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

Clinical Study Protocol, Amendment 1

Health Authority File Number:	EudraCT #: 2019-001401-25
WHO Universal Trial Number (UTN):	U1111-1217-2654
Study Code:	QHD00012
Development Phase:	Phase IIIb/IV
Sponsor:	Sanofi Pasteur, Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	Quadrivalent Influenza Vaccine (split virion, inactivated) High-Dose (QIV-HD)
Form / Route:	Suspension for injection in pre-filled syringe / Intramuscular
Indication For This Study:	Active immunization in adults 65 years of age and older for the prevention of influenza disease as well as complications like cardiovascular and respiratory related hospitalizations
Manufacturer:	Same as Sponsor
Principal Investigator	[redacted] Public Health Evaluation and Projection Unit, Department of Public Health Solutions, the Finnish Institute for Health and Welfare (THL), Tampere, Finland The Principal Investigator and sub-Investigators at THL, the sub-Investigators at the health care centers, THL operating locations, the health care centers, and the health stations are listed in the "List of Investigators and Centers Involved in the Trial" document.
Sponsor's Responsible Medical Officer:	[redacted]

Clinical Team Leader	[redacted]
Global Safety Officer:	[redacted]
Regional Trial Manager:	[redacted]
Version and Date of the Protocol:	Version 4.0 dated 22 July 2020

History of Protocol Versions

Version	Date	Comments
1.0	24 June 2019	Internal version not submitted
2.0	27 June 2019	Version approved by the IEC
3.0	16 September 2019	Version approved by the IEC and first version used in the study

Table of Contents

List of Tables

Synopsis

Company:	Sanofi Pasteur
Investigational Product:	Quadrivalent Influenza Vaccine (split virion, inactivated) High-Dose (QIV-HD), suspension for injection in pre-filled syringe
Active Substances:	A/(H1N1)-like strain, A/(H3N2)-like strain, B (Victoria Lineage)-like strain, B (Yamagata Lineage)-like strain

Title of the Study:	Relative Effectiveness of a High-Dose Quadrivalent Influenza Vaccine versus a Standard-Dose Quadrivalent Influenza Vaccine in Subjects 65 Years of Age and Older
Development Phase:	Phase IIIb/IV
Principal Investigator:	[redacted] Public Health Evaluation and Projection Unit, Department of Public Health Solutions, the Finnish Institute for Health and Welfare (THL), Tampere, Finland
Study Sites:	This will be a single center study conducted by THL in collaboration with multiple health stations (HS) overseen by public health care centers (HCC) in Finland. The health stations are designated as the vaccination sites in this study. The Principal Investigator and sub-Investigators at THL, the sub-Investigators at the HCC, THL operating locations, the HCC, and the HS are listed in the "List of Investigators and Centers Involved in the Trial" document.
Planned Study Period:	Vaccination period: October to December Data collection period: from the date of vaccination up to 31 August of the year following the vaccination
Study Design, Schedule of Study Procedures, and Methodology:	QHD00012 will be a Phase IIIb/IV, randomized, modified double-blind, active-controlled, single center pragmatic study in approximately 121 000 subjects 65 years of age and older in Finland. ***Vaccination*** On Day (D) 0, subjects will be randomized to receive a single intramuscular (IM) injection of either a high-dose quadrivalent influenza vaccine (QIV-HD) or a standard-dose quadrivalent influenza vaccine (QIV-SD). All subjects will be observed for 20 minutes after vaccination to ensure their safety. ***Collection of datasets*** The datasets will be collected using multiple Finnish health registers and compiled by THL into an analysis database**.** ***Collection and reporting of safety data*** The serious adverse reactions (SARs) and adverse events of special interest (AESIs), experienced by the subjects and suspected to be related to the vaccine according to the health care professional (HCP) assessment, will be collected and reported to THL using a SAR/AESI paper form throughout the study (ie, from inclusion up to 31 August of the year following the vaccination). All other serious adverse events (SAEs) (non-fatal SAEs except those included in the primary endpoint) will be collected by THL from the Finnish health registers up to 6 months after vaccination. AESIs and fatal SAEs, which have not been reported by the HCPs, will be collected in the same manner throughout the study.

	An SAE electronic case report form (eCRF) (ie, SAE eCRF) must be completed by the Principal Investigator or delegate sub-Investigators within 24 hours after the first awareness of any THL study personnel of any SAR (suspected to be related to the vaccine by the HCP), fatal SAE, or AESI and will be reported to Sanofi Pasteur's Global Pharmacovigilance (GPV) department. Every SAR must be reported, even if the Principal Investigator considers that it is not related to the vaccine. Data collected in the SAE eCRF for each individual case will include outcome, precise description of medical history, results of the investigations, and the causal relationship between the SAE and the product administered evaluated by the Principal Investigator. In addition to data from the SAR/AESI paper form completed by the HCP, data can be collected from the local medical patient file, as needed. Following this, the Sponsor's Global Safety Officer will also assess the causal relationship to the product, based on the available information and current medical knowledge. Non-fatal SAEs, identified from the health registers, will be reported by THL to the Sponsor in an aggregate tabulated listing twice per month. These events will not be individually assessed for causality. Instead, they will be evaluated statistically by comparing the frequency of SAEs to a baseline incidence estimated from the same health registers. The Sponsor will inform the relevant health authorities of all SARs, fatal SAEs, and AESIs (regardless of causality) according to local regulatory requirements. Non-fatal SAEs will be reported in the Development Safety Update Report (DSUR) to relevant health authorities. The Principal Investigator will report cardiovascular and respiratory effectiveness endpoint-related SARs within 24 hours to the Sponsor using an SAE eCRF in the EDC system. The Sponsor will inform the relevant health authorities of the endpoint-related SAR according to local regulatory requirements. The Sponsor will also provide summaries of endpoint-related SARs on a quarterly basis to the relevant health authorities. Note: AESIs include new onset of Guillain-Barré syndrome, encephalitis / myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis. ***Committees involved in the study*** An Independent Data Monitoring Committee (IDMC), composed of members who are independent from the Sponsor and the Principal Investigator, will be established for this study in order to monitor subject safety by conducting formal reviews of accumulated safety data that will be unblinded. The membership composition, specific responsibilities of members, timing of reviews, objectives for review, and decision criteria will be documented in the IDMC Charter. An Adjudication Review Committee (ARC), composed of members who are independent from the Sponsor and the Principal Investigator, may be established to review the primary outcomes and to adjudicate a subset of cases. The membership composition, specific responsibilities of members, timing of reviews, objectives for review, and decision criteria will be documented in the ARC Charter.

Interruption of the Study	The study may be discontinued based on new data about the investigational product resulting from this study or any other studies; or for administrative reasons; or on advice of the Sponsor, the IDMC, the Principal Investigator, the Independent Ethics committees (IECs), or the governing regulatory authorities in the country where the study is taking place. The study may be paused during the ongoing outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the human population considered as pandemic by the World Health Organization (WHO) on 11 March 2020. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Principal Investigator, the IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Principal Investigator shall promptly inform the study subjects and should assure appropriate subject therapy and/or follow-up.
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 in prevention of cardiovascular and/or respiratory hospitalizations

Primary Endpoints:	***Relative Vaccine Effectiveness***
	• First occurrence of an unscheduled cardiovascular or respiratory inpatient hospitalization (between ≥ 14 days after vaccination and up to 31 May of the year following the vaccination)
	• Inpatient hospitalizations with the following International Classification of Diseases, Tenth Revision (ICD-10) codes entered into the hospital primary discharge code will be considered:
	  • <u>Diseases of the circulatory system:</u>
	  Hypertensive diseases, based on codes I11 and I16
	  Ischemic heart diseases, based on codes I20-I25
	  Pulmonary heart disease and diseases of pulmonary circulation, based on codes I26 and I27
	  Other forms of heart disease, based on codes I30, I31, I33, I38-I42, and I46-I50
	  Cerebrovascular diseases, based on codes I63-I67
	  Diseases of arteries, arterioles and capillaries, based on codes I74-I76
	  • <u>Diseases of the respiratory system:</u>
	  Acute upper respiratory infections, based on codes J00-J06
	  Influenza and pneumonia, based on codes J09-J18
	  Other acute lower respiratory infections, based on codes J20-J22
	  Chronic lower respiratory diseases, based on codes J40-J47
	  Other respiratory diseases principally affecting the interstitium, based on codes J80 and J81
	  Suppurative and necrotic conditions of the lower respiratory tract, based on codes J85 and J86

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 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 major acute cardiovascular events (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 SAEs (including AESIs) for all subjects in both QIV-HD and QIV-SD groups
Secondary Endpoints:	***Relative Vaccine Effectiveness*** 1) First occurrence between ≥ 14 days after vaccination and up to 31 May of the year following the vaccination of each of the following endpoints: • Inpatient hospitalization with primary discharge diagnosis (using ICD-10 codes) for: • Diseases of the respiratory system, based on codes J00-J06, J09-J18, J20-J22, J40-J47, J80, J81, J85, and J86 • Diseases of the circulatory system, based on codes I11, I16, I20-I25, I26, I27, I30, I31, I33, I38-I42, I46-I50, I63-I67, and I74-I76 • Pneumonia, based on codes J12-J18 • Heart failure, based on code I50 • Acute myocardial infarction, based on code I21 • Atrial Fibrillation, based on code I48 • Stroke, based on code I63 • Influenza and pneumonia, based on codes J09-J11 and J12-J18 • Influenza, based on codes J09-J11 • Death, all-cause and based on the diseases and ICD-10 codes listed above • Inpatient hospitalization with primary and secondary admission and discharge diagnoses based on the diseases and ICD-10 codes listed above • Hospital emergency room visits based on the diseases and ICD-10 codes listed above

	• Acute primary care visits to physician based on the diseases and ICD-10 codes listed above (or corresponding International Classification of Primary Care 2nd edition [ICPC-2] codes) 2) First occurrence between ≥ 14 days after vaccination and up to 31 May of the year following the vaccination of MACE as defined by all of the following endpoints: • Ischemic heart diseases based on codes I20-I25 • Non-fatal myocardial infarction based on codes I21-I23 • Fatal or non-fatal stroke based on code I63 • Unstable angina based on codes I20 and I25 3) The following characterization for selected outcomes to be described when applicable: • All occurrences of an unscheduled cardiovascular or respiratory inpatient hospitalization or hospital emergency room visits or primary care visits to physician • Onset of event • Duration of event 4) First occurrence between ≥ 14 days after vaccination and up to 31 May of the year following the vaccination of each of the endpoints listed above by: • Age groups (65-74 years and ≥ 75 years or 65-79 years and ≥ 80 years) • Groups with specific comorbidities (diabetes, cardiovascular history, chronic lung disease) 5) First occurrence of each of the endpoints above during influenza epidemic period as defined by the Finnish epidemic thresholds ***Safety*** The following safety endpoints will be described for all subjects: • Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT] or ICD-10 codes), time to onset, seriousness criteria, and outcome of all SARs, all AESIs, and all fatal cases throughout the study • 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
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

Observational Endpoints:	The following endpoints will be described for all subjects: 1) Clinical relative effectiveness of QIV-HD as compared to QIV-SD (between ≥ 14 days after vaccination and up to 31 August of the year following the vaccination) for the first occurrence of the following endpoints: • Unscheduled cardiovascular or respiratory inpatient hospitalization (primary discharge) • Inpatient hospitalizations with primary discharge codes for diseases of the circulatory system and diseases of the respiratory system based on the diseases and the ICD-10 codes listed in the primary endpoints (for each code separately) • Inpatient hospitalization with primary discharge diagnosis, death, inpatient hospitalization with primary and secondary discharge or admission diagnoses, hospital emergency room visits, and primary care visits to physician based on the ICD-10 codes listed in the secondary endpoints • Death, all-cause 2) Long-term complications and need of care in terms of diagnosis of hip fracture, based on ICD-10 code S72 and disabilities based on the care allowance for pensioners/disability in the Social Insurance Institution register (KELA) 3) The following health care resources for all subjects • Medications such as anti-influenza and antibacterial outpatient medications • All unscheduled hospitalizations and hospital emergency room visits • All acute primary care visits to a physician 4) Clinical relative effectiveness of QIV-HD as compared to QIV-SD against laboratory-confirmed influenza based on routine swabbing and laboratory-confirmed invasive bacterial diseases
Planned Sample Size:	A total of approximately 121 000 subjects 65 years of age and older are planned to be enrolled and randomized in a 1:1 ratio as follows: • QIV-HD Group: n = 60 500 • QIV-SD Group: n = 60 500 This sample size is expected to bring at least 2200 evaluable subjects with at least 1 serious cardiovascular and/or respiratory event for the primary endpoint, as necessary for 90% study power. However, if the number of events is lower than anticipated, the sample size may be adjusted based on the blinded number of cases in order to maintain the likelihood of achieving the expected number of cases for the primary endpoint.

