Sponsor: Sanofi **Drug substance:** Quadrivalent Influenza Vaccine (split virion, inactivated) High Dose (QIV-HD)	**Study Identifiers:** U1111-1217-2654; NCT04137887; EudraCT number: 2019-001401-25 **Study code:** QHD00012
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	
Study center: This study was conducted by 1 center (THL) in collaboration with multiple health stations overseen by public health care centers that enrolled subjects in Finland.	
Study period: 04 November 2019 to 31 August 2020 (first subject first visit to last subject last visit) Study Status: Terminated. Enrolment and data collection were disrupted during the 2020-2021 and 2021-2022 influenza seasons due to worldwide COVID-19 social mitigation efforts and other significant challenges to study conduct including low incidence rates for influenza coupled with high rates of COVID-19 (which impacted data collection and endpoints).	
Phase of development: Phase IIIb/IV	

Objectives:

Primary:

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.

Secondary:

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 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.

Methodology: Study QHD00012 was a pragmatic, Phase IIIb/IV, randomized, modified double-blind, active-controlled, registry-based study conducted by the Finnish Institute for Health and Welfare (THL) in approximately 121 000 subjects 65 years of age and older in Finland. Enrolment was planned to take place over multiple influenza seasons beginning in 2019-2020 and subjects were to be randomized (1:1) to receive QIV-HD or QIV-SD (Vaxigrip Tetra®)
Number of participants: Planned: 121000 Randomized and vaccinated: 33093
Diagnosis and criteria for inclusion: The study was conducted in adults 65 years of age and older.
Study products: Both the QIV-HD investigational product and the QIV-SD control product were injected via intramuscular (IM) route in the upper arm (deltoid area). ***Investigational Product:*** Quadrivalent Influenza Vaccine, (Split Virion, inactivated) High-Dose (QIV-HD) Northern Hemisphere [NH] 2019-2020 strains, provided in a pre-filled 0.7 mL single dose syringe ***Control Product:*** Standard-Dose Inactivated influenza Vaccine Quadrivalent, (QIV-SD) 2019 2020 NH strains, provided in a pre-filled 0.5 mL single-dose syringe (Vaxigrip Tetra manufactured by Sanofi)
Duration of intervention: The duration of each subject's participation was approximately 10 months. The follow-up period in this study was defined as the data collection period. The data collection period varied based on the study objectives with the data collection period extending up to one year.

Criteria for evaluation:

Primary:

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*:
  - Diseases of the circulatory system:
  - Hypertensive diseases, based on code I11
  - 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 code I74
  - 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 and J86

Secondary:

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 †

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

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 serious adverse reactions (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.

* For the primary and secondary endpoints, ICD-10 codes I16, I75 and I76 were not considered as they are not referenced in ICD-10 Finland and/or in ICD-10 WHO version 2019.

† This secondary endpoint was not done as per the Protocol because some details (eg, death status) were not available in the Finnish Care Register for Health Care (HILMO) and Register of Primary Health Care Visits (AVOHILMO) registries. Therefore, the analysis was adapted with ICD-10 codes linked to MACE.

‡ This secondary endpoint was not done as per the Protocol since there was no significant influenza circulation during the study conduct.

Statistical methods:

There was no formal lock of the data. For the primary and secondary objectives, the database was extracted at one time point and was considered as final data for conducting the statistical analysis. At this stage, the study was unblinded.

Primary Objective Analysis

Relative Vaccine Effectiveness:

The rVE of QIV-HD to QIV-SD was 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 were 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 was considered demonstrated if the lower bound of the CI for the rVE was > 0%.

Secondary Objectives Analysis

Relative Vaccine Effectiveness:

Similar analyses as the primary objective were conducted and were described using 95% CIs.

Safety

Safety endpoints were summarized per vaccine group, with 95% CI for the main endpoints. CIs were calculated using Clopper-Pearson method.

Summary Results:

QHD00012 was a pragmatic randomized controlled study in Finland using real-world registry-based data, which was planned to cover 3 seasons beginning in 2019-2020. The primary objective was to assess the rVE of QIV-HD vs QIV-SD in prevention of cardiovascular and/or respiratory hospitalizations in subjects 65 years of age and older.

