Efficacy, Immunogenicity, and Safety of High-Dose Quadrivalent Influenza Vaccine Compared with Standard-Dose Quadrivalent Influenza Vaccine in Children 6 Months through 35 Months of Age

Phase III, randomized, modified double-blind, active-controlled, multi-center study in children 6 months through 35 months of age in Northern and Southern Hemisphere countries

Statistical Analysis Plan (SAP) - Core Body Part

Study Code:	QHD00014
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product(s):	Quadrivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose (QIV-HD)
Form / Route:	Suspension for injection in pre-filled syringe / Intramuscular (IM)
Indication For This Study:	Active immunization for prevention of influenza in children 6 months through 35 months of age
Version and Date of the SAP core body part:	Version 2.0, 29MAY2020

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List of Abbreviations

AE	adverse event
AESI	adverse event of special interest
ALRI	acute lower respiratory infection
AOM	acute otitis media
CBER	Center for Biologics Evaluation and Research
CDC	Center for Disease Control and Prevention
CI	confidence interval
CRB	case report book
CSR	clinical study report
D	day
dil	dilution
EDC	electronic data capture
ELLA	enzyme-linked lectin assay
ESafAS	Expanded Safety Analysis Set
ESDR	early safety data review
FASE	Full Analysis Set for Efficacy
FASI	Full Analysis Set for Immunogenicity
GBS	Guillain-Barré syndrome
GM	geometric mean
GMT	geometric mean titer
GMTR	geometric mean titer ratio
GSK	Glaxo Smith Kline
HA	hemagglutinin
HAI	hemagglutination inhibition
IAS	Immunogenicity Analysis Set
IDMC	Independent Data Monitoring Committee
ILI	influenza-like illness
IRT	interactive response technology
LLOQ	lower limit of quantification
MD	missing data
NA	neuraminidase
NH	Northern Hemisphere
NP	nasopharyngeal
PPASE	Per-Protocol Analysis Set for Efficacy

PPASI	Per-Protocol Analysis Set for Immunogenicity
PCR	polymerase chain reaction
PT	preferred term
Q1; Q3	first quartile; third quartile
QIV-HD	high-dose quadrivalent influenza vaccine
QIV-SD	standard-dose quadrivalent influenza vaccine
RCDC	reverse cumulative distribution curve
rVE	relative vaccine efficacy
SAE	serious adverse event
SafAS	Safety Analysis Set
SAP	statistical analysis plan
SD	standard deviation
SH	South Hemisphere
SN	seroneutralization
SOC	system organ class (primary)
TIV-HD	high-dose trivalent influenza vaccine
ULOQ	upper limit of quantification
V	visit
WHO	World Health Organization

1 Introduction

Influenza is a contagious, acute viral respiratory disease caused by influenza type A and type B viruses. The virus is transmitted easily from person to person via droplets and small particles produced when infected people cough or sneeze. Members of high-risk groups, such as infants and younger children as well as children with underlying medical conditions, are at increased risk of influenza and its complications. Complications in the pediatric population include secondary bacterial pneumonia, acute otitis media, bronchitis, febrile seizures, Reye's syndrome, myositis, neurologic conditions, and exacerbations of underlying conditions (1) (2) (3).

Vaccination currently represents the most effective medical intervention against influenza and its severe complications. Thus, the World Health Organization (WHO) recommends that people who are most at-risk for severe seasonal influenza, including children less than 5 years of age (4) (5), should receive an annual vaccination against influenza because it has been shown to be effective in reducing influenza-associated morbidity and mortality (6) (7).

To overcome the problem of B strain selection and further improve protection against the 2 seasonal influenza B virus strains recommended each influenza season, Sanofi Pasteur has developed a high-dose quadrivalent influenza vaccine (QIV-HD) containing 1 Victoria lineage B strain and 1 Yamagata lineage B strain in addition to the 2 influenza A strains. QIV-HD is produced using the same drug substance process as the licensed high-dose trivalent influenza vaccine (TIV-HD); for the drug product, the licensed TIV-HD manufacturing process was modified slightly to increase the fill volume in order to include the 2nd influenza B strain at the same hemagglutinin (HA) content as the other 3 strains (60 µg HA/strain/dose).

A Phase III immunogenicity bridging study (QHD00013) was conducted in adults 65 years of age and older during the 2017-2018 influenza season and demonstrated the non-inferiority of the hemagglutination inhibition (HAI) antibody responses between QIV-HD and TIV-HD (8). Furthermore, QHD00013 demonstrated that the addition of a 2nd B strain to TIV-HD did not interfere with the immune response to the other vaccine components or adversely affect the safety profile of the vaccine; in order to demonstrate the added value of the 2nd B strain in QIV-HD, superiority of antibody responses to each B strain in QIV-HD compared with the TIV-HD that does not contain the corresponding B strain was also demonstrated. Based on the comparability of responses to the TIV and QIV formulations, QIV-HD is expected to be more efficacious than standard dose influenza vaccines in preventing influenza disease in adults 65 years of age and older.

In November 2019, QIV-HD was licensed in adults 65 years of age and older in the US. In April 2020, QIV-HD also received a positive opinion from the European Union Healthy Authority via Decentralized Procedure with marketing authorizations granted by Norway, France, Latvia, Croatia, Ireland, Denmark, Belgium, the UK, Hungary, Germany, Austria, Spain, and Slovakia as of 19 May 2020. Moreover, QIV-HD has been submitted for licensure in adults 65 years of age and older in Canada (July 2019), Australia (July 2019), South Korea (January 2020), and Switzerland (Mar 2020).

Recognizing a similar need to improve influenza vaccine performance in infants and young children, the impact of increasing the antigen dose on immune responses has recently been evaluated with standard dose vaccines. Several studies have examined the safety and immunogenicity of the pediatric half-dose (0.25mL) versus full-dose (0.5mL) standard dose influenza vaccine (9) (10) (11), and an increase in immunogenicity has been observed, while maintaining safety and tolerability. Thus, QIV-HD, which contains 4 times as much HA per strain per dose as compared to the full-dose (0.5mL) standard dose influenza vaccine, may demonstrate a further increase in immunogenicity which could lead to better protection against influenza and its complications.