Duration of Participation in the Study:	The study will be conducted over a period of 3 influenza seasons beginning in 2019-2020. The subject's active participation in the study will be limited to the enrollment and vaccination visit. Subjects who participated in the study during one influenza season may participate during another influenza season. Those subjects will be re-consented and re-randomized to one of the 2 study vaccines. The follow-up period in this study is defined as the data collection period. The data collection period varies based on the study objectives with the data collection period extending up to 31 August of each study year.
Investigational Product:	Quadrivalent Influenza Vaccine (split virion, inactivated) High-Dose (QIV-HD) (Efluelda® manufactured by Sanofi Pasteur)
Form:	Suspension for injection
Presentation:	Pre-filled single-dose syringe
Composition:	Each 0.7 mL dose of QIV-HD will contain: *Strains to be determined based on WHO and European Union (EU) recommendations for the NH influenza season* **Active Substances:** • A/(H1N1)-like strain 60 µg hemagglutinin (HA) • A/(H3N2)-like strain 60 µg HA • B/(Victoria Lineage)-like strain 60 µg HA • B/(Yamagata Lineage)-like strain 60 µg HA **Excipients:** • Buffered saline solution quantity sufficient (qs) to appropriate volume • Octoxinol-9 ≤ 350 µg
Route:	IM, injected into the upper arm (deltoid area)
Batch Number:	To be determined (TBD)
Control Product:	Standard-Dose Inactivated Influenza Vaccine Quadrivalent, NH strains (QIV-SD) (Vaxigrip Tetra®, manufactured by Sanofi Pasteur)
Form:	Suspension for injection
Presentation:	Pre-filled single-dose syringe
Composition:	Each 0.5 mL dose of QIV-SD will contain: *Strains to be determined based on WHO and EU recommendations for the NH influenza season.* • A/(H1N1)-like strain 15 µg HA • A/(H3N2)-like strain 15 µg HA • B/(B from Primary Lineage)-like strain 15 µg HA • B/(B from Alternate Lineage)-like strain 15 µg HA **Excipient:** • Buffered saline solution qs to appropriate volume
Route:	IM, injected into the upper arm (deltoid area)
Batch Number:	TBD

Inclusion Criteria:	An individual must fulfill *all* of the following criteria to be eligible for study enrollment: 1) Aged 65 years or older on the day of inclusion 2) Informed consent form has been signed and dated
Exclusion Criteria:	An individual fulfilling *any* of the following criteria is to be excluded from study enrollment: 1) Participation at the time of study enrollment (or in the 4 weeks [28 days] preceding the study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine or drug 2) Previous vaccination against influenza (in the preceding 6 months) with either the study vaccines or another vaccine 3) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances
Statistical Methods:	There is no formal lock of the data. For the primary and secondary objectives, the database will be extracted at one time point and will be considered as final data for conducting the statistical analysis. At this stage, the study will be unblinded. For some of the exploratory objectives, the export(s) and analyses will be conducted at a later date. ***Primary Objective Analysis*** Relative Vaccine Effectiveness: The relative vaccine effectiveness (rVE) of QIV-HD to QIV-SD will be estimated for the primary endpoint as follows: rVE= (1- (CQIV-HD/NQIV-HD) / (CQIV-SD/NQIV-SD)) × 100% where: • CQIV-HD and CQIV-SD are the numbers of cardiovascular and respiratory hospitalization cases meeting the primary endpoint definition in the QIV-HD and QIV-SD groups, respectively • NQIV-HD and NQIV-SD are the numbers of subjects in the QIV-HD and QIV-SD groups, respectively Confidence intervals (CIs) for the rVE will be calculated by an exact method assuming a Binomial distribution of the number of cases in the QIV-HD group conditional on the total number of cases in both groups. The superiority of the QIV-HD effectiveness over QIV-SD will be considered demonstrated if the lower bound of the CI for the rVE is > 0%. A subject who is enrolled in several seasons will be evaluated as an independent subject for each season in the main analysis. ***Secondary Objectives Analysis*** Relative Vaccine Effectiveness: Similar analyses as the primary objective will be conducted and will be described using 95% CIs. Safety: Safety endpoints will be summarized per vaccine group, with 95% CI for the main endpoints. CIs will be calculated using Clopper-Pearson method.

Calculation of Sample Size

The sample size needed for the assessment of the primary objective of the study is 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 are anticipated to be 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.

For note, under different rVE assumptions, the study power will be as follows:

rVE (%)	Power (%)
10	68.7
11	77.3
12	84.5
13	90
14	94
15	96.6

Table of Study Procedures

Phase IIIb/IV Study, 1 Visit, 1 Vaccination, approximately 11 months Study Duration Each Year

Visit / Contact	**V01**	**11 months follow-up period***
Study timelines (D)	**D0**	**D330**
Informed consent	X	
Inclusion/exclusion criteria	X	
Randomization	X	
Vaccination (date of vaccination)†	X	
Collection of suspected SARs (reported by HCPs)‡, all AESIs (reported by HCPs or collected from the Finnish health registers)‡§, and all fatal SAEs	Throughout the study	
Collection of all other SAEs (except those included in the primary endpoint)**	Up to 6 months after vaccination	

Abbreviations: AESI, adverse event of special interest; D, day; HCPs, health care professionals; SAE, serious adverse event; SAR, serious adverse reaction; V, visit.

* The study duration will be approximately 11 months each year. The subject's active participation in the study will be limited to the enrollment and vaccination visit (V01).

† Subjects are to be kept under observation for 20 minutes after vaccination to ensure their safety, and any reactions during this period should be documented in the local medical patient file

‡ SARs and AESIs, experienced by the subject and suspected to be related to the vaccine according to the HCP assessment, will be submitted to THL using an SAR/AESI paper form.

§ AESIs include new onset of Guillain-Barré Syndrome, encephalitis/myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis.

** All other SAEs (except those included in the primary endpoint) and AESIs which have not been reported by the HCPs will be collected from the Finnish health registers.

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
COVID-19	Coronavirus disease 19
CQA	Clinical Quality Assessment
CRA	Clinical Research Associate
CTL	Clinical Team Leader
D	day
DSUR	Development Safety Update Report
DVV	Digital and Population Data Services Agency
ECDC	European Centre for Disease Control and Prevention
EDC	electronic data capture
eCRF	(electronic) case report form
EU	European Union
FVFS	first visit, first subject
FVLS	first visit, last subject
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
HA	hemagglutinin
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
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics committee
IM	intramuscular
IME	important medical event
KELA	The Social Insurance Institution of Finland

MACE	major acute cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
NA	neuraminidase
NH	Northern Hemisphere
NIDR	National Infectious Disease Register
NVR	National Vaccination 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
qs	quantity sufficient
RMO	Responsible Medical Officer
rVE	relative vaccine effectiveness
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard-dose
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TMF	trial master file
THL	Finnish Institute for Health and Welfare
TIV	trivalent influenza vaccine
TIV-HD	high-dose trivalent influenza vaccine
TIV-SD	standard-dose trivalent influenza vaccine
V	visit
WHO	World Health Organization

1 Introduction

1.1 Background

This study will evaluate 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 caused by influenza type A and type B viruses, which belong to the genus *Orthomyxoviridae* and are characterized as enveloped, negative strand, segmented ribonucleic acid viruses.

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 highest risk of complications occur among pregnant women, children 6 to 59 months of age, the elderly, healthcare workers, and individuals with specific chronic medical conditions such as HIV/AIDS, asthma, and chronic heart or lung diseases (1). Approximately 29 000 to 73 000 of these deaths are in Europe and around 85% occurring in individuals 65 years of age and older. Cardiopulmonary hospitalizations due to influenza infection range between 2% to 20% in any given year. In the United States, approximately 1.287 to 2.127 million hospitalizations and 961 to 14 715 deaths in older adults are due to influenza infections with secondary pneumonia infections or cardiac complications being the major causes of deaths among this population. Influenza infection also impacts the daily living of older adults by either causing temporary home (67%) or bed (25%) confinement (2).

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 (3) (4) (5).

Different formulations of inactivated, adjuvanted, or non-adjuvanted influenza vaccines are currently marketed for prophylaxis of influenza disease caused by influenza virus types A and B contained in the vaccine by active immunization of adults and children (6).

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 main protective mechanism against influenza viruses elicited by inactivated influenza vaccination is mediated through the production of antibodies against HA. These antibodies are

highly potent in inhibiting virus replication. In addition, neutralizing antibodies interfere with attachment of the virus to cellular receptors.

An immune response to neuraminidase (NA) may also contribute to clinical benefit, especially with respect to viral shedding and severity of influenza disease (7) (8) (9) (10). However, the contribution of anti-NA antibodies is considered as lower than that of hemagglutination inhibition antibodies.

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 (11).

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 (12) (13).

Consequently, people 65 years of age and older may not have sufficient protection against influenza. Therefore, even if vaccination rates could be high in 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 (14).

1.2 Background of the Investigational Product

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. The TIV-HD was licensed by Sanofi Pasteur under the name of Fluzone® High-Dose in the US (2009), Canada (2015), Australia (2017), Brazil (2018), and the United Kingdom (2019) for use in adults 65 years of age and older.

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 (15) and superior vaccine efficacy (16) 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 (17) (18) (19) (20) (21) (22) (23) (24) (25).

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 (16). 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 (26). 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) (19) (20) (21) (22) (23) (24).

Approximately 26 456 subjects were exposed to TIV-HD through its clinical development program and post marketing clinical trials. As of January 2019, a total of 114.75 million doses of TIV-HD have been distributed (US, Canada, and Australia), and post-marketing surveillance data collected up to 30 September 2018 confirmed that TIV-HD is well tolerated with no safety concerns.

To overcome the problem of B-strain selection and improve protection of the population against seasonal influenza virus, Sanofi Pasteur has developed the QIV-HD containing an increased (60 µg) amount of HA of each of 4 virus strains (A/H1N1, A/H3N2, and 1 B strain from each of the Victoria and the Yamagata lineages).

Data obtained in clinical study QHD00013 showed that QIV-HD induced robust immune responses that were comparable to those induced by the comparator TIV-HD for the shared strains in adults 65 years of age and older. QIV-HD was found to be non-inferior immunologically when compared to TIV-HD in terms of geometric mean titers and seroconversion rates. These data suggest that the addition of a 2nd B strain to TIV-HD does not interfere with the immune responses to the other vaccine strains. Furthermore, the data from QHD00013 demonstrated that antibody responses to both B strains in QIV-HD were statistically superior to each control TIV-HD not containing the respective B strain. These data show that QIV-HD has the potential to provide broader coverage against influenza B of both lineages simultaneously compared to TIV-HD.

Given the demonstration of statistically comparable immunogenicity between QIV-HD and TIV-HD in the QHD00013 study, efficacy results as well as effectiveness results of TIV-HD can be conferred to QIV-HD. Therefore, QIV-HD is likely to induce at least the same relative efficacy and effectiveness as the licensed TIV-HD vaccine showed from large, randomized clinical trials, sponsored and not sponsored by Sanofi Pasteur and real-world observational studies in adults 65 years of age and older.

Vaccination with QIV-HD by IM route among 1777 adults 65 years of age and older in the study QHD00013 was found to be safe, with no safety concerns identified in the reported solicited injection site reactions, solicited systemic reactions, and unsolicited adverse events (AEs). The safety profiles of QIV-HD and TIV-HD were found to be similar.

In conclusion, QIV-HD has been shown to be as immunogenic and safe in adults 65 years of age and older and is expected to induce similar efficacy/effectiveness as demonstrated by TIV-HD.

QIV-HD was approved in the US on 04 November 2019, as a supplement to the Fluzone® High-Dose Biological Licensing Application, in Europe since 01 April 2020, and in Canada on 16 June 2020, for persons 65 years of age and older.

