenza caused by any strain relative to the comparator, TIV-SD. TIV-HD also provides benefits against the occurrence of serious events specifically influenza-like illness, influenza related hospitalizations, pneumonia hospitalizations, cardiorespiratory hospitalizations, and all-cause hospitalizations. In addition, TIV-HD may also provide increased benefit against post-influenza mortality and all-cause mortality. Post-licensure studies have further demonstrated the benefit of TIV-HD over SD influenza vaccines for the prevention of serious events (pneumonia and other cardiorespiratory conditions), post-influenza death, and healthcare utilization (eg, hospitalization).

QIV-HD is licensed in the US, Canada, and Australia for active immunization against influenza caused by the specific strains of influenza virus contained in the vaccine in adults 65 years of age and older. An age extension from 65 years of age to 60 years of age was approved in the European Union in February 2021. QIV-HD registration has been granted by Swissmedic on 21 July 2021.

All subjects enrolled in Study QHD00012 receive an influenza vaccine which is either QIV-HD or QIV-SD. Therefore, they are vaccinated against the influenza viruses recommended by the WHO for the respective Northern Hemisphere (NH) influenza season. These older adults may be protected against those strains and may be less likely to catch influenza or develop complications during the respective influenza season.

Published evidence shows that influenza infection can be a trigger of myocardial infarction, stroke, and heart failure. Influenza vaccination shows benefit in the reduction of cardiovascular disease mortality, cardiovascular hospitalizations, major acute cardiovascular events (MACE), stroke, and myocardial infarction.

The QHD00012 clinical study which compares 2 influenza vaccines (QIV-HD and QIV-SD) on a primary endpoint related to the complications of influenza in persons 65 years of age and older in Europe, complements and reinforces data generated with the TIV-HD. The aim of this study is to demonstrate that vaccination with QIV-HD decreases complications of influenza illness in persons 65 years of age or older.

Thus, this study emphasizes the clinically relevant outcome reductions gained by annual vaccination with QIV-HD that are most impactful for patients, healthcare professionals, and policymakers.

Approximately 121 000 subjects 65 years of age and older were to be enrolled over multiple influenza seasons in the phase IIIb/IV registry-based trial (QHD00012).

The study was initiated in 2019-2020 influenza season and more than 33 000 subjects were enrolled. The first subject was included in November 2019 and the cut-off date for the subject data was August, 31st 2020.

However, the impact of the COVID-19 global pandemic created significant challenges to conducting this clinical study such as:

- Low incidence rates for influenza and high COVID-19 rates had an impact on our study plan
- Low incidence rates for influenza hindered data collection and endpoints

Therefore, the study was on pause ie, no enrollment for the two seasons 2020-2021 and 2021-2022.

In April, 1st 2022, Sanofi Pasteur reported the premature end of the study to FIMEA as uncertainties on influenza circulation for the coming seasons still remained.

Therefore, the study finally includes only a unique season (season 2019-2020), without significant flu circulation.

2 Trial Objectives

2.1 Primary Objective

Relative Vaccine Effectiveness

To demonstrate the superior relative effectiveness of QIV-HD as compared to QIV-SD among persons 65 years of age and older for the prevention of cardiovascular and/or respiratory hospitalizations

The endpoints for the primary objective are presented in Section 9.1 of the protocol.

2.2 Secondary Objectives

Relative Vaccine Effectiveness

1) To assess the clinical relative effectiveness of QIV-HD as compared to QIV-SD in prevention of:
   - inpatient hospitalization (using primary discharge diagnosis) for selected International Classification of Diseases, Tenth Revision (ICD-10) codes separately
   - death, either all-cause or cardiovascular or respiratory causes
   - inpatient hospitalization (using primary and secondary discharge diagnoses)
   - inpatient hospitalization (using admission diagnoses)
   - hospital emergency room visits
   - primary care visits to physician
2) To assess the clinical relative effectiveness of QIV-HD as compared to QIV-SD in prevention of MACE
3) To assess the characteristics of inpatient hospitalization or hospital emergency room visits or primary care visits to physician due to cardiovascular or respiratory event by QIV-HD and QIV-SD groups
4) To describe the clinical relative effectiveness of QIV-HD as compared to QIV-SD by age group and by group with specific comorbidities
5) To describe the clinical relative effectiveness of QIV-HD as compared to QIV-SD for different periods of observation

Safety

To describe all serious adverse events (SAEs) (including adverse events of special interest [AESIs]) for all subjects in both QIV-HD and QIV-SD groups

The endpoints for the secondary objectives are presented in Section 9.2 of the protocol.