In order to assess the safety and immunogenicity of QIV-HD compared with standard-dose quadrivalent influenza vaccine (QIV-SD), a Phase II study in children 6 months through 17 years of age (QHD04) was conducted in the US and Canada during the 2018-2019 influenza season. Three different dose formulations (30 µg, 45 µg, and 60 µg of HA/strain/dose) of QIV-HD were evaluated in this dose exploration study to determine the appropriate QIV-HD dose in children for Phase III studies. Two comparator vaccines were used in the study: a QIV-SD vaccine (Glaxo Smith Kline's [GSK's] Fluarix® Quadrivalent) at US sites and an adjuvanted trivalent influenza vaccine (Seqirus' Fluad®) at Canadian sites. The QHD04 study results showed that of the 3 dose formulations of QIV-HD studied, when compared to QIV-SD, the 60µg HA/strain/dose QIV-HD formulation generated higher immune responses as assessed by HAI geometric mean titer (GMT), seroconversion rates, and seroneutralization (SN) GMT. In all 4 age groups assessed, the highest GMT ratios were seen in children 6 through 35 months of age who received the QIV-HD 60 µg dose formulation versus children who received QIV-SD. No safety issues were observed with QIV-HD administered in children 6 months through 17 years of age. Slightly higher injection site reactogenicity was seen in the QIV-HD group compared with QIV-SD group, but systemic reactogenicity was similar between groups. Similar injection site and systemic reactogenicity profiles were seen between the QIV-HD and adjuvanted TIV groups. Reactogenicity was also similar between all 3 QIV-HD dose formulations (30 µg, 45 µg, and 60 µg of HA/strain/dose) evaluated. In children who received 2 doses of QIV-HD 28 days apart, no trend towards increased reactogenicity was seen between the 1st and 2nd dose administered.

Despite the limitations of the sample size, the safety profile of QIV-HD and the higher immune responses support a pediatric dose selection of 60 µg HA/strain/dose, the same dose indicated for adults 65 years of age and older, as the most appropriate dose to evaluate in a Phase III efficacy study in order to provide the highest probability of success in demonstrating superior protection against influenza when compared with a licensed standard dose influenza vaccine.

Thus, the goal of this Phase III study is to demonstrate the safety, superior efficacy, and superior immunogenicity of QIV-HD compared with a QIV-SD (GSK's Fluarix® Quadrivalent or other tradenames) in children 6 through 35 months of age.

2 Study Objectives

2.1 Primary Objective

Efficacy

To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 35 months of age for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type.

2.2 Secondary Objectives

Confirmatory objectives

- To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 35 months of age for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type using a more stringent threshold
- To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 35 months of age for the prevention of laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine
- To compare the clinical efficacy of QIV-HD to QIV-SD in subjects 6 months through 23 months of age for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type

Other Secondary Objectives are for descriptive assessment

Efficacy

To assess the relative clinical efficacy of QIV-HD compared to QIV-SD in subjects for the prevention of:

- laboratory-confirmed influenza illness caused by any influenza A or B type according to previous influenza vaccination status in prior seasons
- laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine according to previous vaccination status
- laboratory-confirmed influenza illness associated with acute otitis media (AOM) based on clinical diagnosis caused by any influenza A or B type
- laboratory-confirmed influenza illness associated with AOM based on clinical diagnosis caused by viral strains similar to those contained in the vaccine
- laboratory-confirmed influenza illness associated with acute lower respiratory infection (ALRI) based on a clinical and/or x-ray diagnosis caused by any influenza A or B type
- laboratory-confirmed influenza illness associated with ALRI based on a clinical and/or x-ray diagnosis caused by viral strains similar to those contained in the vaccine
- Polymerase chain reaction (PCR)-confirmed influenza illness caused by any influenza A or B type
- PCR-confirmed influenza illness caused by viral strains similar to those contained in the vaccine

- culture-confirmed influenza illness caused by any influenza A or B type
- culture-confirmed influenza illness caused viral strains similar to those contained in the vaccine
- laboratory-confirmed influenza illness associated with hospitalization and caused by any influenza A or B type
- laboratory-confirmed influenza illness associated with hospitalization and caused by viral strains similar to those contained in the vaccine

Immunogenicity

- To compare the HAI immune response of QIV-HD to QIV-SD in subjects 6 months through 35 months of age
- To describe the HAI immune response induced by each vaccine against the 4 vaccine strains and according to the different strain formulations used in each of the study influenza seasons
- To describe the SN immune response induced by QIV-HD or QIV-SD against the 4 QIV-HD vaccine strains in a randomized subset of subjects
- To describe the anti-neuraminidase (NA) immune response induced by QIV-HD or QIV-SD in a randomized subset of subjects

Re-vaccination response

To describe the immune response (HAI method) to vaccination in Season 3 (Northern Hemisphere [NH]) among subjects re-enrolled from Season 1 (NH) to Season 3 (NH), according to the vaccines received in both Season 1 (NH) and Season 3 (NH)

Safety

- To describe the safety profile (injection site reactions and systemic events) of each vaccine during the 28 days following each vaccination for the Expanded Safety Analysis Set (ESafAS) (all subjects from the Sentinel Safety Cohort, all subjects from Season 1, and a subset of subjects from Seasons 2 and 3)
- To describe all serious adverse events (SAEs) (including adverse events of special interest [AESIs]) up to at least 180 days after the last vaccination in all subjects

2.3 Observational Objectives

Efficacy

The following objectives will be assessed for laboratory-confirmed influenza illness due to any influenza A or B type and due to viral strains similar to those contained in the vaccine. To assess the relative clinical efficacy of QIV-HD compared to QIV-SD in subjects 6 months through 35 months of age for the prevention of:

- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination caused by each circulating influenza virus A subtype and B lineage

- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination by age subgroup
- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination by season
- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination in previously unvaccinated subjects after 1st injection
- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination in previously unvaccinated subjects between 1st and 2nd injections
- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination and over the first 3 months after vaccination
- laboratory-confirmed influenza illness starting ≥ 14 days after vaccination according to other influenza-like illness (ILI) definitions (modified Center for Disease Control and Prevention [CDC]-defined ILI)