1.3 Potential Benefits and Risks

1.3.1 Potential Benefits to Subjects

All subjects enrolled in Study QHD00012 will receive an influenza vaccine which will be either QIV-HD or QIV-SD. Therefore, they will be 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.

1.3.2 Potential Risks to Subjects

1.3.2.1 Potential Risks and Possible Side Effects of QIV-HD Vaccination

As with any vaccine, QIV-HD may not protect all recipients against the disease it is designed to prevent (ie, influenza).

The QIV-HD is safe and well tolerated in this population. However, as with any vaccine, the QIV-HD vaccine may cause side effects in certain people.

Expected Adverse Events

The safety of QIV-HD is based on adverse reactions (ARs) that were recorded following vaccination with QIV-HD during study QHD00013 (1777 adults 65 years of age and older) and ARs reported during clinical development and post-marketing experience with TIV-HD.

The very common reactions (may affect more than 1 in 10 people) occurring after QIV-HD administration were injection site pain, myalgia, headache, and malaise.

The following reactions have been also observed:

- Reactions at the injection site such as erythema, swelling, bruising, induration, and shivering. Their frequencies have been estimated as common (may affect up to 1 in 10 people)
- Injection site pruritus and systemic reactions such as fever, lethargy, nausea, diarrhea, cough, asthenia, muscle weakness, dyspepsia, night sweats, rash, and vertigo. Their frequencies have been estimated as uncommon (may affect up to 1 in 100 people)
- Fatigue, flushing, arthralgia, dizziness, vomiting, pruritus, urticaria, and pain in extremities. Their frequencies have been estimated as rare (may affect up to 1 in 1000 people)

Most of these reactions usually occurred within the 3 days following vaccination and resolved within 3 days of vaccination. The intensity of these reactions was mostly Grade 1 (mild) to Grade 2 (moderate).

Other Potential Adverse Events

In addition to the expected AEs, the following additional AEs have been spontaneously reported during the post-marketing use of TIV-HD (27) or during clinical trials conducted on TIV-HD, and may occur in people receiving QIV-HD.

These events are reported voluntarily from a population of uncertain size, consequently it is not always possible to reliably estimate the frequency of the events or establish a causal relationship to vaccine exposure. The AEs were included based on one or more of the following factors: severity, frequency of reporting, or strength of evidence for a causal relationship to TIV-HD:

- *Blood and Lymphatic System Disorders*: thrombocytopenia, lymphadenopathy
- *Immune System Disorders*: anaphylaxis, other allergic/hypersensitivity reactions (including angioedema)

- *Eye Disorders*: ocular hyperemia
- *Nervous System Disorders*: Guillain-Barré syndrome (GBS), convulsions, febrile convulsions, myelitis (including encephalomyelitis and transverse myelitis), facial palsy (Bell's palsy), optic neuritis/neuropathy, brachial neuritis, syncope (shortly after vaccination), paresthesia
- *Vascular Disorders*: vasculitis, vasodilatation
- *Respiratory, Thoracic and Mediastinal Disorder*s: dyspnea, wheezing, throat tightness, oropharyngeal pain, rhinorrhea
- *General Disorders and Administration Site Conditions*: chest pain

For further details, refer to the Summary of Product Characteristics of the marketed QIV-HD (Efluelda®).

1.3.2.2 Potential Risks and Possible Side Effects of QIV-SD Vaccination

Refer to the Summary of Product Characteristics of the marketed QIV-SD (Vaxigrip Tetra®) for information regarding potential risks.

1.4 Rationale for the Study

Published evidence shows that influenza infection can be a trigger of Myocardial infarction (28) (29) (30), stroke (31) (30) (32) (33), and heart failure (34). Influenza vaccination shows benefit in the reduction of cardiovascular disease mortality, cardiovascular hospitalizations, major acute cardiovascular events (MACE), stroke, and myocardial infarction (35) (36) (37) (38) (39) (40) (41).

The TIV-HD randomized controlled studies and post-licensure effectiveness studies, conducted in the US, have shown the improved benefit of TIV-HD over SD influenza vaccines for a variety of clinical endpoints that contribute a significant healthcare burden to aging societies, such as hospitalizations due to influenza-like illness, pneumonia, cardiorespiratory events, all-cause deaths, and in some cases against post-influenza death in a consistent manner and over multiple influenza seasons (17) (18) (19) (20) (21) (22) (23) (24) (25) (26).

The QHD00012 clinical study which will compare 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, will complement and reinforce 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 will emphasize the clinically relevant outcome reductions gained by annual vaccination with QIV-HD that are most impactful for patients, healthcare professionals, and policymakers.

2 Study 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.

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.

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.

3 Investigators and Study Organization

This study will be conducted by 1 center, the Finnish Institute for Health and Welfare (THL), which has multiple operating locations in Finland. THL will collaborate with multiple health stations (HS) overseen by selected public health care centers (HCC). The HS are designated as the vaccination sites in this study. The number of health care centers and health stations may be adapted during the study to reach the enrollment target.

Details of the Principal Investigator and sub-Investigators at THL, the sub-Investigators at the HCC, THL operating locations, the HCC, and HS locations are provided in the "List of Investigators and Centers Involved in the Trial" document.

Monitoring activities on site will be conducted by the clinical study unit (CSU, Sanofi) under the responsibility of Sanofi Pasteur SA. The development and conduct of the data management activities, writing of narratives for serious adverse reactions (SARs), AESIs, and fatal SAEs will be conducted by contract research organizations under the responsibility of Sanofi Pasteur SA.

An Independent Data Monitoring Committee (IDMC), composed of members independent from the Sponsor and the Principal Investigator, will be established for this study in order to monitor subject safety by conducting formal reviews of accumulated safety data that will be unblinded. The membership composition, specific responsibilities of members, timing of reviews, objectives for review, and decision criteria will be documented in the IDMC Charter.

An Adjudication Review Committee (ARC), composed of members who are independent from the Sponsor and the Principal Investigator, may be established to review the primary outcomes and to adjudicate a subset of cases. The membership composition, specific responsibilities of members, timing of reviews, objectives for review, and decision criteria will be documented in the ARC Charter.

The Sponsor's Responsible Medical Officer (the RMO, the person authorized to sign this protocol and any amendments on behalf of the Sponsor) is [redacted]

4 Independent Ethics Committee

Before the investigational product can be shipped to the investigational site and before the inclusion of the first subject, this protocol, the informed consent form (ICF), subject recruitment procedures, and any other written information to be provided to subjects must be approved by, and / or receive favorable opinion from, the appropriate Independent Ethics Committee (IEC).

In accordance with Good Clinical Practice (GCP) and local regulations, the Principal Investigator and / or the Sponsor are responsible for obtaining this approval and / or favorable opinion before the start of the study. If the protocol is subsequently amended, approval must be re-obtained for each substantial amendment. Copies of these approvals, along with information on the type, version number, and date of document, and the date of approval, must be forwarded by the Principal Investigator to the Sponsor together with the composition of the IEC (the names and qualifications of the members attending and voting at the meetings).

The Principal Investigator will submit written summaries of the status of the study to the IEC annually, or more frequently if requested. All SAEs occurring during the study that are related to the product administered will be reported by the Principal Investigator to the IEC, according to the IEC policy.

5 Investigational Plan

5.1 Description of the Overall Study Design and Plan

5.1.1 Study Design

QHD00012 will be 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 adults 65 years of age and older in Finland.

This study will be 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, will collaborate with multiple HS overseen by selected HCC to carry out the study and will be responsible for the coordination of the operational aspects of the study conduct. THL will also provide medical and study related expertise.

The study is 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 will be trained on the study procedures and considered qualified on the study. The sub-Investigators will guarantee medical oversight during vaccination visits (eg, in case of emergency such as anaphylactic shock) and to respond, where needed, to any medical questions (primarily through telephone consultations). The HS nurses are responsible for routine health follow-up and immunizations.

The study will be conducted over a period of 3 influenza seasons beginning in 2019-2020; enrollment during each influenza season is planned to start in the fall. The subject's active participation in the study will be limited to the enrollment and vaccination visit. Subjects who participated in the study during one influenza season may participate during another influenza season. Those subjects will be re-consented and re-randomized to one of the 2 study vaccines.

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

5.1.2 Justification of the Study Design

The goal of this study is to show that vaccination with QIV-HD decreases complications of influenza illness in persons 65 years of age or older. The primary objective is to demonstrate the superior clinical relative effectiveness of QIV-HD as compared to QIV-SD, among persons 65 years of age or older, with respect to prevention of cardiovascular and/or respiratory hospitalizations. Analyses will also be performed to assess secondary and observational objectives for the study which include evaluation of the effectiveness of QIV-HD compared to QIV-SD vaccine in preventing hospitalization, primary care visits, death, quality of life, laboratory-confirmed influenza, and SAEs.

Given the study objectives and to allow a high sample size recruitment (approximately 121 000 adults 65 years of age and older), QHD00012 will be a pragmatic randomized clinical study in real-world health system practice with data collection from health registers. Finland was identified as a feasible country to conduct this study based on the existing health care system that allows the collection of data supporting the objectives of this study using Finnish health registers. Therefore, this study will be conducted by THL who will be the principal Investigator and will collaborate with public HCC and HS considered as vaccination locations in Finland.

Justification of the different periods of observation

Different periods of observation will be considered in the study to assess benefits of QIV-HD as compared to QIV-SD:

- The influenza season, from 14 days post-vaccination up to the end of May of the year following the vaccination (for the primary and secondary objectives): This period of observation was chosen based on the benchmarking for other studies assessing similar endpoints (17) (18) (22) (25). In addition, since the manner in which influenza triggers or worsens cardiovascular outcomes is not fully known (in particular the type of outcomes and the timing of such events) and given that some cardiovascular outcomes may occur 1 month after experiencing influenza illness (29) (30) (33), the primary outcome will be collected up to the end of May.
- The influenza epidemic period as defined by the Finnish epidemic thresholds (for the secondary and observational objectives) where the influenza incidence is high.
- An extended period of time from ≥14 days after vaccination until 31 August of the year following the vaccination (for the observational objectives).

Justification of the selection of ICD-10 codes

The study is designed to extract data from the Finnish health registers for diseases of the circulatory and respiratory systems based on the ICD-10 codes. Thus, the goal was to combine and use all the ICD-10 codes related to those diseases in the primary endpoint with the exception of a few codes, based on the absence of biological plausibility such as I00-I02 (acute rheumatic fever) or if the codes were non-specific such as I95-I99 (other and unspecified disorders of the circulatory system). The same approach was used for the selection of the respiratory system diseases.

Additionally, for the diseases where influenza vaccination may or may not have an impact, the codes were kept since the primary objective is to demonstrate the impact of vaccination with QIV-HD on cardiovascular and respiratory outcomes in general and not for specific diseases.

Justification for no collection of reactogenicity data

Taking into consideration the extensive post-marketing experience with TIV-HD and Phase III clinical trial experience with QIV-HD, demonstrating that TIV-HD and QIV-HD have similar safety profiles (see Section 1.2), a full safety assessment of reactogenicity is not deemed necessary in the proposed study.

Justification of the modified double-blind design

Given the volume difference between QIV-HD and Vaxigrip Tetra, the study will be conducted in a modified double-blind manner; therefore, an un-blinded administrator (ie, qualified nurse) at the HS will administer the vaccine but will not be involved in any of the effectiveness and safety study assessments. The subject, the HCC sub-Investigators, the HCPs in the hospitals and outpatient care, the Principal Investigator and sub-Investigators at THL, and the Sponsor will remain blinded.

Additional details will be provided in the THL Coordinating and Working Instructions for the study.

5.1.3 Study Plan

Randomization and Vaccination

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

Subjects, who will participate in several influenza seasons, will be re-consented and re-randomized to one of the 2 study vaccine groups during enrollment.

Recording of Data

Finland uses multiple registers to collect different health and population data. Subject data will be recorded in the local medical patient file and the corresponding Finnish health registers (hospital diagnosis/treatment and SAEs) by health care professionals (HCPs) (See Table 11.1 for description of the registers).

Collection of Datasets

The datasets will be collected using multiple Finnish health registers and compiled by THL into an analysis database. The subject's Personal Identity Code (PIC) is used in all of the registers and will be used by THL to link individual data from the different registers. On a regular basis, THL will extract the study data from the different Finnish registers and when required from local medical patient files. THL will submit 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

The SARs and AESIs, experienced by the subject and suspected to be related to the vaccine according to the HCP assessment, will be collected using an SAR/AESI paper form throughout the study (ie, from inclusion up to 31 August of the year following the vaccination). Additional data can be collected from the local medical patient file, as needed.