2.3 Observational Objectives

To evaluate the QIV-HD as compared to QIV-SD in terms of:

1) Clinical relative effectiveness over an extended period of time
2) Follow-up of functionality / dependence during the 3 periods of follow-up (ie, between ≥ 14 days after vaccination and up to 31 May and 31 August of each year and during the influenza peak period)
3) Health Care Utilization during the 3 periods of follow-up described above
4) Laboratory-confirmed influenza and invasive bacterial diseases as captured in the database based on routine practice between ≥ 14 days after vaccination and up to 31 May of the year following the vaccination and during the influenza epidemic period as defined by the Finnish epidemic thresholds

The endpoints for the observational objectives are presented in Section 9.3 of the protocol.

3 Description of the Overall Trial Design and Plan

3.1 Study Design

QHD00012 was a Phase IIIb/IV, randomized, modified double-blind, active-controlled, single center pragmatic study to assess the relative vaccine effectiveness of the QIV-HD as compared to QIV-SD in approximately 121 000 adult subjects 65 years of age and older were to be enrolled over multiple influenza seasons beginning in 2019-2020 in Finland.

This study was conducted in Finland by THL, a research institute under the Finnish Ministry of Social Affairs and Health which undertakes research projects using national registers carried out in close collaboration with either Finnish or international partner. THL, as the Principal Investigator, collaborated with multiple Heath Stations (HSs) overseen by selected Heath Care Centers (HCC) to carry out the study and was responsible for the coordination of the operational aspects of the study conduct. THL also provided medical and study related expertise.

The study was designed to follow the routine vaccination medical practices used at the HS during the influenza vaccination campaign. The Sub-Investigators at the HCC (ie, HCC physicians) and the HS nurses were trained on the study procedures and considered qualified on the study. The Sub-Investigators guaranteed medical oversight of the vaccination visits and to respond, where needed, to any medical questions (primarily through telephone consultations). The HS nurses were responsible for routine health follow-up and immunizations.

The subject's active participation in the study was limited to the enrollment and vaccination visit.

The follow-up period in this study was defined as the data collection period. The data collection period varied based on the study objectives with the data collection period extending up to 31 August of the year following the vaccination (approximately 11 months).

However, due to the impact of the COVID-19 global pandemic which created significant challenges to conducting this clinical study (see section 1. Introduction for further details), the QHD00012 study was conducted from November 2019 (first subject included) to August 2020 (cut-off subject data date) only. A total of 33 096 subjects signed an ICF and 33 093 subjects were vaccinated in one of the two study groups.

3.2 Study Plan

Randomization and Vaccination

All eligible subjects were randomized to receive a single IM injection of either QIV-HD or QIV-SD at Day 0. A scratchable list was used to randomly assign subjects to either the QIV-HD group or the QIV-SD group. All subjects were observed for 20 minutes after vaccination to ensure their safety.

Recording of Data

Finland uses multiple registers to collect different health and population data. Subject data were recorded in the local medical patient file by health care professionals (HCPs). From patient files the data was transferred automatically to the corresponding Finnish health registers (hospital diagnosis/treatment and SAEs).

Collection of Datasets

The datasets were collected using multiple Finnish health registers and compiled by THL into an analysis database. The subject's Personal Identity Code (PIC) constituted the common key between all of the registers. On a regular basis, THL extracted the study data from the different Finnish registers and when required from local medical patient files. THL submitted protocol-defined datasets to Sanofi Pasteur in a pseudonymised manner (ie, PIC will not be transferred to Sanofi Pasteur to maintain data privacy).