Enrollment and data collection were disrupted during the 2020-2021 and 2021-2022 influenza seasons due to worldwide coronavirus disease 2019 (COVID-19) social mitigation efforts and other significant challenges to study conduct including low incidence rates for influenza coupled with high rates of COVID-19 (which impacted data collection and endpoints). Thus, the study was terminated prematurely on 01 April 2022 after only one influenza season (2019-2020).

Data collected up to 31 August 2020 were analyzed but the study was statistically inconclusive on the primary endpoint due to:

- SARS-CoV-2 circulation as a competing trigger for the outcomes measured
- Public health measures to control SARS-CoV-2 circulation and subsequent low influenza virus circulation, resulting in low frequency of outcome events linked to influenza
- Small sample size for one season only and limited cardiovascular and/or respiratory hospitalizations collected during the low 2019-2020 influenza season, which impacted the study power and led to large confidence intervals

Demographic and Other Baseline Characteristics:

A total of 33 093 subjects were randomized and vaccinated between 04 November 2019 and 23 December 2019 in the study. Among these subjects, 16 549 subjects were randomized to the QIV-HD group and 16 544 subjects to the QIV-SD group.

Overall, the demographic and baseline characteristics were similar between the QIV-HD and QIV-SD groups and between the age groups.

The subjects included 16 514 females (49.9%) and 16 579 males (50.1%). The QIV-HD group included 8273 females (49.9%) and 8276 males (50.0%), and the QIV-SD group included 8241 females (49.8%) and 8303 males (50.1%). The mean age was 72.6 years (± 5.7) in the QIV-HD group and 72.5 years (± 5.6) in the QIV-SD group.

The proportion of subjects with a comorbidity was slightly higher in the QIV-HD group vs the QIV-SD group. A total of 11 471 (34.66%) subjects reported at least one comorbidity: 5811 (35.11%) subjects in the QIV-HD group and 5660 (34.21%) subjects in the QIV-SD group.

The majority of subjects were in the basic rate baseline care allowance. There were 311 (1.8%) subjects in the QIV-HD group and 305 (1.8%) subjects in the QIV-SD group.

The proportion of subjects with a previous influenza vaccination was similar among the different vaccine groups. A total of 25 303 subjects (76.46%) reported a previous influenza vaccination in the 2018-2019 season up to the study: 12 675 (76.59%) subjects in the QIV-HD group and 12 628 (76.33%) subjects in the QIV-SD group.

Effectiveness Results:

A total of 529 cases (QIV-HD, N=257; QIV-SD, N=272) of respiratory and/or cardiovascular hospitalizations were recorded among the 33 093 subjects. QIV-HD was associated with lower rates of hospitalization than QIV-SD, with an rVE of 5.54% (95% CI: 12.43; 20.66) for prevention of respiratory and circulatory events. Data from over 30 000 subjects during the 2019 2020 season show point estimates are consistent and support a clinical benefit of QIV HD over QIV-SD. There was a statistical trend (CI > 0) for ischaemic heart diseases, with an rVE of 32.37% (95% CI: 0.24; 54.52). It should be noted that the level of SARS CoV 2 circulation was unknown in the early weeks of 2020, as formal assessment only began from week 10 onwards. As SARS-CoV-2 and influenza viruses are transmitted through similar mechanisms and both COVID-19 and influenza disease can present with overlapping clinical features, the outcomes studied could have been triggered by COVID 19 cases and not only influenza, thus potentially diluting the number of cases related to influenza.

Safety Results: The frequencies of SARs considered to be related to the vaccine were low (< 0.01%) in both vaccine groups. Cardiac disorders-related mortalities were more prevalent in subjects receiving QIV-HD than QIV-SD (0.14% vs 0.09%). This may be explained by a trend for higher frequency of pre-existing cardiac comorbidities in the QIV-HD group. No safety concern was observed based on the safety data collected during the study.
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