All other SAEs (non-fatal SAEs except those included in the primary endpoint) will be collected by THL from the Finnish health registers up to 6 months after vaccination. AESIs and fatal SAEs, which have not been reported by the HCPs, will be collected in the same manner throughout the study.

Note: AESIs include new onset of GBS, encephalitis / myelitis (including transverse myelitis), Bell's palsy, optic neuritis, and brachial neuritis.

Detailed description of the data reporting process from the HCPs to the Principal Investigator and from the Principal Investigator to Sanofi Pasteur is outlined in Section 10.

COVID-19 Risk Assessment

The QHD00012 study may be conducted during the ongoing outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the human population considered as pandemic by the WHO on 11 March 2020.

QIV-HD is an inactivated influenza vaccine and is not expected to cause immune suppression. Therefore, the risk that a subject in this study will contract Coronavirus disease 19 (COVID-19) solely due to the administration of the study vaccine will be similar to the risk that a person not participating in this study will contract COVID-19. However, the risk of exposure to infected people cannot be completely excluded as the subjects in QHD00012 may be exposed to people and surfaces commuting to the study and in waiting rooms and exam rooms at the study site. The risk of exposure to COVID-19 in persons who will receive influenza vaccinations in context of the national vaccination program can be considered similar.

COVID-19 Risk Mitigation:

- Reevaluate the start of the study enrollment for the next influenza season as the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are evaluated by the study team.
- Continued risk assessment by the Principal Investigator and the Sponsor prior to the study enrollment of each season of the study.

5.1.4 Visit Procedures

Visit 1 (Day 0): Inclusion, Randomization, and Vaccination

The qualified HS nurse will:

- Give the subject the relevant information about the study
- Answer any questions to ensure that the subject is informed of all aspects of the study that are relevant to their decision to participate, and obtain informed consent
    - Remind the subject regarding the process for study withdrawal (ie, to contact the HCC or THL in case the subject decides to withdraw from the study)
    - Remind the subject to report adverse events after vaccination to the study personnel of the HCC or THL
- Date and sign the ICF after it has been signed and dated by the subject
- Check with the subject if experiencing any increase in body temperature
- Check all inclusion and exclusion criteria (see Sections 5.2.4 and 5.2.5, respectively) for eligibility and document this process on the ICF
- Perform randomization order as per the THL Working Instructions
- Complete all the fields in the corresponding line in the scratchable randomization list
    - Affix 1 detachable label of the vaccine dose number (note: the labels are attached to the vaccine box)
    - Fill out all applicable fields (eg, name or initials of the unblinded administrator, date, time, and signature)
- Record the randomization order number in the ICF
- Administer the appropriate vaccine intramuscularly into the deltoid muscle of the upper arm
- Affix 1 detachable label of the vaccine dose number to the original ICF
- Affix the label containing study information to the subject's national insurance card (KELA card)
    - Remind the subjects to inform their HCPs of their participation in this study
- Ensure that the following information is documented in the ICF:
    - Subject's PIC
    - Inclusion / exclusion criteria check
    - Vaccination date if different than the ICF signature date
    - the randomization order number
- Retain the signed original ICF for sending to THL, keep a signed copy at the HS, and give a signed copy to the subject

- Additionally, the dose given will be documented in the local electronic patient file, from which the data will be transferred daily to the Register of Primary Health Care Visits (AvoHILMO) and the National Vaccination Register (NVR)
- Keep the subject under observation for 20 minutes, document this observation period in the ICF, and record any adverse reaction in the local medical patient file

5.1.5 Planned Study Calendar

The following dates are approximate. The actual dates may differ as, for example, the study will not start until all the appropriate regulatory and ethical approvals have been obtained.

Planned inclusion / vaccination period - FVFS (first visit, first subject) to FVLS (first visit, last subject): October to December

Planned data collection period: from the date of vaccination up to 31 August of the year following the vaccination

Note: Historical data for the subjects will also be collected for background characteristics, morbidity, and previous vaccinations.

Planned end of study (ie, data collection period): Quarter (Q) 3 2022

Planned date of final clinical study report: Q1 2023

5.2 Enrollment and Retention of Study Population

5.2.1 Recruitment Procedures

For each study year, THL will use the Finnish population information system to pre-select based on age, native language, and other factors as applicable, the potentially eligible subjects prior to being contacted and invited to participate in the study.

THL will send invitation letters which includes a 1 page invitation, the full study information sheet, and an example of the ICF.

THL may also use media such as information folders, posters, leaflets, web pages, videos, key professionals' interviews, and articles in local newspapers and magazines to increase awareness of the study among the population. Presentations in society meetings of the elderly will be considered (eg, selected patient organizations and societies for pensioners).

A service will be available where THL will answer questions via telephone calls and emails. THL will ensure that any advertisements used to recruit subjects (letters, information folders, posters, leaflets, etc.) are submitted to Sanofi Pasteur prior to submission to the IEC for approval.

5.2.2 Informed Consent Procedures

Informed consent is the process by which a subject voluntarily confirms his or her willingness to participate in a particular study. Informed consent must be obtained before any study procedures

are performed. The process is documented by means of a written, signed, and dated ICF. In addition, the subject will be informed about the use of the health register data in this study.

In accordance with GCP, prior to signing and dating the consent form, the subject must be informed by appropriate study personnel about all aspects of the study that are relevant to making the decision to participate (including the use of the health register data), and must have sufficient time and opportunity to ask any questions.

The informed consent form will be presented to the subject in Finnish or Swedish language. The subject must be able to read and understand the document adequately.

Any change to the content of the ICF must be approved by the Sponsor and the IEC prior to the form being used.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a letter to the subject.

Informed consent forms will be provided in triplicate, or a photocopy of the signed consent will be made. The original ICF will be provided to THL for data entry, 1 copy will be kept by the subject, and 1 copy will remain at the HS.

The ICF will be used to document the following information in addition to the subject's consent:

- subject's PIC
- inclusion / exclusion criteria check
- the subject is not experiencing any increase in body temperature
- vaccination date if different than the ICF signature date
- the randomization order number
- the vaccine dose number
- the 20 minutes post-vaccination surveillance period

5.2.3 Screening Criteria

There are no screening criteria other than the inclusion and exclusion criteria.

5.2.4 Inclusion Criteria

An individual must fulfill *all* of the following criteria to be eligible for study enrollment:

1) Aged 65 years or older on the day of inclusion[a]
2) Informed consent form has been signed and dated[b]

[a] "65 years" means from the day of the 65th birthday

[b] Informed consent form will be in Finnish or Swedish language

5.2.5 Exclusion Criteria

An individual fulfilling *any* of the following criteria is to be excluded from study enrollment:

1) Participation at the time of study enrollment (or in the 4 weeks [28 days] preceding the study vaccination) or planned participation during the present study period in another clinical study investigating a vaccine or drug
2) Previous vaccination against influenza (in the preceding 6 months) with either the study vaccines or another vaccine
3) Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances[a]

The subject's study vaccination details will be recorded in the local medical patient file.

5.2.6 Medical History

Subject's medical history will be collected through the national registers. The following information will be collected as part of the subject medical history:

- Previous vaccinations during the last 5 years (administered product and date of vaccination)
- Diabetes
- Chronic coronary heart disease
- Chronic heart insufficiency
- Chronic cardiac arrhythmias
- Chronic lung disease (asthma and chronic obstructive pulmonary disease)

5.2.7 Contraindications for Vaccinations

5.2.7.1 Temporary Contraindications

Should a subject experience moderate or severe febrile illness or acute infection on the day of vaccination, the HS nurse will postpone vaccination until the condition is resolved in which case the agreement for participation in the study and the eligibility ofthe participant should be re-checked.

5.2.8 Conditions for Withdrawal

Subjects will be informed that they have the right to withdraw their consent from the study at any time. The subject is not required to provide a reason for withdrawal.

[a] The components of QIV-HD are listed in Section 6.1 and in the Investigator's Brochure. The components of QIV-SD are listed in Section 6.1.2 and in the Summary of Product Characteristics

The withdrawal should be clearly documented in the subject's medical records and the Principal Investigator should be informed.

Starting from the date of withdrawal, the subject's data will no longer be collected for this study.

Withdrawn subjects will not be replaced.

5.3 Modification of the Study and Protocol

Any amendments to this study plan and protocol must be discussed with and approved by the Sponsor. If agreement is reached concerning the need for an amendment, it will be produced in writing by the Sponsor, and the amended version of the protocol will replace the earlier version. All substantial amendments (eg, those that affect the conduct of the study or the safety of subjects) require IEC approval, and must also be forwarded to regulatory authorities.

A non-substantial amendment to a protocol is one that modifies some administrative, logistical, or other aspect of the study but does not affect its scientific quality or have an impact on the subjects' safety. The IECs will either be notified of or will approve non-substantial amendments.

The Principal Investigator is responsible for ensuring that changes to an approved study, during the period for which IEC approval has already been given, are not initiated without IEC review and approval, except to eliminate apparent immediate hazards to subjects.

5.4 Interruption of the Study

The study may be discontinued if new data about the investigational product resulting from this or any other studies become available; or for administrative reasons; or on advice of the Sponsor, the IDMC, the Principal Investigator, the IECs, or the governing regulatory authorities in Finland where the study is taking place.

The study may be paused during the ongoing outbreak of SARS-CoV-2 in the human population considered as pandemic by the WHO on 11 March 2020.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by applicable regulatory requirements. The Principal Investigator shall promptly inform the study subjects and should assure appropriate subject therapy and/or follow-up.

6 Products Administered

6.1 Identity of the Investigational Product

6.1.1 Identity of Study Product (QIV-HD)

The investigational QIV-HD (Efluelda® manufactured by Sanofi Pasteur) is a split virion inactivated quadrivalent influenza vaccine (60 µg HA/strain/dose) containing virus strains recommended by the WHO and European Union (EU) for the NH influenza season related to this study. The vaccine contains 2 antigens of type A (H1N1 and H3N2) and 2 antigens of type B (one each from Yamagata and Victoria lineages).

Each pre-filled syringe, (Type I glass) equipped with a plunger stopper (bromobutyl rubber) and a tip cap, contains a total of 240 µg HA antigen per 0.7 mL dose provided in sterile suspension for IM injection.

QIV-HD vaccine is prepared from influenza viruses propagated in embryonated chicken eggs, inactivated with formaldehyde, disrupted using octoxynol-9 and purified.

6.1.1.1 Composition

Each 0.7 mL dose of vaccine contains the following components:

Strains will be determined based on WHO and EU recommendations for the NH influenza season related to this study

Active substances:

- A/H1N1 strain 60 µg HA
- A/H3N2 strain 60 µg HA
- B/(Victoria Lineage) strain 60 µg HA
- B/(Yamagata Lineage) strain 60 µg HA

Excipients:

- Buffered saline solution qs to appropriate volume
- Octoxinol-9 not more than 350 µg

It may also contain residual traces of eggs, such as ovalbumin, formaldehyde, and octoxynol-9. It does not contain more than 1 µg of ovalbumin per dose.

Batch number: to be determined (TBD).

6.1.1.2 Preparation and Administration

The vaccine is provided in a pre-filled single-dose syringe (Type I glass). The needle will be provided separately. The vaccine should be allowed to reach room temperature before use. It must

be shaken before use to obtain a homogeneous suspension. The vaccine is to be administered intramuscularly into the deltoid muscle of the upper arm.

Prior to administration, all study products must be inspected visually for cracks, broken seals, correct label content (see Section 6.3.1), and particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the vaccine must not be administered. Another dose is to be used according to the instructions given in the THL Coordinating and Working Instructions, and the event is to be reported to the Sponsor.

Subjects must be kept under observation for 20 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the local medical patient file. Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction. The sub-Investigators at the HCC will not attend the vaccination visits but will see that medical care is available in case of emergency (eg, anaphylactic shock).

6.1.1.3 Dose Selection and Timing

The vaccination schedule of a single dose for the influenza season is per standard practice for receipt of annual influenza vaccination.

6.1.2 Identity of Control Product (Vaxigrip Tetra®)

The control product is an inactivated, split-virion influenza vaccine which will contain the 4 NH influenza strains recommended by WHO and EU, cultivated on eggs, and then purified, split and inactivated and purified.