Collection of safety data

Serious adverse reactions (SARs) and AESIs, experienced by the subject and suspected to be related to the vaccine according to the HCP assessment, were collected using an SAR/AESI paper form throughout the study (ie, from inclusion up to 31 August of the year following the vaccination). All fatal SAEs, irrespective of causality, were collected for the same period using real-time surveillance of population data. Additional data could be collected from the local medical patient file, as needed.

All SAEs resulting in hospitalization were collected by THL from the Finnish health registers up to 6 months after vaccination. AESIs, which had not been reported by the HCPs, were collected from the Finnish health registers up to 6 months after vaccination, and reported as eSAE.

Note: AESIs included new onset of Guillain-Barré syndrome (GBS), encephalitis / myelitis (including transverse myelitis), Bell’s palsy, optic neuritis, and brachial neuritis.

4 Endpoints and Assessment Methods

See Section 9 of the protocol.

With the decision of stopping the study after the first year, the endpoints correspond only for the season 2019-2020. In addition, no influenza epidemic period was defined for 2019-2020 season, as only low/moderate flu incidence was observed in Finland.

Focus on input data:

A Data Transfer Agreement (DTA) document is available as version 4.0, and describes all data available for the study. The 12 panels available are the following:

- Thl_enr, linked to enrollment and injection
- Thl_drop, that identified subject withdrawal
- Thl_dev, that identified deviations at subject level
- Thl_hilm, corresponding to hospitalizations from HILMO registry
- Thl_er, corresponding to emergency room visits from HILMO registry
- Thl_avoh, corresponding to primary care visits to the physician from AVOHILMO registry
- Thl_hvac, corresponding to previous vaccinations (flu and pneumonia) from AVOHILMO registry
- Thl_lab, corresponding to positive flu and invasive bacterial detection from NIDR registry
- Thl_chro, corresponding to aggregated data for chronic diseases (comorbidity) from Social Insurance Institution (KELA) reimbursement registry
- Thl_cara, corresponding to aggregated data for care allowance due to disability from Social Insurance Institution (KELA) reimbursement registry
- Thl_med, corresponding to aggregated data for antimicrobial medications from Social Insurance Institution (KELA) reimbursement and prescription registries
- eSAE, corresponding to SAE entered by THL in SP eCRF database (death, related SAE, and AESI), and later available in SP PV database with MedDRA coding

In addition, 3 dictionaries are available for statistical analysis:

- ICD-10 codes: It corresponds to ICD-10 codes used at Finland level. Some adaptations are also applied (eg, code such as '###*' are simplified with '###').
- ICPC-2 codes: It corresponds to ICPC-2 codes used at Finland level.
  - One file contains all codes (even not linked to selected I/J ICD-10 codes).
  - One file with only codes linked to primary objectives, and with correspondences to the ICD-10 codes.

- MedDRA: eSAE panel already contains the MedDRA codes/labels. Therefore, no external dictionary is used.

Complementary to the files above, we also have two randomization files: the randomization of the subjects based on randomization order, and the randomization of the product (dose number).

We also have a file corresponding to the 41 HS (name, link with HCC) involved in the study.

The statistics Finland registry is finally not used as source data. The eSAE is used for death information.

4.1 Primary Endpoints and Assessment Methods

See Section 9.1 of the protocol.

As Section 5.7 of the SAP Core Body, the following I16, I75 and I76 codes were not included in the primary objective/endpoint. This was also applicable for secondary objectives.

On the primary analysis, no exclusion of potential Covid-19 cases was conducted.

4.2 Secondary Endpoints and Assessment Methods

4.2.1 Effectiveness

See Section 9.2.1 of the protocol.

As described in Section 5.7 of the SAP Core Body:

- the following I16, I75 and I76 codes were not included in the secondary objectives
- the MACE was not produced, but an analysis linked to MACE ICD-10 codes
- the flu peak period was not conducted as statistical analysis
- The panels from KELA were based on aggregated data

Based on HILMO data, no status on death was available. Death is reported through the eSAE panel. No formal cross analysis between HILMO and eSAE was conducted.