Influenza-associated events/health care utilization

- To describe in each vaccine group the occurrence of AOM (based on clinical and/or x-ray diagnosis), within 30 days after the onset of a laboratory-confirmed ILI
- To describe in each vaccine group the occurrence of AOM (based on clinical and/or x-ray diagnosis), within 30 days after the onset of any ILI
- To describe in each vaccine group the occurrence of ALRI (based on clinical and/or x-ray diagnosis), within 30 days after the onset of a laboratory-confirmed ILI
- To describe in each vaccine group the occurrence of ALRI (based on clinical and/or x-ray diagnosis), within 30 days after the onset of any ILI
- To describe in each vaccine group the occurrence, duration, and intensity of ILI symptoms occurring within 30 days after the onset of a laboratory-confirmed ILI
- To describe in each vaccine group the occurrence, duration, and intensity of ILI symptoms occurring within 30 days after the onset of ILI
- To describe in each vaccine group the use of antibiotics and antivirals that are associated with cases of laboratory-confirmed ILI, within 30 days after the onset of the ILI
- To describe in each vaccine group the use of antibiotics and antivirals that are associated with any ILI, within 30 days after the onset of the ILI
- To describe in each vaccine group hospitalizations that are associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI
- To describe in each vaccine group hospitalizations that are associated with any ILI, within 30 days after onset of the ILI
- To describe in each vaccine group emergency room visits that are associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI
- To describe in each vaccine group emergency room visits that are associated with any ILI, within 30 days after onset of the ILI
- To describe in each vaccine group non-routine medical office visits (including urgent care visits) that are associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI

- To describe in each vaccine group non-routine medical office visits (including urgent care visits) that are associated with any ILI, within 30 days after onset of the ILI
- To describe in each vaccine group medication use that is associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI
- To describe in each vaccine group medication use that is associated with any ILI, within 30 days after onset of the ILI
- To describe in each vaccine group absenteeism (Parent(s) / guardian's absenteeism due to child sick days) that is associated with cases of laboratory-confirmed ILI, within 30 days after onset of the ILI
- To describe in each vaccine group absenteeism (Parent(s) / guardian's absenteeism due to child sick days) that is associated with any ILI, within 30 days after onset of the ILI

Correlates of protection objective

To assess the association of HAI titers to the 4 vaccine strains with the occurrence of laboratory-confirmed ILI of any influenza A or B type, or of viral strains similar to those contained in the vaccine.

Antibody persistence

To describe the persistence of immune response 1 year after vaccination among subjects from Season 1 (NH) who are re-enrolled for Season 3 (NH) according to the vaccine received in Season 1 (NH).

3 Description of the Overall Study Design and Plan

3.1 Study Design

QHD00014 is planned to be a Phase III, randomized, modified double-blind, active-controlled, multi-center study to be conducted in 13,320 (100 subjects will be in an open-label Sentinel Safety Cohort with no comparator vaccine while 13,220 will be randomized and double-blinded) children 6 months through 35 months of age to evaluate the relative efficacy, immunogenicity, and safety of QIV-HD administered by intramuscular (IM) route versus a QIV-SD vaccine.

QHD00014 is planned to be conducted during the 2020-2021 NH influenza season (Sentinel Safety Cohort), the 2021-2022 NH influenza season (Season 1), the 2021 Southern Hemisphere (SH) influenza season (Season 2), and the 2021-2022 NH influenza season (Season 3). During Seasons 1 through 3, subjects will be randomized in a 1:1 ratio to receive either QIV-HD or QIV-SD prior to the start of the influenza season. Subjects will receive either 1 or 2 doses of study vaccine depending on whether they were previously vaccinated against influenza or previously unvaccinated against influenza, respectively.

During the 2020-2021 NH influenza season, a Sentinel Safety Cohort of 100 US subjects will be enrolled in an uncontrolled, open-label design without a comparator vaccine to evaluate the safety of QIV-HD prior to the enrollment of additional subjects. These subjects will not provide blood samples and will not be followed for ILI surveillance. Following the enrollment of the Sentinel Safety Cohort and prior to the start of Season 1 (2020-2022 NH), an Independent Data Monitoring

Committee (IDMC) will review the safety of this sentinel cohort. If the IDMC determines there is no significant safety issue during their review of the Sentinel Safety Cohort's data, approximately [redacted] subjects will subsequently be allowed to be enrolled in Season 1.

The sample size in the subsequent seasons may be adjusted to maintain the likelihood of achieving the overall expected number of cases for the primary endpoint. The current estimated sample size for the efficacy cohort in Seasons 2 and 3 is [redacted] subjects [redacted] and an additional [redacted] subjects from Season 1's Immunogenicity Subset will be re-enrolled in Season 3 but will not be included in efficacy analysis for Season 3, for a total of 13,320 subjects in the entire study. Sentinel Safety Cohort subjects will be excluded from reenrollment in any subsequent seasons.

During each influenza season, a subset of subjects (hereafter referred to as the Immunogenicity Subset) will be randomly selected using Interactive Response Technology (IRT) across participating sites to provide blood samples for immunogenicity testing:

- Total subjects with blood draws = approximately [redacted] subjects
- Season 1, NH = [redacted] subjects
- Season 2, SH = [redacted] of randomized subjects (approximately [redacted] subjects)
- Season 3, NH = [redacted] of randomized subjects (approximately [redacted] subjects) and [redacted] re-enrolled subjects who were part of Season 1*

An ESafAS will also be selected for collection of reactogenicity and unsolicited adverse events as follows:

- Total subjects in ESafAS = [redacted] subjects
- Sentinel Safety Cohort (2020-2021 NH) = 100 subjects†
- Season 1, NH = [redacted] subjects (all subjects) †
- Season 2, SH = [redacted] of randomized subjects (approximately [redacted] subjects)
- Season 3, NH = [redacted] of randomized subjects (approximately [redacted] subjects) and [redacted] re-enrolled subjects from Season 1

*A subset of approximately [redacted] subjects from Season 1 (2021-2022 NH) who are in the Immunogenicity Subset will be re-enrolled and re-randomized in Season 3 (hereafter referred as the Re-vaccination Cohort) and included in the ESafAS and the Immunogenicity Subset; these [redacted] subjects will not be followed for ILI surveillance during their participation in Season 3.

†Note: For the Sentinel Safety Cohort season and Season 1: all enrolled subjects will be included in the ESafAS.

For Seasons 2 and 3: the Immunogenicity Subset and the ESafAS will include the same subjects.

Following the end of Season 2, if the likelihood of achieving the expected [redacted] influenza cases at the end of the Season 3 is low an extension of the study to a 4th season may be considered, and if at least [redacted] evaluable influenza cases meeting the primary endpoint have occurred, an interim analysis of the efficacy of QIV-HD relative to QIV-SD for the primary efficacy endpoint is planned to be conducted by an independent statistician and reviewed by an IDMC during Season 3. The IDMC may recommend stopping the study at the end of Season 3 without adding any additional study seasons if the primary objective and first secondary objectives are demonstrated,

if there is a high probability to demonstrate these objectives at the end of the ongoing season, or for futility if the probability to demonstrate the primary objective at the end of the study is too low.