It is a suspension for injection to be administered by IM injection, presented in a 0.5 mL, prefilled syringe (type I glass) equipped with a plunger stopper (elastomer bromobutyl or chlorobutyl), and a tip cap.

6.1.2.1 Composition

Each 0.5 mL dose of Vaxigrip Tetra contains the following components:

Strains will be determined based on WHO and EU recommendations for the NH influenza season related to this study

- A/H1N1 strain 15 µg HA
- A/H3N2 strain 15 µg HA
- B/(Victoria Lineage) strain 15 µg HA
- B/(Yamagata Lineage) strain 15 µg HA

Excipients:

- Buffered saline solution qs 0.5 mL

It may also contain residual traces of octoxynol-9, neomycin, and formaldehyde. It does not contain more than 0.05 µg of ovalbumin per dose.

Batch number: TBD.

6.1.2.2 Preparation and Administration

The procedures for preparing and administering the control product are the same as those described for the study product in Section 6.1.1.2.

6.1.2.3 Dose Selection and Timing

The amount of antigen contained in QIV-SD is based on EU Pharmacopoeia (Monograph 0158) (15 µg HA of each strain per dose). The vaccination schedule of a single dose for the influenza season is per standard practice for receipt of annual influenza vaccination.

6.2 Identity of Other Products

Not applicable.

6.3 Product Logistics

6.3.1 Labeling and Packaging

The QIV-HD and QIV-SD will be provided by the Sponsor and will be labeled in accordance with national regulations.

The QIV-HD and QIV-SD will be supplied in single dose syringes with investigational labeling and packaging. Each single dose will be identified by a unique dose number on the label and on the carton. The carton labels will also have detachable vaccine labels containing the dose number. See the THL Coordinating and Working Instructions for additional label detail.

6.3.2 Product Shipment, Storage, and Accountability

6.3.2.1 Product Shipment

Each vaccine shipment will include a temperature-monitoring device to verify maintenance of the cold chain during transit. On delivery of the product to the site, the person in charge of product receipt will follow the instructions given in the THL Coordinating and Working Instructions, including checking that the cold chain was maintained during shipment (ie, verification of the temperature recorders). If there is an indication that the cold chain was broken, this person should refer to the tolerance data provided by the Sponsor and determine if the vaccines are suitable for use. If the temperature is out of tolerance, the vaccines must be quarantined and the Sponsor should be alerted. Temperature deviations will be documented according to the THL Coordinating and Working Instructions.

6.3.2.2 Product Storage

The Investigator or a delegate will be personally responsible for product management or will designate a staff member to assume this responsibility.

At the HS, products must be kept in a secure place with restricted access. Vaccines will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The vaccines must not be frozen. The temperature must be monitored and documented (see the THL Coordinating and Working Instructions) for the entire time that the vaccine is at the study site. In case of accidental freezing, the vaccines must not be administered and must be quarantined. In case of disruption of the cold chain, refer to the tolerance data provided by the Sponsor. Temperature deviations will be documented according to the THL Coordinating and Working Instructions.

6.3.2.3 Product Accountability

The person in charge of product management at the HS will maintain records of product delivery and the disposal of or return to the Sponsor of unused doses. The product inventory can be manually checked on a daily basis at the HS using the randomization list and at THL using the NVR. The dose given to each subject will be documented in the ICF and in the scratchable randomization list by affixing the label of the vaccine dose number to each document.

In case of any expected or potential shortage of product during the study, the Principal Investigator or an authorized designee should alert the Sanofi Pasteur representative as soon as possible, so that a shipment of extra doses can be arranged.

6.3.3 Replacement Doses

If a replacement dose is required (eg, because the syringe broke or particulate matter was observed in the syringe), the site personnel must follow the instructions given in the THL Coordinating and Working Instructions.

6.3.4 Disposal of Unused Products

Unused or wasted products will be either disposed of or returned to the Sponsor in accordance with the instructions in the THL Coordinating and Working Instructions. Product accountability will be verified throughout the study period.

6.3.5 Recall of Products

If the Sponsor makes a decision to launch a retrieval procedure, the Principal Investigator will be informed of what needs to be done.

6.4 Blinding and Code-breaking Procedures

This study has a modified double-blind design where an unblinded administrator will administer the vaccine. The subjects, the HCC sub-Investigators, the HCPs in the hospitals and outpatient care, the Principal Investigator and sub-Investigators at THL, and the Sponsor will remain blinded to the vaccine assignment in order to avoid any bias in reporting and evaluating outcome illnesses or SAEs.

The need for code-breaking procedures in the event of an SAE is not required since the treatment of the subject by the HCP will not be influenced by which vaccine the subject had received. The

HCPs will be instructed to contact the Principal Investigator and the sub-Investigators using the contact details available at the public internet webpage of the study.

A request for the code to be broken may be made

- by the Global Pharmacovigilance (GPV) Department through an internal system for reporting to health authorities in the case of an SAE as described in ICH E2A[a]. In this case, the code will be broken only for the subject(s) in question. The information resulting from code-breaking (ie, the subject's vaccine or group assignment) will not be communicated to either the Principal Investigator or the immediate team working on the study, except for the GPV representative.
- By the IDMC if needed to facilitate their assessment of safety

The IEC will be notified of the code-breaking as per local IEC guidelines. All documentation pertaining to the event must be retained at THL and in the Sanofi Pasteur files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

6.5 Randomization and Allocation Procedures

Subjects will be randomized in a 1:1 ratio into the QIV-HD group or the QIV-SD group, using a block randomization method. The vaccine doses will be identified by a unique dose number and will be randomized in order to maintain the blind in the health registers and the database.

The full detailed procedures for randomization are described in the THL Coordinating and Working Instructions.

The Biostatistics platform of the Sponsor will provide a scratchable randomization list (split into the different HS, each year). This list will mention the randomization order of the subject and the corresponding study group covered by a silver-colored patch. For each enrolled subject, the HS nurse will use the next available randomization order number in the list to assign him/her to a coded vaccine group (eg, Product A or Product B). Once scratched, the HS nurse will complete all the fields of this list as described in Section 5.1.4. The scratchable randomization list will be returned to Sanofi Pasteur by the end of the study. Each subject will be vaccinated with the product corresponding to the group mentioned on the randomization list. If the dose initially taken for the vaccination is broken or cannot be used, the HS nurse will take another dose of the same vaccine (eg, Product A or product B).

Subject numbers will be assigned at THL during the ICF data entry process. Further details will be described in the Data Management Plan.

Subject numbers should not be reassigned for any reason.

6.6 Treatment Compliance

Not applicable.

[a] All unexpected and related SAEs submitted to European Union competent authorities must be unblinded.

6.7 Concomitant Medications and Other Therapies

The concomitant medications can be retrieved from the appropriate health register.

7 Management of Samples

Samples will not be collected in this study.

8 Clinical Supplies

Sanofi Pasteur will supply THL with protocols, ICFs, and other study documents, as well as with the following study materials: all study vaccines, needles for vaccination, scratchable lists, and temperature recorders.

The HCC/HS will supply all vaccine administration supplies, including biohazard and / or safety supplies. The biohazard and safety supplies include examination gloves, laboratory coats, sharps disposal containers, and absorbent countertop paper. The HCC/HS will ensure that all biohazard wastes are disposed of in accordance with local practices. The HCC/HS will also provide appropriate space in a temperature-monitored refrigerator for the storage of the products.

In the event that additional supplies are required, THL must contact Sanofi Pasteur, indicating the quantity required.

9 Endpoints and Assessment Methods

The endpoints in the study are defined using combinations of various definitions for follow-up periods.

The follow-up periods (ie, the data collection periods) will be defined starting ≥ 14 days after vaccination until 31 August of the year following the vaccination. Regarding endpoints definition, 3 periods are identified for this study:

- from ≥ 14 days after vaccination until 31 May of the year following the vaccination (for the primary and secondary objectives)
- from ≥ 14 days after vaccination until 31 August of the year following the vaccination (for the observational objectives)
- during the influenza epidemic period as defined by the Finnish epidemic thresholds (for the secondary and observational objectives)

The start date of hospitalization or the date of the hospital emergency room/primary care visits will be collected and used in the database to determine whether the event would be included in an endpoint analysis or not. For example, if the start date of an event occurs before the start of the influenza epidemic period, then this event would not be included in the analysis for the endpoints related to this period.

9.1 Primary Endpoints and Assessment Methods

9.1.1 Effectiveness

The primary endpoints for the evaluation of relative vaccine effectiveness (rVE) are:

- First occurrence of an unscheduled cardiovascular or respiratory inpatient hospitalization (between ≥ 14 days after vaccination and up to 31 May of the year following the vaccination)
- Inpatient hospitalizations with the following ICD-10 codes entered into the hospital primary discharge code will be considered:
  - Diseases of the circulatory system:

    Hypertensive diseases, based on codes I11 and I16

    Ischemic heart diseases, based on codes I20-I25

    Pulmonary heart disease and diseases of pulmonary circulation, based on codes I26 and I27

    Other forms of heart disease, based on codes I30, I31, I33, I38-I42, I46-I50,

    Cerebrovascular diseases, based on codes I63-I67

    Diseases of arteries, arterioles and capillaries, based on codes I74-I76
  - Diseases of the respiratory system:

    Acute upper respiratory infections, based on codes J00-J06

    Influenza and pneumonia, based on codes J09-J18

    Other acute lower respiratory infections, based on codes J20-J22

    Chronic lower respiratory diseases, based on codes J40-J47

    Other respiratory diseases principally affecting the interstitium, based on codes J80 and J81

    Suppurative and necrotic conditions of the lower respiratory tract, based on codes J85-J86

9.1.2 Safety

There are no primary objectives for safety.

9.2 Secondary Endpoints and Assessment Methods

9.2.1 Effectiveness

The secondary endpoints for the evaluation of rVE are:

1) First occurrence between ≥ 14 days after vaccination and up to 31 May of the year following the vaccination of each of the following endpoints:

- Inpatient hospitalization with primary discharge diagnosis (using ICD-10 codes) for:
  - Diseases of the respiratory system, based on codes J00-J06, J09-J18, J20-J22, J40-J47, J80, J81, J85, and J86
  - Diseases of the circulatory system, based on codes I11, I16, I20-I25, I26, I27, I30, I31, I33, I38-I42, I46-I50, I63-I67, and I74-I76
  - Pneumonia, based on codes J12-J18
  - Heart failure, based on code I50
  - Acute myocardial infarction, based on code I21
  - Atrial Fibrillation, based on code I48
  - Stroke, based on code I63
  - Influenza and pneumonia, based on codes J09-J11 and J12-J18
  - Influenza, based on codes J09-J11
- Death, all-cause and based on the diseases and ICD-10 codes listed above
- Inpatient hospitalization with primary and secondary admission and discharge diagnoses based on the diseases and ICD-10 codes listed above
- Hospital emergency room visits based on the diseases and ICD-10 codes listed above
- Acute primary care visits to physician based on the diseases and ICD-10 codes listed above (or corresponding International Classification of Primary Care 2nd edition [ICPC-2] codes)

2) First occurrence between ≥ 14 days after vaccination and up to 31 May of the year following the vaccination of MACE as defined by all of the following endpoints:
   - Ischemic heart diseases based on codes I20-I25
   - Non-fatal myocardial infarction based on codes I21-I23
   - Fatal or non-fatal stroke based on code I63
   - Unstable angina based on codes I20 and I25
3) The following characterization for selected outcomes to be described when applicable:
   - All occurrences of an unscheduled cardiovascular or respiratory inpatient hospitalization or hospital emergency room visits or primary care visits to physician
     - Onset of event
     - Duration of event
4) First occurrence between ≥ 14 days after vaccination and up to 31 May of the year following the vaccination of each of the endpoints listed above by:
   - Age groups (65-74 years and ≥ 75 years or 65-79 years and ≥ 80 years)
   - Groups with specific comorbidities (diabetes, cardiovascular history, chronic lung disease)
5) First occurrence of each of the endpoints above during influenza epidemic period as defined by the Finnish epidemic thresholds

9.2.2 Safety

9.2.2.1 Safety Definitions

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

Serious Adverse Event (SAE):

The term serious is based on subject / event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness serves as a guide for defining regulatory reporting obligations.