When analysis is based on "primary and secondary", the number of occurrences refers to the number of events with at least one diagnostic (either primary or secondary) compatible with the outcome definition.

4.2.2 Safety

See Section 9.2.2 of the protocol.

4.3 Observational Endpoints and Assessment Methods

See Section 3 of the protocol and Section 4.2.1 of the SAP Core Body.

Regarding "Previous vaccinations during the last 5 years (administered product and date of vaccination)" as described in Section 5.2.6 of the protocol, data collected were restricted to flu and pneumonia vaccinations.

4.3.1 Safety

4.3.1.1 Codifications

eSAE were coded using MedDRA, and using primary SOC and PT. Codification was directly accessible via eSAE panel data. In addition, the ICD-10 codes were indicated at least for fatal eSAE.

For safety data from Finnish registers, the data were coded using a Finland ICD-10 codes (or occasionally ICPC-2 used in primary care registry). Each individual diagnosis code reported during the hospitalization is considered an individual SAE. The dictionary was the source to de-code with clear label using hierarchy ICD-10 methodology (used as hierarchy 0 to 2 or 3 in the statistical analysis).

For codification of ICPC-2, two files were available. A first file contained all possible ICPC-2 codes with the label of de-code. A second file select ICPC-2 codes linked to the primary objective, with a correspondence with an ICD-10 code. The list refers to ICPC-2 following selected codes:

- R (respiratory system): R72, R74 to R81, R83, R95 and R96
- K (circulatory system): K70, K74 to K80, K82, K84, K87 and K90 to K93.

4.3.1.2 Time to Onset

Time to onset is defined as:

- Start date of the eSAE minus vaccination date
- Admission date for SAE from HILMO minus vaccination date
- Visit date for hospital emergency room visits or primary care visits to physician minus vaccination date

The class of analysis for presentation is:

- Missing onset
- 0 to 13 days
- 14 to 30 days
- 31 to 60 days
- 61 to 90 days
- 91 to 120 days
- 121 days and above

4.3.1.3 Duration

Duration of an eSAE is defined as stop date minus start date plus 1.

Duration of an SAE from HILMO is defined as discharge date minus admission date plus 1.

The duration is not applicable for hospital emergency room visits or primary care visits to physician.

The class of analysis for presentation is:

- Missing duration
- 1 to 3 days
- 4 to 7 days
- 8 to 14 days
- 15 to 28 days
- 29 days and above

4.3.1.4 Nature of the eSAE

eSAE refers to at least one of the following classes: SAR, AESI or fatal. It's an extraction of pharmacovigilance database and keeping key variables.

In addition, potentially related SAE (eg, in paper form) by any HCP but assessed as unrelated by the investigator are presented. Therefore, such eSAE are considered as "Other eSAE" in the statistical analysis.

4.3.1.5 Causal Relationship for eSAE

The relationship is the final investigator assessment, and refers to Yes/Related or No/Not related. If Yes, the eSAE is a SAR.

4.3.2 Derived Other Variables

4.3.2.1 Seriousness for eSAE

Seriousness was collected (and analyzed) for eSAE using the following modalities:

- Congenital Anomaly
- Significant Disability
- Death
- Hospitalized
- Life Threatening
- Medically Significant
- Missing seriousness (modality for analysis)

Modalities were not mutually exclusive.

4.3.2.2 Outcome for eSAE

Outcome were collected (and analyzed) for eSAE using the following modalities:

- Fatal
- Not recovered / Not resolved
- Recovered / Resolved
- Recovered / Resolved with sequelae
- Recovering / Resolving
- Unknown

4.3.3 Derived Other Variables

4.3.3.1 Age for Demographics

The age (in full years, expressed as an integer) corresponds to the age at the time of injection.

Some analyses are done using predefined age groups (eg, 65-74y vs 75y and above, or focus on 85y and above).

4.3.3.2 Other Baseline Characteristics

The following baseline data are also collected: sex, flu and pneumonia vaccines in the last 5 years, comorbidities (in 5 different factors), and baseline care allowance status.