Due to the unpredictable epidemiology of influenza, the sample size and / or the duration of the study may be adjusted based on the total number of influenza cases, blinded so that the Sponsor does not know which study vaccine each subject received, in order to maintain the likelihood of achieving the expected number of influenza cases for the primary endpoint.

3.2 Study Plan

The study plan is summarized in the Table of Study Procedures (Table 3.1, Table 3.2, Table 3.3, Table 3.4, Table 3.5, Table 3.6, and Table 3.7).

The study will span several influenza seasons in different countries. Subjects may receive 1 or 2 vaccinations, depending on previous influenza vaccination history, and may provide blood draws according to the protocol-defined objectives.

Vaccination

For the Sentinel Safety Cohort, eligible subjects will receive QIV-HD with no comparator vaccine as follows:

- Subjects who were previously vaccinated against influenza will receive 1 dose of the QIV-HD on Day (D) 0.
- Subjects who have not previously been vaccinated against influenza will receive 2 doses of QIV-HD. Each dose will be administered 28 days apart (at D0 and D28).

For all other eligible subjects in the study who are not part of the sentinel safety cohort, these subjects will be randomized to receive either QIV-HD or QIV-SD:

- Subjects who were previously vaccinated against influenza will receive 1 dose of QIV-HD or QIV-SD on D0.
- Subjects who had not previously been vaccinated against influenza will receive 2 doses of QIV-HD or QIV-SD. Each dose will be administered 28 days apart (at D0 and D28).

An unblinded administrator at each site will administer the vaccine.

Surveillance for influenza-like illness (not applicable for Sentinel Safety Cohort or Re-vaccination Cohort):

Passive Surveillance: Following randomization and vaccinations, all subjects' parents / guardians (except those in the Sentinel Safety Cohort or the Re-vaccination Cohort) will be instructed to contact the site if the subject experiences symptoms of a protocol-defined ILI during the annual

surveillance periods, from the 1st vaccination (D0) until 30 April of the following year for subjects in the NH or until 31 October of the same year for subjects in the SH.

Active Surveillance: During a period from the 1st vaccination (D0) until approximately 30 April for NH seasons or 31 October for SH seasons, subjects' parents/guardians will be contacted by telephone once a week.

Collection of nasopharyngeal (NP) swabs

During the period from the 1st vaccination (D0) until 30 April of the following year for NH subjects or until 31 October of the same year for SH subjects, the site will arrange for an NP swab to be taken if the subject experiences a new onset of fever concomitantly with one or more of the above mentioned symptoms of protocol-defined ILI (that persists for or reoccurs after a period of at least 12 hours).

The NP swab will be obtained as soon as possible and no later than 7 days (between D0 and D6) from the onset of the ILI.

Reporting of events temporally associated with an ILI

In addition to obtaining an NP swab, the site will collect detailed information about the ILI, as well as information on occurrence of ALRI, otitis media, healthcare utilization events (hospitalizations, emergency room visits, and non-routine office visits [including urgent care visits]) and medication use (eg, antibiotics, antivirals).

In the event that an NP swab cannot be collected, the research site will still obtain the above information. All subjects' parents / guardians reporting a suspected ILI will have a 30 day follow-up telephone call.

Laboratory testing for the confirmation of influenza and determination of similarity to vaccine components

All NP specimens will be submitted for analysis by both culture and PCR, and a positive result on either test will be considered a laboratory-confirmed case of influenza.

Positive cultures or positive PCR samples will undergo additional testing (typing, subtyping, and strain identification, utilizing genetic sequencing) to determine if the virus detected is similar to any of those contained in the vaccine formulation for the respective season.

Blood sampling

A subset of randomly selected subjects (the Immunogenicity Subset) will provide 2 blood samples (5mL each):

- Previously vaccinated subjects will provide a pre-vaccination (baseline) blood sample at Visit (V) 01 (D0) and a post-vaccination blood sample at V02 (D28 [+7 days]) for HAI testing and potential SN and enzyme-linked lectin assay (ELLA) testing.
- Previously unvaccinated subjects will provide a pre-vaccination (baseline) blood sample at V01 (D0) and a post-vaccination blood sample at V03 (28 days after V02 [+7 days]) for HAI testing and potential SN and ELLA testing.

Note: the Re-vaccination Cohort will automatically be part of the Immunogenicity Subset

Collection of safety data

All subjects will be observed for 30 minutes after vaccination, and any unsolicited systemic adverse events (AEs) occurring during that time will be recorded as immediate unsolicited systemic AEs in the case report book (CRB) for subjects in the sentinel cohort and ESafAS and in the source documentation for all other subjects.

For subjects in the Sentinel Safety Cohort and Season 1 (NH), solicited reactions will be collected through day 7 after each vaccination, and unsolicited AEs will be collected through day 28 after each vaccination in all subjects. During study Seasons 2 (2022 SH) and 3 (2022-2023 NH), solicited reactions and unsolicited AEs will only be collected for those in the ESafAS. SAEs and AESIs will be collected in all subjects throughout the study (D0 through approximately 6 to 7 months after vaccination in each season). AESIs will be captured as SAEs in this study. AESIs include Guillain-Barré syndrome (GBS), encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis.

Parents / guardians of subjects will be asked to notify the site immediately about any potential SAEs (including AESIs) at any time during the study.

Staff will review the safety data with subjects' parents / guardians at each visit. The IRT system will be used to randomly assign subjects to a study product and subsets and to assign subject numbers in each of the groups.

COVID-19 risk Assessment

The QHD00014 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 QHD00014 may be exposed to people and surfaces commuting to the study and in waiting rooms and exam rooms at the study site.

COVID-19 risk mitigation

- Reevaluate the start of the study at a site or in a region as the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are evaluated by the study team.
- The number of on-site study visits has been decreased for the sentinel safety cohort to reduce risk.
- Continued risk assessment by the Investigator and Sponsor prior to each study visit and throughout each season of the study.

Electronic data capture (EDC) will be used for the collection of data.