An SAE is any untoward medical occurrence that at any dose

- Results in death
- Is life-threatening[a]
- Requires inpatient hospitalization or prolongation of existing hospitalization[b]
- Results in persistent or significant disability / incapacity[c]
- Is a congenital anomaly / birth defect
- Is an important medical event (IME)

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

An SAE may or may not have a causal relationship with the administered vaccine.

Serious Adverse Reaction (SAR) and suspected SAR:

All noxious and unintended responses to the study vaccine related to any dose administered that results in death, is life-threatening, requires hospitalization or prolongation of existing

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

[b] All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of: elective hospitalizations planned either before or after inclusion into the study or outpatient treatment with no hospitalization, or hospitalizations due to an AE defined in the primary endpoint.

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

hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

A SAR refers to a potential causal relationship between the study vaccines and an SAE, based on the HCP assessment.

A suspected SAR refers to individual SAR cases reported by the HCPs where a causal relationship between the SAE and the study vaccines is suspected by either the Principal Investigator or the Sponsor.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reaction (SUSAR) is the term used to refer to an adverse event that occurs in a clinical trial subject, which is assessed by the sponsor and / or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study drug. Reports of these reactions are subject to expedited submission to health authorities.

Adverse Event of Special Interest (AESI):

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

AESIs are identified based on toxicological studies, clinical or nonclinical research, and / or experiences with similar compounds, or from post-marketing experiences. The following adverse events are considered AESIs for the QIV-HD in studies with adults 65 years of age and older population (42) (43).

- GBS
- Encephalitis / Myelitis (including transverse myelitis)
- Bell's palsy
- Optic neuritis
- Brachial neuritis

9.2.2.2 Safety Endpoints

The following endpoints for the evaluation of safety will be described for all subjects:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT] or ICD-10 codes), time to onset, seriousness criteria, and outcome of all SARs, all AESIs, and all fatal cases throughout the study
- Occurrence and nature (MedDRA PT or ICD-10 code) of non-fatal SAEs by time to onset and seriousness criteria up to 6 months after vaccination

9.2.2.3 Safety Assessment Methods

9.2.2.3.1 Immediate Post-vaccination Observation Period

Subjects will be kept under observation for 20 minutes after vaccination to ensure their safety. The post-vaccination adverse events should be documented in the local medical patient file. SAEs will be recorded in the appropriate health register and reported to the Sponsor in the same way as any other SAEs, according to the procedures described in Section 10.

9.2.2.3.2 Serious Adverse Events

Information on non-fatal SAEs will be collected from the health registers, from inclusion until 6 months after vaccination. Non-fatal SAEs will not be individually assessed for causality. Instead, they will be evaluated statistically by comparing the frequency of SAEs to a baseline incidence estimated from the same health registers.

Information on SARs (suspected to be related to the vaccine by the HCPs), fatal SAEs, and AESIs will be collected and assessed throughout the study. Every SAR must be reported, even if the Principal Investigator considers that it is not related to the vaccine.

Any SAR (suspected to be related to the vaccine by the HCPs), fatal SAE, or AESI occurring at any time during the study will be reported by the Principal Investigator using the SAE electronic case report form (SAE eCRF) in the electronic data capture (EDC) system according to the Completion Instructions provided by the Sponsor. All information concerning the SAE is to be reported either as part of the initial reporting or during follow-up reporting if relevant information became available later (eg, outcome, medical history, results of investigations, copy of hospitalization reports. See Section 10 for further details on SAE reporting).

For each SAR/AESI, the following information is to be recorded:

- Diagnostic (SAR/AESI) or ICD-10 code (Fatal: non SAR/AESI)
- Start and stop dates
- Whether the SAE was related to the investigational product

  The Principal Investigator will assess the causal relationship between the SARs (suspected to be related to the vaccine by the HCPs), fatal SAEs, and AESIs and the investigational product as either “Not related” or “Related”, as described in Section 9.2.2.3.3.
- Action taken for each SAE (eg, medication)

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

  - None
  - Medication
  - Health care provider contact
  - Hospitalized

For each SAR/AESI, the Principal Investigator or a delegate will complete all the following criteria: outcome, elapsed time, and relationship to study procedures.

9.2.2.3.3 Assessment of Causality

The Principal Investigator or delegate sub-Investigator will assess the ***causal relationship*** between each SAR (suspected to be related to the vaccine by the HCPs), fatal SAE, and AESI and the product administered as either ***not related*** or ***related***, based on the following definitions:

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

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

Note: By convention, all SAEs reported at the injection site are considered to be related to the administered product and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

Serious adverse events likely to be related to the product that persist at the end of the study will be followed up by the Principal Investigator until their complete disappearance or the stabilization of the subject's condition. The Principal Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

9.3 Observational Endpoints and Assessment Methods

The observational endpoints for the evaluation of rVE are:

1) Clinical relative effectiveness of QIV-HD as compared to QIV-SD (between ≥ 14 days after vaccination and up to 31 August of the year following the vaccination) for the first occurrence of the following endpoints:
   - Unscheduled cardiovascular or respiratory inpatient hospitalization (primary discharge)
   - Inpatient hospitalizations with primary discharge codes for diseases of the circulatory system and diseases of the respiratory system based on the diseases and the ICD-10 codes listed in the primary endpoints (for each code separately)
   - Inpatient hospitalization with primary discharge diagnosis, death, inpatient hospitalization with primary and secondary discharge or admission diagnoses, hospital emergency room visits, and primary care visits to physician based on the ICD-10 codes listed in the secondary endpoints
   - Death, all-cause
2) Long-term complications and need of care in terms of diagnosis of hip fracture, based on ICD-10 code S72 and disabilities based on the care allowance for pensioners/disability in the Social Insurance Institution register (KELA)

3) The following health care resources for all subjects
   - Medications such as anti-influenza and antibacterial outpatient medications
   - All unscheduled hospitalizations and hospital emergency room visits
   - All acute primary care visits to a physician
4) Clinical relative effectiveness of QIV-HD as compared to QIV-SD against laboratory-confirmed influenza based on routine swabbing and laboratory-confirmed invasive bacterial diseases

Details of the assessment methods will be described in the statistical analysis plan (SAP).

10 Reporting of Serious Adverse Events

10.1 Initial Reporting by the Health Care Professionals and the Principal Investigator

Data collected in the SAE eCRF for each individual case will include outcome, precise description of medical history, results of the investigation and the causal relationship between the SAE and the product administered, as evaluated by the Principal Investigator.

The HCPs at the HCC/HS will be trained to report SARs (experienced by the subjects and suspected to be related to the vaccine according to HCP assessment), and AESIs. In Addition, other HCPs in Finland will be informed about this clinical study and will be requested to report SARs and AESIs directly to the Principal Investigator (ie, THL). For reporting purposes, all HCPs will use an SAR/AESI paper form.

All fatal SAEs will be collected on an ongoing basis from the registers using the available register data as the primary source data for reporting.

Upon receipt of any SAR/AESI paper form from a HCP or identification of an AESI or fatal SAE from the health registers, the Principal Investigator or delegate sub-Investigators must report the event which occurred during a subject's participation in the study or experiment, within 24 hours after the first awareness of any THL study personnel to the Sponsor's GPV Department, the Clinical Research Associate (CRA), and the Clinical Team Leader (CTL) using an SAE eCRF in the EDC system. Every SAE must be reported, even if the Principal Investigator considers that it is not related to the vaccine. The Principal Investigator or a delegate sub-Investigator must validate the information entered on the SAE eCRF by completing the investigator validation form.

The Principal Investigator must indicate on the SAE eCRF that the event was serious and must complete the relevant SAE section of this form. An e-mail alert will automatically be sent by the EDC system to the GPV mailbox, the CRA and the CTL with relevant SAE information details.

If the EDC system is unavailable, the Principal Investigator must notify the Sponsor, using the paper version of the SAE eCRF.

The Principal Investigator must complete the paper copies of the SAE eCRF and send them to the Sponsor by one of the following means:

- In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com
- By express mail, to the following address
  Global PharmacoVigilance, Sanofi Pasteur SA
  14, Espace Henry Vallée
  69007 LYON, France

When the EDC system becomes available, the Principal Investigator must transcribe the information from the paper forms into the SAE eCRF in the EDC system.

To comply with current regulations on SAE reporting to health authorities, the Principal Investigator must document SARs (suspected to be related to the vaccine by the HCPs), fatal SAEs, and AESIs regardless of causal relationship, and notify the Sponsor and the CRA within the notification timelines stated in the following sections. The Principal Investigator will provide the Sponsor and the CRA with all necessary information to allow the Sponsor to conduct a detailed analysis of the safety of the investigational product. It is the responsibility of the Principal Investigator to request all necessary documentation (eg, medical records, discharge summary, in order to provide comprehensive safety information). All relevant information must then be transcribed onto the SAE eCRF.

Once the Sponsor confirms the reported event as SUSAR, the case will be managed according to SUSAR case management process (unblinding done by GPV; provide SUSAR case with unblinding information to the IDMC for further recommendation on relatedness of the case).

THL will report all non-fatal SAEs (except cardiovascular and respiratory hospitalizations [primary endpoints]) twice per month in the form of an aggregate table of SAEs with an evaluation based on background information and providing observed versus expected analysis of reported non-fatal SAEs.

The Sponsor will perform aggregate analysis of the non-fatal SAEs during safety management meeting every month for the first few months and every 3 months subsequently (depending on the need) during the study periods and at the end for final evaluation. For the blinded follow-up period, signal detection processes will be set up by comparing the frequency of safety outcomes to a baseline incidence estimated from the registers. This allows the safety assessment to be objectively based on probabilistic and statistical methods. The tabulated outputs will be generated by THL, under the Sanofi Pasteur GPV process.

10.2 Follow-up Reporting by the Principal Investigator

The SAE eCRF completed initially must be updated by the Principal Investigator or delegate sub-Investigators within 24 hours after the awareness of any THL study personnel of any new relevant information concerning the SAE (eg, outcome, precise description of medical history, results of the investigation). All relevant information must be included directly in the SAE eCRF.

An e-mail alert will be sent automatically to the GPV Department, the CRA, and the CTL. Copies of documents (eg, medical records, discharge summary, autopsy) may be requested by the GPV Department.

The anonymity of the subject must always be respected when forwarding this information.

10.3 Reporting of SAEs Occurring After a Subject Has Completed the Study

Not applicable.

10.4 Assessment of Causality

The causal relationship between the SAE (ie, fatal SAE, AESI, or SAR) and the product administered will be evaluated by the Principal Investigator as described in Section 9.2.2.3.3.

Following this, the Sponsor's Global Safety Officer will also assess the causal relationship to the product, based on the available information and current medical knowledge.

The causal relationship to study procedures will also be assessed in the SAE eCRF.

The decision to modify or discontinue the study may be made after mutual agreement between the Sponsor and the Principal Investigator.

10.5 Reporting SAEs to Health Authorities and IECs

The Sponsor will inform the relevant health authorities of all SARs, fatal SAEs, and AESIs (regardless of causality) according to local regulatory requirements. Non-fatal SAEs will be reported in the Development Safety Update Report (DSUR) to relevant health authorities.

The Sponsor's RMO will notify the Principal Investigator in writing of the occurrence of any reportable SAEs. The Principal Investigator / Sponsor will be responsible for informing the IECs that reviewed the study protocol based on the national requirements.

10.6 Reporting of Cardiovascular and Respiratory Events

Cardiovascular and respiratory effectiveness endpoints as specified in this protocol will not be considered as SAEs and are waived from regulatory reporting to health authorities except if the Principal Investigator according to his/her best medical judgment considers these events as endpoint-related SARs. In that case, the Principal Investigator or delegate sub-Investigators must report the endpoint-related SAR within 24 hours after the awareness of any THL study personnel to the Sponsor's GPV Department, the CRA, and the CTL using an SAE eCRF in the EDC system. The Sponsor will inform the relevant health authorities of the endpoint-related SAR according to local regulatory requirements.

In addition, the Sponsor will provide summaries of endpoint-related SAR on a quarterly basis to the relevant health authorities.

11 Data Collection and Management

11.1 Data Collection

At enrollment, the data related to Visit 1 will be collected by qualified HS nurses and documented in the ICF (refer to Section 5.2.2). The original ICFs will be sent to the THL on a regular basis (ie, preferably weekly and at least every month) for data entry.