The variables are used as they are or identified such as: "at least one".

4.3.3.3 Durations of a Subject in the Trial

The date of injection corresponds to the start date of the subject. The ICF date is also available for information in the individual data appendix. All subjects were injected between 04NOV2019 and 23DEC2019.

For key duration computations, the start date is the vaccination plus 14 days.

The final date corresponds to:

- 31AUG2020 or 31MAY2020, depending on analysis

  or

- Censoring occurs at the following situations:
  - When a case occurs (for rVE analysis and Kaplan-Meier [KM] figure), date of the event
  - When withdrawal of consent, date of withdrawal of consent
  - When death (using eSAE data), date of death

The duration is the 'final date' minus 'start date' plus 1.

The minimum is 1 day, and the maximum is 302 days (31AUG2020-04NOV2019+1).

The duration is also used for person-year computations (1 year = 365.25 days).

5 Statistical Methods and Determination of Sample Size

The statistical analyses for the study report will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS®.

The SAP v1 is approved before the official final database and before the unblinding steps.

Post-hoc additional exploratory analyses may also occur in later step (eg, deeper sub-analyses, or eventually explore additional data after amendment of the DTA).

The database is locked before unblinding the subjects.

For descriptive purposes, the following statistics will be presented:

Table 5.1: Key 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.
Effectiveness results	**Categorical data**	Number and percentage (95% CIs) of subjects. Number of occurrences, rVE and 95% CIs.
Safety events	**Categorical data**	Number and percentage (95% CIs) of subjects, and number of events.

The Confidence Interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe).

For the percentage in the tables, two decimals will be kept, except in the following cases:

- If numerator is 0, then the value of percentage will be presented as "0" (no decimal).
- Else if numerator is >0 and numerator = denominator, then the value of percentage will be presented as "100" (no decimal).
- Else if numerator is >0 and the directly calculated percentage is <0.01, the value of percentage will not be presented as "0.00" but will be presented as "<0.01".
- Else if the frequencies of numerator and denominator are both >0 and numerator does not equal to denominator, and the directly calculated percentage is >99.99, the value of percentage will not be presented as "100.00" but will be presented as ">99.99".

The description of the database is presented in Section 4.

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objective

5.1.1.1 Hypotheses

The rVE of QIV-HD to QIV-SD in terms of prevention of cardiovascular and/or respiratory hospitalization will be estimated for the primary endpoint as follows:

$$rVE = \left(1 - \frac{C_{QIV-HD} / N_{QIV-HD}}{C_{QIV-SD} / N_{QIV-SD}} \right) x\ 100\%$$

where:

- C_{QIV-HD} and C_{QIV-SD} are the numbers of cardiovascular and respiratory hospitalization cases (first occurrence) meeting the considered primary endpoint definition in the QIV-HD and QIV-SD groups, respectively
- N_{QIV-HD} and N_{QIV-SD} are the numbers of subjects in the QIV-HD and QIV-SD groups, respectively

The following hypotheses will be tested:

$H_0: rVE \leq 0\%$

$H_1: rVE > 0\%$

5.1.1.2 Statistical Methods

Primary endpoint will be derived using database extracted from the Finnish national registers.

In case of more than one occurrence for the same subject, only the first occurrence will be considered in the estimation of rVE.

The two-sided 95% CIs for rVE will be calculated by an exact method assuming a binomial distribution of the number of cases in QIV-HD group conditional on the total number of cases in both groups:

Let $q = \frac{C_{QIV-HD}}{C_{QIV-HD} + C_{QIV-SD}}$, the proportion of cases belonging to QIV-HD group among the total number of cases. Given the total number of cases, C_{QIV-HD} has a binomial distribution (q,$C_{QIV-HD} + C_{QIV-SD}$). Thus, a CI for q may be constructed using the exact Clopper-Pearson method for binomial proportions.