Table 3.1: Table of Study Procedures 1 - Previously vaccinated subjects in the Sentinel Safety Cohort

Phase III Study, 2 Visits, 2 Telephone Calls, 1 Vaccination, approximately 180 Days' Duration per Subject

Visit/Contact	**V01**	**Telephone Call 01**	**V02**	**TC02**
Study timelines (days)	D0	D8	D28	180 days after V01
Time windows (days)		+2	+7	+14
Informed consent form signed and dated	X			
Inclusion / exclusion criteria	X			
Physical examination*	X		X	
Collection of demographic data	X			
Medical history†	X			
History of seasonal influenza vaccination	X			
Collection of concomitant medications	At any time during the study period			
IRT Contact allocation of subject number and unique dose number‡	X			
Vaccination	X			
Immediate surveillance (30 min)	X			
DC provided§	X			
DC reviewed and collected			X	
Reporting of solicited injection site and systemic reactions (for 7 days after vaccination	X			
Collection of unsolicited adverse events (for 28 days after vaccination)	X			
MA provided**			X	
Study active phase termination record			X	
Follow-up telephone call		X††		X‡‡
Reporting of SAEs (including AESIs)§§	To be reported at any time during the study			

Abbreviations: AESI, adverse event of special interest; D, day; DC, diary card; MA, memory aid; SAE, serious adverse event; TC, telephone call; V, visit.

* Targeted physical examination based on medical history will be performed at V01. Targeted physical examination may also be performed at V02, if necessary.

† With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ Before vaccine injection.

§ Subject's parents / guardians will use the diary card to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D0 to D7 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D8 to V02

** Subject's parents / guardians will use this MA to collect information on medications, SAEs and AESIs from V02 to the end of the 6-month safety follow-up period.

†† During this telephone call, staff will record relevant information concerning the subject's health status, will find out whether the subject experienced any SAEs and AESIs not yet reported, and will remind the subjects' parent / guardian to bring the completed diary card to the next visit.

‡‡ During this telephone call, staff will review the MA to record medications and identify the occurrence of any SAEs and AESIs that have not yet been reported.
§§ AESIs will be captured as SAEs. These include Guillain-Barré syndrome, encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis.

Table 3.2: Table of Study Procedures 2 - Previously unvaccinated subjects in the Sentinel Safety Cohort

Phase III Study, 3 Visits, 3 Telephone Calls, 2 Vaccinations, approximately 208 Days' Duration per Subject

Visit/Contact	**V01**	**Telephone Call 01**	**V02**	**TC02**	**V03**	**TC03**
Study timelines (days)	D0	D8	D28	8 days after V02	28 days after V02	180 days after V02
Time windows (days)		+2	+7	+2	+7	+14
Informed consent form signed and dated	X					
Inclusion / exclusion criteria	X					
Physical examination*	X		X		X	
Collection of demographic data	X					
Medical history†	X					
History of seasonal influenza vaccination	X					
Collection of concomitant medications	At any time during the study period					
IRT Contact -allocation of subject number and unique dose number‡	X					
Allocation of unique dose number			X			
Temporary and definitive contraindications			X			
Vaccination	X		X			
Immediate surveillance (30 min)	X		X			
DC provided§	DC1		DC2			
DC reviewed and collected			DC1		DC2	
Recording of solicited injection site and systemic reactions (for 7 days after vaccination)	X		X			
Collection of unsolicited adverse events (for 28 days after vaccination)	X			X		
MA provided**					X	
Study active phase termination record					X	
Follow-up telephone call		X††		X††		X‡‡
Reporting of serious adverse events (SAEs) (including AESIs) §§	To be reported at any time during the study					

Abbreviations: AESI, adverse event of special interest; BL, blood sampling; D, day; DC, diary card; SAE, serious adverse event; TC, telephone call; V, visit.

* Targeted physical examination based on medical history will be performed at V01. Targeted physical examination may also be performed at V02 and V03, if necessary.

† With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ Before vaccine injection

§ Subject's parents / guardians will use the diary cards to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs after each vaccination (from V01 to TC01 and from V02 to TC02) and will continue to record information about unsolicited AEs, SAEs, and AESIs from TC01 to V02 and D36 to V03.

**Subject's parents / guardians will use this MA to collect information on medications, SAEs and AESIs from V03 to the end of the 6-month safety follow-up period.

†† During this telephone call, staff will record relevant information concerning the subject's health status, will find out whether the subject experienced any SAEs and AESIs not yet reported, and will remind the subjects' parent / guardian to bring the completed diary card to the next visit.

‡‡ During this telephone call, staff will review the MA to record medications and identify the occurrence of any SAEs and AESIs that have not yet been reported.

§§ AESIs will be captured as SAEs. These include Guillain-Barré syndrome, encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis.

Table 3.3: Table of Study Procedures 3 - previously influenza vaccinated subjects 6 months through 35 months of age

Phase III Study, 1 Visit, 1 Telephone Call, 1 Vaccination, approximately 6 Months Duration per Subject per Study Year

Visit/Contact	**V01**	**Follow-up Telephone Call**
Study timelines (days)	D0	D180 + 14 after V01 or end of influenza season if later than D180
Time windows (days)		+14
Informed consent form signed and dated	X	
Inclusion / exclusion criteria	X	
Physical examination*	X	
Collection of demographic data	X	
Medical history†	X	
History of seasonal influenza vaccination	X	
Collection of concomitant medications	At any time during the study period	
Contact IRT system for randomization, subject number, and unique dose number allocation ‡	X	
Vaccination	X	
Immediate surveillance (30 min)	X	
Provision of Memory Aid§	X	
Review of Memory Aid		X
Study active phase termination record		X
Reporting of SAEs (including AESIs) **	To be reported at any time during the study	
Collection of ILI symptoms through passive and active surveillance	Passive Surveillance: All subjects' parents/guardians will be instructed to contact the study site if the subject experiences symptoms of ILI from D0 post-vaccination until 30 April of the following year for NH seasons subjects or until 31 October of the same year for SH subjects. Active Surveillance: For NH seasons subjects, during a period from D0 post-vaccination until approximately 30 April of the following year, subjects' parents/guardians will be contacted once a week. For SH seasons subjects, during a period from D0 post-vaccination until approximately 31 October of the same year, subjects' parents/guardians will be contacted once a week.	
Collection of nasopharyngeal swabs for laboratory confirmation of influenza††	From D0 post-vaccination 1 until 30 April of the following year for NH subjects or until 31 October of the same year for SH subjects. Every effort has to be made to obtain the NP specimen on the same or the following day after confirmation of qualifying ILI symptoms and no later than 7 days after onset of the ILI (start date = start date of fever) (ie, sample is to be collected through D6 of the illness, considering that D0 was the day of ILI onset).	