The suspected SARs, fatal SAEs, and AESIs will be individually collected electronically by the Principal Investigator or authorized designee using the SAE eCRF in the EDC system. This form has been designed specifically for this study under the responsibility of the Sponsor, using a validated Electronic Records / Electronic Signature-compliant platform (21 CFR Part 11).

To ensure the correct and consistent completion of the SAE eCRF, the Sponsor or authorized representative will provide all necessary tools, instructions, and training to the Principal Investigator and designated THL staff involved in data entry prior to study start. Additional instructional documents such as training manuals and completion instructions will be provided to assist with data entry during the course of the study.

Upon completion of training, each user requiring access to the EDC system will be issued a unique username and password. In the event of a change in study personnel, each newly assigned individual will receive a unique username and password; the username and password of a previous user may not be reissued. If any study personnel leave the study, the Principal Investigator is responsible for informing the Sponsor immediately so that their access is deactivated. An audit trail will be initiated in the EDC system at the time of the first data entry to track all modifications and ensure database integrity.

The Principal Investigator or delegate sub-Investigator is responsible for the timeliness, completeness, and accuracy of the information in the SAE eCRF; must provide explanations for all missing information; and must sign the form using an e-signature.

In addition to the safety data collected, data in the national health registers will be collected at THL through linkage of registers using the Finnish PIC.

These data will include prospective and retrospective data for the subjects, but may also include collection of aggregated data from individuals not enrolled in the study to be used in the study safety evaluation as baseline data for signal detection regarding non-fatal SAEs.

Table 11.1 describes the different Finnish health registers that will be used to collect data for this study.

Table 11.1: List and description of the Finnish health registers

Digital and Population Data Services Agency (DVV), previously Population Register Centre	The Finnish Population Information System, maintained by the Digital and Population Data Services Agency (DVV), is a computerized national register that contains exact enumeration and basic information about Finnish citizens and foreign citizens residing permanently in Finland (44). Data will be used for retrieving the address of the study source population to send invitation letters by mail. Additionally, data from population information system will be used for the follow-up of the vital status with minimal delays. Demographic data can be collected through DVV.
National Care Registers (HILMO and AVOHILMO)	**The Care Register for Health Care (HILMO),** a hospital discharge register maintained by THL (previously known as STAKES) since 1994, will be used for identification of hospital visits, inpatient hospitalizations, and the occurrence of complications and resource use (45). The HILMO contains all outpatient and inpatient diagnoses (ICD-10) for patients who received care at the Finnish hospitals. The discharge notifications include the personal identification data (including PIC), site of treatment, medical specialty code, admission and discharge dates, ICD-10 codes, type of admission (emergency/schedule/transfer). The data are collected locally on an ongoing basis, but transfers to the national register are in batches. The process of data collection may be expedited with monthly or even more frequent data collection. The data for this study will be collected monthly.
	The Register of Primary Health Care Visits (AVOHILMO) contains data on outpatient primary health care visits in public health care centers (46). The data collection includes all public outpatient primary health care delivered in Finland since 2011. Private outpatient clinics are not covered at the moment. The data dispatch from the health care centers is scheduled to occur every night. The national vaccination register is part of the Avohilmo register. Data on all vaccinations administered at the public HCC/HS are sent overnight to THL.
Social welfare **(THL Care register for Social Welfare)**	THL Care register for Social Welfare contains data on nursing home admissions, supported accommodation services, and home care customer status annually on 30 November. These data cannot be obtained in the study database as directly identifiable linked individual-based data, but aggregate data only. The data linkage will be performed centrally at the THL Department of Information Services. The feasibility of social welfare data to be used in the study will be explored.

National Infectious Disease Register (NIDR)	Data from the National Infectious Disease Register (NIDR), maintained by KTL/THL since 1995 can be used for identifying laboratory-confirmed influenza cases. There has been a recent increase in the number of reported influenza cases due to increased testing (access, media attention) and reporting. Additionally, NIDR can be used for identification of secondary infections, like laboratory-confirmed invasive bacterial disease (Escherichia coli, Staphylococcus aureus and Klebsiella species being the most common findings). The NIDR is a population-based and laboratory-based surveillance system (47) (48). All Finnish clinical microbiology laboratories are required to notify detections of influenza (either by culture, serology, antigen detection, or polymerase chain reaction [PCR]). Each notification includes the date and type of specimen, microbe detection method, date of birth, sex, and place of sample obtaining. Duplicate reports of cases within 3 months are merged into episodes at THL. Cases are generally recorded into the NIDR database within 2 weeks of the date of sample collection. The PIC is available for linkage of the cases in the NIDR since 2004. There is also sentinel surveillance for influenza in selected outpatient clinics and in the hospital intensive care units. Respiratory tract samples are requested to be sent to THL based on a specified sampling frame. These are analyzed by real-time PCR which detects various influenza subtypes and lineages. Additional analyses may include sensitivity to antiviral drugs and genetic and antigenic changes.
Statistics Finland	The cause of death register is controlled by the Statistics Finland (49).
Social Insurance Institution registers (KELA)	The Social Insurance Institution (KELA) benefits register may be used for evaluation of baseline comorbidity, resource use related to complications of influenza and to the use of medications as explorative endpoints (50). KELA register has been operational since 1964 with multiple changes and adaptations to current Finnish laws. Expanding data has been collected on national insurance reimbursements including drug prescriptions since 1995. Currently, the register includes data on reimbursable medications only, and therefore, the register may not be complete for all prescribed medications. Delay for data collection purposes is minimum 4 months. Special reimbursement decision can be used for identification of chronic diseases like diabetes, heart disease, lung disease, etc. KELA collects also data on disability benefits and services that might be relevant for long-term cost evaluation. Changes in the *Care allowance for pensioners* will be collected (before and after the influenza season). The Prescription Centre of the Social Insurance Institution (KELA) has the e-prescription data since its introduction in 2010. The data collection has been nationwide since 2017.

11.2 Data Management

Management of SAE Data

During the study, the SARs, all fatal SAEs, and all AESIs reported by THL will be integrated into the Sponsor's centralized GPV database upon receipt of the SAE eCRFs. Each case will be assigned a case identification number. Each case will be assessed by the case management platform or its delegate before being reported to the relevant authorities as necessary. The assessment of related cases will be done in collaboration with the Global Safety Officer and the RMO. Follow-up information concerning a completed case will be entered into the GPV database, and a new version of the case will be created.

Management of Clinical Data

Copies of analysis datasets, including registry data, will be transferred from THL to Sanofi Pasteur without the Finnish PICs via a secure service ensuring the traceability and confidentiality of all exchanged data.

12 Statistical Methods and Determination of Sample Size

The statistical analyses for the study report or the observational objectives will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® and/or R.

There is no formal lock of the data. For the primary and secondary objectives, the database will be extracted at one time point and will be considered as final data for conducting the statistical analysis. At this stage, the study will be unblinded. For the SAEs, the data will be captured in the GPV database and extracted from the SAE eCRF or the health registers to the database for statistical analysis. For some of the observational objectives, the export(s) and analyses will be conducted at a later date.

The data which will be analyzed will be further described in the SAP and available before the final transfer of the data for the primary and secondary objectives from THL.

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

For descriptive purposes, the following statistics will be presented:

Table 12.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
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).

12.1 Statistical Methods

12.1.1 Hypotheses and Statistical Methods for Primary Objective

12.1.1.1 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:

$H_0: rVE \leq 0\%$

$H_1: rVE > 0\%$

12.1.1.2 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. More information on the endpoint derivation will be given in the SAP.

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%.

12.1.2 Hypotheses and Statistical Methods for Secondary and Observational Objectives

12.1.2.1 Hypotheses

No hypotheses will be tested.

12.1.2.2 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.

Several analyses will be displayed per factors such as season, delay since vaccination, site localization, age (in class or continuous variable), sex, or specific comorbidities.

Kaplan-Meier 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 or date of death or lost to follow-up (expected to be rare).

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.

12.2 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.

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

12.3 Handling of Missing Data and Outliers

12.3.1 Effectiveness

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

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

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

12.3.2 Safety

No replacement will be done. If necessary, details will be described in the SAP.

12.4 Interim / Preliminary Analysis

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

For some of the exploratory objectives (to be defined in the SAP), the export(s) and analyses will be conducted at a later date (ie, after the unblinding of the data).

12.5 Determination of Sample Size and Power Calculation

The sample size needed for the assessment of the primary objective of the study is 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 (16) (25) (51) (52)
- 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 are anticipated to be collected 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 12.2.

Table 12.2: Different rVE assumptions and associated study power

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

13 Ethical and Legal Issues and Investigator / Sponsor Responsibilities

13.1 Ethical Conduct of the Study / Good Clinical Practice

The conduct of this study will be consistent with the standards established by the Declaration of Helsinki and compliant with the ICH guidelines for GCP as well as with all local and / or national regulations and directives.

13.2 Source Data and Source Documents

“Source data” are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, medical and hospital records, and informed consent forms. The purpose of study source documents is to document the existence of subjects and to substantiate the integrity of the study data collected. Investigators must maintain source documents so that they are accurate, complete, legible, and up to date.

The source data for the subjects in this study will be the ICF, the SAR/AESI paper form, the SAE eCRF (which will also include the assessment of causality), and the Finnish health registers described in Table 11.1.

The pre-selection subject list will include all individuals contacted by the Principal Investigator (via the invitation letter or other forms of communication) to participate in the study, regardless of the outcome.

Good Documentation Practices should be followed by the Principal Investigator and the site staff managing source documents for all the records generated for this study.

13.3 Confidentiality of Data, Data Protection, and Access to Subject Records

Prior to initiation of the study, the Principal Investigator will sign a fully executed confidentiality agreement with Sanofi Pasteur. In the event a subject's medical records are not at the HS/HCC, it is the responsibility of the Principal Investigator to obtain those records if needed.

All personal data collected related to subjects, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the General Data Protection Regulation. Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Subjects will be assigned a unique identifier by THL. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assessment (CQA) auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

When archiving or processing personal data pertaining to the Investigator and/or to the subjects, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4 Monitoring, Auditing, and Archiving

13.4.1 Monitoring

The clinical study will be conducted according to Good Clinical Practices with a risk based monitoring strategy (ie, on site monitoring at THL and the HCC/HS will be performed on a random sample of documents such as ICFs, Investigational products documentation, SAR/AESI paper form, SAE eCRF, and health registers).

Before the start of the study (ie, before the inclusion of the first subject), the Principal Investigator and the Sponsor's staff or a representative will meet at the site-initiation visit to discuss the study protocol and the detailed study procedures. Emphasis will be placed on inclusion and exclusion criteria, informed consent procedures, SAE reporting procedures, and the handling of products.

The Sponsor's staff or a representative will ensure and document that all material to be used during the study has been received at the THL/HS; and that the study investigator team and local Sponsor/delegate staff have been properly informed about the study, GCP and regulatory requirements, and the study procedures. Specific training sessions for the study investigator team and the CRAs on these topics may be performed as necessary, and should be documented.

The following instruction manuals will be provided: the Completion Instructions for entering data into the SAE eCRF will be provided by the Sponsor; the Coordinating Instructions for initiation and follow-up of the study activities at the HS and the Working Instructions for guiding the HS activities will be provided by THL.

After the start of the study, the Principal Investigator and designated THL study staff will provide oversight (including training and site visits) and follow-up of the HS activities. The Sponsor's staff or a representative will be in regular contact with THL through telephone calls and regular follow-up visits. The Principal Investigator or delegate must be available for these visits, and must allow the Sponsor/delegate staff direct access to subject study documents.

During these visits, the Sponsor/delegate staff will:

- Evaluate the quality of the study progress by performing a sample check on selected documents and activities including but not limited to: recruitment materials used, training documentation, delegation of responsibilities, ongoing filing of documents, adherence to protocol and any study-specific guidelines such as ICF signature, quality of data collection, and document completion, signature of consent forms, product management, cold-chain monitoring, and verification of proper oversight of THL on the HS and THL quality system maintenance.
- Source-verify completed SAE eCRF and any corresponding answered queries.
- Determine the number of complete or ongoing issues identified at monitoring visits (eg, protocol deviations, SAEs). Any identified problems will be discussed with the Principal Investigator, and corrective or preventive actions will be determined, as appropriate.
- After all protocol procedures have been completed, the Principal Investigator must still be available to answer any queries forwarded by the Sponsor. All data-related queries must be completed prior to database lock.