As $\frac{q}{1-q} = \frac{C_{QIV-HD}}{C_{QIV-SD}}$, the rVE estimate given above may be restated as follows:

$rVE = \left(1 - \frac{C_{QIV-HD}/N_{QIV-HD}}{C_{QIV-SD}/N_{QIV-SD}}\right) x\ 100\% = \left(1 - \frac{N_{QIV-SD}}{N_{QIV-HD}} \times \frac{q}{1-q}\right) x\ 100\%$, which is a strictly decreasing function of q.

Finally, for the primary endpoint, a CI of the rVE may be constructed based on the CI of q.

For the primary endpoint, the superiority of the QIV-HD effectiveness over QIV-SD will be considered demonstrated if the lower bound of the two-sided 95% CI for the rVE is above 0%.

5.1.2 Hypotheses and Statistical Methods for Secondary and Observational Objectives

5.1.2.1 Hypotheses

No hypotheses will be tested.

5.1.2.2 Statistical Methods

The estimated rVE with 2-sided 95% CI will be computed in the same way as the primary objective. No hypotheses will be tested, but depending on the number of the first occurrence observed, the lower bound of the 2-sided 95% CI may be used for results interpretation.

The rVE with 95% CI will be computed only if at least 5 occurrences in total of the both groups and at least 1 for QIV-SD group are present.

Several analyses will be displayed per factor such as season, delay since vaccination, site localization, age (in class or continuous variable), sex, or specific comorbidities. An analysis will be also done excluding cases potentially linked to a COVID-19 occurrence.

In addition, a complementary analysis available in the appendix 15 of the Clinical Study Report (CSR) will be conducted based on person-year as denominator.

KM curves will be also produced for some endpoints. The occurrences are based on first occurrence corresponding to the endpoint analyzed. The data collection period will vary depending on the injection date, and censored in case of first occurrence of the endpoint or date of death or voluntary withdrawal (expected to be rare). See also 4.3.3.3.

The safety endpoints, per subject, will be summarized per vaccine group, with 95% CI for the main endpoints. CIs will be calculated using Clopper-Pearson method.

5.2 Analysis Sets

The analysis will be performed on the total of vaccinated subjects included in the study. The analysis will be conducted using injected group (QIV-HD vs QIV-SD) for almost all analysis. For analysis(ses) according to randomized group, a clear information will be available on the title of the output.

Sub-analysis sets will be considered when other factors are used (eg, age, sex).

5.3 Handling of Missing Data and Outliers

5.3.1 Effectiveness

A subject lost to follow-up are considered rare in the register follow-up. Therefore, denominators will be subjects in the injected group.

Hospitalizations are captured throughout the usual process of national registry, and that permits a minimization of missing occurrences compared to a classical clinical study.

For subject who withdraws their consent, the data are also partial.

End dates for SAE will be also censored if they occur 31AUG2020, even if they continue thereafter.

In any case, no replacement of data will be done.

5.3.2 Safety

No replacement will be done.

5.4 Interim / Preliminary Analysis

No interim / preliminary analyses are planned up to the analysis of the primary and secondary objectives.

The analysis is planned to be conducted in one final step taking into account the full 2019-2020 season. A possibility is still open to explore more data later, if necessary, based on the main analysis.

5.5 Determination of Sample Size and Power Calculation

The sample size needed for the assessment of the primary objective of the study was expected to be approximately 121 000 subjects and may be adjusted based on the blinded number of cases in order to maintain the likelihood of achieving approximately 2200 evaluable subjects with at least 1 cardiovascular and/or respiratory hospitalization.

The 2200 evaluable cases would provide approximately 90% power (by exact method) to conclude on the primary objective under the following assumptions:

- The true rVE of QIV-HD over QIV-SD is 13% against prevention of cardiovascular and respiratory hospitalization
- 0.025 one sided type I error
- A lower bound on the rVE above 0%
- An allocation ratio between groups of 1:1

Considering:

- Approximately 450 cases were collected during the first season of the study.
- The expected attack rate of first occurrence of primary endpoint is approximately 2%, in the next seasons in Finland

The study power using different rVE assumptions is presented in Table 5.2.