Collection of ALRI, AOM, absenteeism, and health care information ‡‡	At any time during the study season (for NH subjects through 30 April and for SH subjects through 31 October) in association with an ILI, and for 30 days (+ 7 days) following the start of ILI regardless of whether or not an NP swab is obtained.

Abbreviations: AESI, adverse event of special interest; ALRI, acute lower respiratory infection; AOM, acute otitis media; D, day; DC, diary card; ILI, influenza-like illness; IRT, Interactive Response Technology; MA, memory aid; NP, nasopharyngeal; SAE, serious adverse event; TC, telephone call; V, visit.

* Targeted physical examination will be performed at V01.

†With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ Before vaccine injection

§Subject's parents / guardians will use this MA to collect information on medications, SAEs, AESIs, and ILI from V01 through approximately 6 to 7 months after vaccination in each season.

** AESIs will be captured as SAEs. These include Guillain-Barré syndrome, encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis.

††Collected from any subject who is identified as having a protocol-defined ILI from D0 of vaccination 1 and later (start date after D0).

‡‡Occurrences of any of the following in association with any protocol-defined ILI on or after D0 will be followed up for 30 days after the illness start date: ALRI (eg, pneumonia), AOM, hospitalizations, emergency room visits, and non-routine medical office visits (including urgent care visits), as well as the diagnoses associated with those instances.

Table 3.4: Table of Study Procedures 4 - previously influenza unvaccinated subjects 6 months through 35 months of age

Phase III Study, 2 Visits, 1 Telephone Call, 2 Vaccinations, approximately 7 months' Duration per Subject per Study Year

Visit/Contact	**V01**	**V02**	**Follow-up Telephone Call**
Study timelines (days)	D0	D28	D208 (180+14 days after V02) or the end of influenza season if later than D208
Time windows (days)		+7	+14
Informed consent form signed and dated	X		
Inclusion / exclusion criteria	X		
Physical examination*	X	X	
Collection of demographic data	X		
Medical history†	X		
History of seasonal influenza vaccination	X		
Collection of concomitant medications	At any time during the study period		
Contact IRT system for randomization, subject number, and unique dose number allocation‡	X		
Temporary and definitive contraindications		X	
IRT Contact for allocation of unique dose number		X	
Vaccination	X	X	
Immediate surveillance (30 min)	X	X	
Provision of Memory Aid§	X		
Review of Memory Aid		X	X
Study active phase termination record			X
Reporting of SAEs (including AESIs)**	To be reported at any time during the study		
Collection of ILI symptoms through passive and active surveillance	Passive Surveillance: All subjects' parents/guardians will be instructed to contact the study site if the subject experiences symptoms of ILI from D0 post vaccination until 30 April of the following year for NH seasons subjects or until 31 October of the same year for SH subjects. Active Surveillance: For NH seasons subjects, during a period from D0 post-vaccination until approximately 30 April, subjects' parents/guardians will be contacted once a week. For SH seasons subjects, during a period from D0 post-vaccination until approximately 31 October, subjects' parents/guardians will be contacted once a week.		

Collection of nasopharyngeal swabs for laboratory confirmation of influenza††	From D0 post-vaccination 1 until 30 April of the following year for NH subjects and until 31 October of the same year for SH subjects. Every effort has to be made to obtain the NP specimen on the same or following day after confirmation of qualifying ILI symptoms and no later than 7 days after onset of the ILI (start date = start date of fever) (ie, sample is to be collected through D6 of the illness, considering that D0 was the day of ILI onset).
Collection of ALRI, AOM, absenteeism, and health care information‡‡	At any time during the study season (for NH subjects through 30 April and for SH subjects through 31 October) in association with an ILI, and for 30 days (+ 7d) following the start of ILI regardless of whether or not an NP swab is obtained.

Abbreviations: AESI, adverse event of special interest; ALRI, acute lower respiratory infection; AOM, acute otitis media; D, day; DC, diary card; ILI, influenza-like illness; IRT, Interactive Response Technology; MA, memory aid; NP, nasopharyngeal; SAE, serious adverse event; TC, telephone call; V, visit.

* Targeted physical examination will be performed at V01. Targeted physical examination may also be performed at V02, as necessary.

†With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ IRT will also be used to randomly select subjects to participate in the immunogenicity subset

§ Subject's parents / guardians will use this MA to collect information on medications, ILI, SAEs and AESIs from V01 through approximately 6 to 7 months after vaccination in each season.

** AESIs will be captured as SAEs. These include Guillain-Barré syndrome, encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis.

†† Collected from any subject who is identified as having a protocol defined ILI from D0 of vaccination 1 and later (start date after D0).

‡‡ Occurrences of any of the following in association with any protocol defined ILI on or after Day 0 will be followed up for 30 days after the illness start date: ALRI (eg, pneumonia), AOM, hospitalizations, emergency room visits, and non-routine medical office visits (including urgent care visits), as well as the diagnoses associated with those instances.

Table 3.5: Table of Study Procedures 5 - previously influenza vaccinated subjects in the Expanded safety analysis set [ESafAS] with or without inclusion in the Immunogenicity Subset

Phase III Study, 2 Visits, 1 Telephone Calls, 1 Vaccination, 2 blood samples, approximately 7 months' Duration per Subject per Study Year

Visit/Contact	**V01**	**V02**	**Follow-up Telephone Call**
Study timelines (days)	D0	D28	D180 (180 +14 after V01) or the end of influenza season if later than D180
Time windows (days)		+7	+14
Informed consent form signed and dated	X		
Inclusion / exclusion criteria	X		
Physical examination*	X	X	
Collection of demographic data	X		
Medical history†	X		
History of seasonal influenza vaccination	X		
Collection of concomitant medications	At any time during the study period		
Contact IRT system for randomization, subject number, and unique dose number allocation‡	X		
Blood sampling (BL) for immunogenicity subset only, 5 mL	BL0001§	BL0002	
Vaccination	X		
Immediate surveillance (30 min)	X		
DC provided**	X		
DC reviewed & collected		X	
Reporting of solicited injection site and systemic reactions (for 7 days after vaccination)	X		
Collection of unsolicited adverse events (for 28 days after vaccination)	X		
Provision of Memory Aid††		X	
Review of Memory Aid			X
Study active phase termination record			X
Reporting of serious adverse events (SAEs) (including AESIs) ‡‡	To be reported at any time during the study		