At the end of the study, close-out activities will be performed by both the Sponsor and the Principal Investigator. The Principal Investigator will perform the close-out activities required for the HS/HCCs. The Sponsor will perform the close-out activities with THL to ensure that:

- THL has all the documents necessary for archiving
- All unused materials and products have been either destroyed or returned to the Sponsor

13.4.2 Audits and Inspections

A quality assurance audit may be performed at any time by the Sponsor's CQA department or by independent auditors to verify that the study has been conducted according to the protocol, GCP and ICH requirements, and other applicable regulations. An inspection may be conducted by regulatory authorities. THL must allow access to study documents and health registers during these inspections and audits.

13.4.3 Archiving

THL shall retain and preserve 1 copy of the study file containing the essential documents related to the study and records generated during the study ("Study File") for the longer of the 2 following periods ("Retention Period"):

- 25 years after the signature of the final study report or
- such longer period as required by applicable regulatory requirements

If during the Retention Period, THL is no longer able to retain the Study File due to exceptional circumstances (such as bankruptcy), THL shall contact the Sponsor to organize the transfer of the Study File to the Sponsor's designee at the Sponsor's expense. Following the Retention Period, THL is responsible to dispose of the Study File according to the applicable regulations. Patient medical records shall be retained in compliance with local regulations.

Archived data may be held on electronic records, provided that a back-up exists and that a hard copy can be obtained if required. The protocol, documentation, approvals, and other documents related to the study will be kept by the Sponsor in the Trial Master File (TMF). Data on SAEs are included in the TMF. All data and documents will be made available if requested by relevant authorities.

13.5 Financial Contract and Insurance Coverage

A Clinical Trial Agreement will be signed by THL and Sanofi Pasteur involved in the study's performance. The Sponsor has an insurance policy to cover any liabilities that may arise from use of the product and / or the study protocol.

13.6 Stipends for Participation

There is no compensation for study participation. However, the study visit and the administered study vaccine are free of charge.

13.7 Publication Policy

Any publication or presentation related to the study initiated by either THL or Sanofi Pasteur must be submitted to the other party for review before submission of the manuscript. Sanofi Pasteur and THL shall be offered an association with all publications, it being understood that Sanofi Pasteur or THL are entitled to refuse the association.

Each Party agrees to provide the other party with a copy of any abstract, presentation, or manuscript related to the Study prior to submission for publication with sufficient time (abstracts: thirty (30) calendar days; presentation: thirty (30) calendar days; manuscripts: forty five (45) calendar days) for review and comment, and to remove any THL or Sanofi pasteur confidential information, it being understood that the results of this study are not to be considered confidential.

Sanofi Pasteur's review can be expedited to meet publication guidelines.

14 Reference List

1 World Health Organization. Influenza (seasonal). Fact sheet. [homepage on the internet]. 30 March 2018. [cited on 25 October 2018]. Available from: http://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal).

2 Talbot HK. Influenza in older adults. Infect Dis Clin N Am. 2017;31(4):757-66.

3 Gross PA, Hermogenes AW, Sacks HS, et al. The efficacy of influenza vaccine in elderly persons. Ann Intern Med 1995;123:518-27.

4 Demicheli V, Di Pietrantonj C, Jefferson T, Rivetti A, Rivetti D. Vaccines for preventing influenza in healthy adults. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD001269.

5 European Centre for Disease Control and Prevention. Risk groups for severe influenza. Available at: https://ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/risk-groups.

6 European Centre for Disease Control and Prevention. Types of seasonal influenza vaccine. Available at: https://ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/risk-groups.

7 Dormitzer PR, Galli G, Castellino F, Golding H, Khurana S, Del Giudice G, et al. Influenza vaccine immunology. Immunological Reviews 2011;239:167-77.

8 Marcelin G, Sandbulte MR, Webby RJ. Contribution of antibody production against neuraminidase to the protection afforded by influenza vaccines. Rev Med Virol. 2012;22(4): 267-79.

9 Wohlbold TJ, Krammer F. In the shadow of hemagglutinin: a growing interest in influenza viral neuraminidase and its role as a vaccine antigen. Viruses. 2014;6:2465-94.

10 Monto AS, Petrie JG, Cross RT, Johnson E, Liu M, Zhong W, et al. Antibody to influenza virus neuraminidase: an independent correlate of protection. The Journal of Infectious Diseases 2015;212:1191-9.

11 European Centre for Disease Prevention and Control. Influenza vaccine effectiveness. Available from: https://ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccine-effectiveness.

12 Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine. 2006;24(8):1159-69.

13 Rivetti D, Jefferson T, Thomas R, et al. Vaccines for preventing influenza in the elderly. Cochrane Database Syst Rev. 2006;3:CD004876. Review.

14 European Centre for Disease Prevention and Control. Available from: https://ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/vaccination-coverage.

15 Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis. 2009;200(2):172-80.

16 DiazGranados CA, Dunning AJ, Kimmel M, Kirby D, Treanor J, Collins A, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med. 2014;371(7):635-45.

17 Gravenstein S, Davidson HE, Han LF, Ogarek JA, Dahal R, Gozalo PL, et al. Feasibility of a cluster-randomized influenza vaccination trial in U.S. nursing homes: Lessons learned. Hum Vaccin Immunother. 2018;14:1-736-43.

18 Gravenstein S, Davidson HE, Taljaard M, Ogarek J, Gozalo P, Han L, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. Lancet Respir Med. 2017;5(9):738-46.

19 Izurieta, Thadani N, Shay DK, Lu Y, Maurer A, Foppa IM, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis. 2015;15(3):293-300.

20 Shay DK, Chillarige Y, Kelman J, Forshee RA, Foppa IM, Wernecke M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US Medicare beneficiaries in preventing post influenza deaths during 2012-2013 and 2013-2014. JID 2017;215:510-7.

21 Richardson DM, Medvedeva EL, Roberts CB, Linkin DR. Comparative effectiveness of high-dose versus standard-dose influenza vaccination in community-dwelling veterans. Clin Infect Dis. 2015;61(2):171-6.

22 Young-Xu Y, van Aalst R, Mahmud SM, Rothman KJ, Snider JT, Westreich D,et al. Relative vaccine effectiveness of high-dose versus standard-dose influenza vaccines among veterans health administration patients. J Infect Dis. 2018;217(11):1718-27.

23 Robison SG, Thomas AR. Assessing the effectiveness of high-dose influenza vaccine in preventing hospitalization among seniors, and observations on the limitations of effectiveness study design. Vaccine. 2018;36(45):6683-7.

24 Izurieta HS, Chillarige Y, Kelman J, Wei Y, Lu Y, Xu W, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among the U.S. elderly, 2017-18. J Infect Dis. Dec 2018; doi: 10.1093/infdis/jiy716. [Epub ahead of print]. [cited 18 Jan 2019]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30561688.

25 Young-Xu Y, Snider JT, Van Aalst R, Mahmud SM, Thommes EW, Lee JKH. Analysis of relative effectiveness of high-dose versus standard-dose influenza vaccines using an instrumental variable method. Vaccine. 2019;37(11):1484-90.

26 DiazGranados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine. 2015;33(38):4988-93.

27 Fluzone High-Dose prescribing information. Swiftwater, Pennsylvania, USA, Sanofi Pasteur Inc. June 2018.

28 Warren-Gash C, Bhaskaran K, Hayward A, Leung GM, Lo SV, Wong CM, et al. Circulating influenza virus, climatic factors, and acute myocardial infarction: a time series study in England and Wales and Hong Kong. J Infect Dis. 2011;203(12):1710-8.

29 Kwong JC, Schwartz KL, Campitelli MA, Chung H, Crowcroft NS, Karnauchow T, et al. Acute Myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med. 2018;378(4):345-53.

30 Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. 2004;351(25):2611-8.

31 Blackburn R, Zhao H, Pebody R, Hayward A, Warren-Gash C. Laboratory-Confirmed Respiratory Infections as Predictors of Hospital Admission for Myocardial Infarction and Stroke: Time-Series Analysis of English Data for 2004-2015. Clin Infect Dis. 2018;67(1):8-17.

32 Warren-Gash C, Blackburn R, Whitaker H, McMenamin J, Hayward AC. Laboratory-confirmed respiratory infections as triggers for acute myocardial infarction and stroke: a self-controlled case series analysis of national linked datasets from Scotland. Eur Respir J. 2018;51(3).

33 Boehme AK, Luna J, Kulick ER, Kamel H, Elkind MSV. Influenza?like illness as a trigger for ischemic stroke. Ann Clin Transl Neurol. 2018;5(4):456-63.

34 Kytömaa S, Hedge S, Claggett B, Udell JA, Rosamond W, Temte J, et al. Association of influenza-like illness activity with hospitalizations for heart failure: The Atherosclerosis Risk in Communities Study. JAMA Cardiol. 2019;doi: 10.1001/jamacardio.2019.0549. [Epub ahead of print].

35 Gurfinkel EP, de la Fuente RL, Mendiz O, Mautner B. Influenza vaccine pilot study in acute coronary syndromes and planned percutaneous coronary interventions: the FLU Vaccination Acute Coronary Syndromes (FLUVACS) Study. Circulation. 2002;105(18):2143-7.

36 Gurfinkel EP, de la Fuente RL, Mendiz O, Mautner B. Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions (FLUVACS) Study: One-year follow-up. Eur Heart J. 2004;25(1):25-31.

37 Ciszewski A, Bilinska ZT, Brydak LB, Kepka C, Kruk M, Romanowska M, et al. Influenza vaccination in secondary prevention from coronary ischaemic events in coronary artery disease: FLUCAD study. Eur Heart J. 2008. 29(11):1350-8.

38 Phrommintikul A, Kuanprasert S, Wongcharoen W, Kanjanavanit R, Chairwarith R, Sukonthasam A. Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome. Eur Heart J. 2011;32(14):1730-5.

39 Modin D, Jorgensen ME, Gislason G, Jensen JS, Kober L, Clagget B, et al. Influenza Vaccine in Heart Failure: Cumulative Number of Vaccinations, Frequency, Timing, and Survival: A Danish Nationwide Cohort Study. Circulation. 2018;139:00-00.

40 Lam F, Chen TL, Shih CC, Lin CS, Yeh CC, Lee YJ, et al. Protective effect of influenza vaccination on outcomes in geriatric stroke patients: A nationwide matched cohort study. Atherosclerosis. 2019;282:85-90.

41 Macintyre CR, Heywood AE, Kovoor P, Ridda I, Seale H, tan T, et al. Ischaemic heart disease, influenza and influenza vaccination: a prospective case control study. 2013;99(24):1843-8.

42 Sejvar JJ, Kohl KS, Gidudu J, Amato A, Bakshi N, Baxter R, et al; and Brighton Collaboration GBS Working Group. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612.

43 Sejvar JJ, Kohl KS, Bilynsky R, Blumberg D, Cvetkovich T, Galama J, et al; and Brighton Collaboration Encephalitis Working Group. Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2007;25(31):5771-92.

44 Digital and Population Data Services Agency. Available from: https://dvv.fi/en/about-the-agency.

45 The Care Register for Health Care (HILMO). Available from: https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/care-register-for-health-care.

46 The Register of Primary Health Care Visits (AVOHILMO). Available from: https://thl.fi/en/web/thlfi-en/statistics/information-on-statistics/register-descriptions/register-of-primary-health-care-visits.

47 The National Infectious Disease Register. Available from: https://thl.fi/en/web/infectious-diseases/surveillance/infectious-disease-register.

48 The National Infectious Disease Register. Available from: https://thl.fi/en/web/infectious-diseases/surveillance/influenza-surveillance.

49 Statistics Finland. Available from: http://www.stat.fi/index_en.html.

50 Social Insurance Institution (KELA). Available from: https://www.kela.fi/web/en.

51 Gravenstein S, Davidson HE, Mcconeghy K, Han L, Canaday D, Saade E, et al. cluster-randomized trial of adjuvanted trivalent influenza vaccine vs. standard dose in U.S. nursing homes. Poster abstract session. ID Week 2018 San Francisco CA, October 3-7.

52 Lee JKH, Lam GKL, Shin T, Kim J, Krishnan A, Greenberg DP, et al. Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: A systematic review and meta-analysis. Exp Rev Vaccines. 2018;17(5):435-43.

15 Signature Page

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