Table 5.2: Different rVE assumptions and associated study power for the sample size of 121000

rVE (%)	Study Power (%)
10	68.7
11	77.3
12	84.5
13	90.0
14	94.0
15	96.6

5.6 Data Review for Statistical Purposes

No formal data review was performed. The data from registry are not modifiable by nature. Some post-hoc exploration (on blinded data) will be done such as the review of the deviations, the randomization number and product number on data from OCE, the presence of codes in the dictionaries.

5.7 Changes in the Conduct of the Trial or Planned Analyses

Approximately 121 000 subjects 65 years of age and older were to be enrolled over multiple influenza seasons in the phase IIIb/IV registry-based trial (QHD00012).

The study was initiated in 2019-2020 influenza season and more than 33 000 subjects were enrolled. The first subject was included in November 2019 and the last subject data was collected in August 2020.

However, the impact of the COVID-19 global pandemic created significant challenges to conducting this clinical study such as:

- Low incidence rates for influenza and high COVID-19 rates had an impact on our study plan
- Low incidence rates for influenza hindered data collection and endpoints

Therefore, the study was on pause ie, no enrollment for the two seasons 2020-2021 and 2021-2022.

In Q1 2022, Sanofi Pasteur took the decision to stop the study, as uncertainties on influenza circulation for the coming seasons still remained.

Therefore, the study finally consists of a unique season (season 2019-2020), without significant flu circulation. This will result in inadequate power for the primary endpoint analysis.

For the primary endpoints, 3 codes will not be considered as not referenced in ICD-10 Finland and/or in ICD-10 WHO version 2019. The codes are: I16, I75 and I76.

The Finnish registries HILMO and AVOHILMO collect ICD-10 with start date of the event. Nevertheless, some details are not available (eg, death status). Therefore, MACE criteria is not formerly possible. The analysis is adapted with ICD-10 codes linked to MACE as follows:

- Any I20-I25 + I63 (linked to MACE)
- Ischaemic heart diseases (I20-I25)
    - Myocardial infarction (I21-I23) [I21 (Acute myocardial infarction), I22 (Subsequent myocardial infarction), and I23 (Certain current complications following acute myocardial infarction)]
    - Unstable angina (I20 + I25) [I20 (Angina pectoris) and I25 (Chronic ischaemic heart disease)]
- Cerebral infarction (I63)

The death is managed throughout eSAE information, as reported by THL. No panel are specifically identified coming from Statistics Finland registry.

After discussion with KELA, it was decided to obtain only aggregated data for 3 panels due to complex data privacy processes. Thus, this prevents submission of individual data for these secondary and observational endpoints to authorities such as FDA or EMA.

No analysis is anticipated linked to Social Welfare registry identified in the Table 11.1 of the protocol. Of note: No specific links objectives/endpoints are mentioned for these data in the protocol.

Additionally, in safety endpoint, we have in the protocol: "Occurrence and nature (MedDRA PT or ICD-10 codes) of non-fatal SAEs by time to onset and seriousness criteria up to 6 months after vaccination". Nevertheless, information around hospitalizations (from HILMO) don't include the

fatality. The hospitalization analysis (all SAE) will be conducted without considering fatality (non-fatal or fatal). Secondly, the seriousness analysis is based only on eSAE, as not available in all hospitalizations via HILMO registry.

Of note:

- Due to the context of the study no Adjudication Review Committee (ARC) was put in place. It was a possibility identified in the protocol to review primary outcomes.
- During the 2019-2020, no anti-influenza medications were observed in the study cohort. Therefore, only antibacterial data are present in thl_med.
- Regarding "Previous vaccinations during the last 5 years (administered product and date of vaccination)" as described in Section 5.2.6 of the protocol, data collected were restricted to flu and pneumonia vaccinations.
- For the 3 panels referring to aggregated data, a first run will be done without considering the intervention group. When unblind is managed, THL will generate a second run, in order to obtain dataset taking into account injected group information, i.e. aggregation by treatment group.

6 References List

1 Newcombe R.G., Two-sided confidence intervals for the single proportion: comparison of seven methods, Statistics in Medicine, (1998) 17, 857-872