Collection of ILI symptoms through passive and active surveillance§§	Passive Surveillance: All subjects' parents/guardians will be instructed to contact the study site if the subject experiences symptoms of ILI from D0 post vaccination until 30 April of the following year for NH seasons subjects or until 31 October of the same year for SH subjects. Active Surveillance: For NH seasons subjects, during a period from D0 post-vaccination until approximately 30 April, subjects' parents/guardians will be contacted once a week. For SH seasons subjects, during a period from D0 post-vaccination until approximately 31 October, subjects' parents/guardians will be contacted once a week. *Excluding the Season 3 Re-vaccination Cohort.*
Collection of nasopharyngeal swabs for laboratory confirmation of influenza***	From D0 post-vaccination until 30 April of the following year for NH subjects and until 31 October of the same year for SH subjects. Every effort has to be made to obtain the NP specimen on the same or following day after confirmation of qualifying ILI symptoms and no later than 7 days after onset of the ILI (start date = start date of fever) (ie, sample is to be collected through D6 of the illness, considering that D0 was the day of ILI onset). *Excluding the Season 3 Re-vaccination Cohort.*
Collection of ALRI, AOM, absenteeism, and health care information†††	At any time during the study season (for NH subjects through 30 April and for SH subjects through 31 October) in association with an ILI, and for 30 days (+ 7d) following the start of ILI regardless of whether or not an NP swab is obtained. *Excluding the Season 3 Re-vaccination Cohort.*

Abbreviations: AESI, adverse event of special interest; ALRI, acute lower respiratory infection; AOM, acute otitis media; BL, blood sampling; D, day; DC, diary card; ILI, influenza-like illness; IRT, Interactive Response Technology; MA, memory aid; NP, nasopharyngeal; SAE, serious adverse event; V, visit.

* Targeted physical examination will be performed at V01. Targeted physical examination may also be performed at V02, as necessary.

†With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ Before vaccine injection. IRT will also be used to randomly select subjects to participate in the immunogenicity subset

§ Blood sampling to occur prior to vaccination.

** Subjects / parents / guardians will use the diary cards to record information about solicited reactions, unsolicited AEs, SAEs, AESIs, ILI symptoms after each vaccination (from D0 to D7) and will continue to record information about unsolicited AEs, SAEs, and AESIs from D8 to V02.

††Subjects / parents / guardians will use this MA to collect information on SAEs, AESIs, and ILI from V02 to the end of the 6-month safety follow-up period.

‡‡AESIs will be captured as SAEs. These include Guillain-Barré syndrome, encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis.

§§ The subset of approximately [redacted] subjects from Season 1 (2021-2022 NH) who are in the Immunogenicity Subset and who will be re-enrolled and re-randomized in Season 3 will not participate in collection of ILI symptoms through passive and active surveillance in Season 3 (NH).

***Collected from any subject who is identified as having a protocol-defined ILI from D0 of vaccination and later (start date after D0).

†††Occurrences of any of the following in association with any protocol-defined ILI on or after Day 0 will be followed up for 30 days after the illness start date: ALRI (eg, pneumonia), AOM, hospitalizations, emergency room visits, and non-routine medical office visits (including urgent care visits), as well as the diagnoses associated with those instances.

Table 3.6: Table of Study Procedures 6 - previously influenza unvaccinated subjects the Expanded safety analysis set [ESafAS] with and without inclusion in the Immunogenicity Subset

Phase III Study, 3 Visits, 1 Telephone Call, 2 Vaccinations, 2 blood samples, approximately 7 months' Duration per Subject per Study Year

Visit/Contact	**V01**	**V02**	**V03**	**Follow-up Telephone Call**
Study timelines (days)	D0	D28	28 days after V02	D208 (180 +14 days after V02) or at the end of influenza season if later than D208
Time windows (days)		+7	+7	+14
Informed consent form signed and dated	X			
Inclusion / exclusion criteria	X			
Physical examination*	X	X		
Collection of demographic data	X			
Medical history†	X			
History of seasonal influenza vaccination	X			
Collection of concomitant medications	At any time during the study period			
Contact IRT system for randomization, subject number, and unique dose number allocation‡	X			
IRT Contact for allocation of unique dose number		X		
Temporary and definitive contraindications		X		
Blood sampling (BL) for immunogenicity subset only, 5 mL	BL0001§		BL0002	
Vaccination	X	X		
Immediate surveillance (30 min)	X	X		
DC provided**	DC1	DC2		
DC reviewed & collected		DC1	DC2	
Reporting of solicited injection site and systemic reactions (for 7 days after vaccination)	X	X		
Collection of unsolicited adverse events (for 28 days after vaccination)	X			
Provision of Memory Aid††			X	
Review of Memory Aid				X

Study active phase termination record				X
Reporting of serious adverse events (SAEs) (including AESIs) ‡‡	To be reported at any time during the study			
Collection of ILI symptoms through passive and active surveillance§§	Passive Surveillance: All subjects' parents/guardians will be instructed to contact the study site if the subject experiences symptoms of ILI from D0 post vaccination until 30 April of the following year for NH seasons subjects or until 31 October of the same year for SH subjects. Active Surveillance: For NH seasons subjects, during a period from D0 post-vaccination until approximately 30 April, subjects' parents/guardians will be contacted once a week. For SH seasons subjects, during a period from D0 post-vaccination until approximately 31 October, subjects' parents/guardians will be contacted once a week. *Excluding the Season 3 Re-vaccination Cohort.*			
Collection of nasopharyngeal swabs for laboratory confirmation of influenza***	From D0 post-vaccination until 30 April of the following year for NH subjects and until 31 October of the same year for SH subjects. Every effort has to be made to obtain the NP specimen on the same or following day after confirmation of qualifying ILI symptoms and no later than 7 days after onset of the ILI (start date = start date of fever) (ie, sample is to be collected through D6 of the illness, considering that D0 was the day of ILI onset). *Excluding the Season 3 Re-vaccination Cohort.*			
Collection of ALRI, AOM, absenteeism, and health care information†††	At any time during the study season (for NH subjects through 30 April and for SH subjects through 31 October) in association with an ILI, and for 30 days (+ 7d) following the start of ILI regardless of whether or not an NP swab is obtained. *Excluding the Season 3 Re-vaccination Cohort.*			

Abbreviations: AESI, adverse event of special interest; ALRI, acute lower respiratory infection; AOM, acute otitis media; BL, blood sampling; D, day; DC, diary card; ILI, influenza-like illness; IRT, Interactive Response Technology; MA, memory aid; NP, nasopharyngeal; SAE, serious adverse event; V, visit.

* Targeted physical examination will be performed at V01. Targeted physical examination may also be performed at V02 and V03, as necessary.

†With the collection of medical history, information on breastfeeding status should be collected from subjects < 2 years old and information on gestational age should be collected from all subjects

‡ IRT will also be used to randomly select subjects to participate in the immunogenicity subset

§ Blood sampling to occur prior to vaccination.

** Subjects / parents / guardians will use the diary cards to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs after each vaccination (from D0 to D7) and will continue to record information about unsolicited AEs, SAEs, and AESIs from D8 to V02 and D36 to V03.

††Subjects / parents / guardians will use this MA to collect information on SAEs, AESIs, and ILI from V03 to the end of the 6-month safety follow-up period.

‡‡AESIs will be captured as SAEs. These include Guillain-Barré syndrome, encephalitis / myelitis (including transverse myelitis), Bell's palsy, convulsions, optic neuritis, and brachial neuritis.

§§ The subset of approximately [redacted] subjects from Season 1 (2021-2022 NH) who are in the Immunogenicity Subset and who will be re-enrolled and re-randomized in Season 3 will not participate in collection of ILI symptoms through passive and active surveillance in Season 3 (NH).

***Collected from any subject who is identified as having a protocol-defined ILI from D0 of vaccination 1 and later (start date after D0).

†††Occurrences of any of the following in association with any protocol-defined ILI on or after Day 0 will be followed up for 30 days after the illness start date: ALRI (eg, pneumonia), AOM, hospitalizations, emergency room visits, and non-routine medical office visits (including urgent care visits), as well as the diagnoses associated with those instances.

Table 3.7: Table of Study Procedures 7 -Follow-up of ILI

Days After protocol defined ILI Onset	**D0*- D6**	**D0 – D6**	**D30** (+ 7 d) †
Contact type	Telephone Call	Visit	Telephone Call
Verify information on respiratory illnesses, and schedule appointment for an NP swab within 7 days of illness start date	X		
Remind subject to complete Memory Aid or Diary Card	X		
Collection of NP swab		X	
Collection of ALRI, AOM, absenteeism, and health care information	X	X	X
Collection of information on protocol defined ILI symptoms ‡	X	X	X

* Day 0 (protocol defined ILI Start Date) refers to the first day of Fever. The end of an ILI episode is considered as the last day of fever ≥ 38°C. An interval of 2 days will have to have passed after the end of an ILI episode to be consider a new ILI episode.

† The 7-day window allows provision to complete the telephone call. The data collected are inclusive from Day 0 through Day 30 of protocol defined ILI; information > 30 days from protocol defined ILI onset does not need to be collected.

‡ During collection of information on protocol defined ILI symptoms, the presence, or not, of concurrent ILI symptoms (ie, cough, wheezing, difficulty breathing, nasal congestion, rhinorrhea, sore throat, pharyngitis, otitis, vomiting, diarrhea, chills [shivering], tiredness [fatigue], headache, or myalgia [muscle aches])

Note: *The subset of approximately [redacted] subjects from Season 1 (2021-2022 NH) who are in the Immunogenicity Subset and who will be re-enrolled and re-randomized in Season 3 will not participate in collection of ILI symptoms through passive and active surveillance in Season 3 (NH).*

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

See Section 9.1 of the protocol.

4.2 Secondary Endpoints and Assessment Methods

See Section 9.2 of the protocol.

AOM, ALRI, and hospitalization recorded in the CRB as associated to an ILI and occurring within 30 days after the ILI onset of any will be considered as associated with the ILI.

4.3 Observational Endpoints and Assessment Methods

See Section 9.3 of the protocol.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

4.4.1.1 Solicited Reactions

4.4.1.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

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

- Solicited reactions (except Fever / Pyrexia) with an investigator presence recorded as "No" and with all daily records missing then all daily intensities will be derived as None.
- For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3.

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity / measurement after the end of the solicited period following the rule described above.

Solicited reactions (except Fever / Pyrexia) with an investigator presence recorded as "No" and with all daily records missing then all daily intensities will be derived as None.

4.4.1.1.2 Maximum Overall Intensity

Maximum overall intensity will be derived from the daily intensities computed as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

4.4.1.1.3 Presence

Presence will be derived from the maximum overall intensity on the period considered:

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing: Missing presence

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

4.4.1.1.4 Time Period

Time period when at least one daily intensity Grade 1, Grade 2 or Grade 3 of a solicited reaction is present will be categorized and displayed as D0-D3, D4-D7, D8 or later.

4.4.1.1.5 Time of Onset

Time of onset will be derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Time of onset will be categorized into and displayed as D0-D3 and D4-D7.

Note: If a reaction was not continuous (ie, reaction occurs over 2 separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset was the first day of the first occurrence.

4.4.1.1.6 Number of Days of Occurrence

Number of days of occurrence over the period considered will be derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponded to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3.

Number of days of occurrence will be categorized into and displayed as 1-3 days, 4-7 days, and 8 days.

4.4.1.1.7 Ongoing

Ongoing will be derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

If the last daily intensity of the solicited period was at least Grade 1 and maximum intensity on the ongoing period is also at least Grade 1, then the reaction is considered ongoing. In any other cases the reaction is not be considered as ongoing.

4.4.1.2 Unsolicited Non-serious AEs

4.4.1.2.1 Presence

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

4.4.1.2.2 Intensity

Intensity for unsolicited non-serious AE will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited AE is measurable and its preferred term (PT) is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule than the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

Intensity for the other unsolicited non-serious AEs will correspond to the value reported in the CRB.

The maximum intensity corresponds to the highest intensity for a unique term.

4.4.1.2.3 Last Vaccination

The last vaccination before an unsolicited non-serious AE is derived from the visit numbers provided in the clinical database and is calculated as follows:

- If an unsolicited non-serious AE has a non-missing visit number, the visit number should be used to determine the last vaccination before the unsolicited non-serious AE
- If the visit number is missing, then the start date should be used to determine the last vaccination before the unsolicited non-serious AE

4.4.1.2.4 Time of Onset

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

- start date of the unsolicited non-serious AE – date of previous vaccination

The time of onset should be considered as missing only if one or both of the dates are missing or partially missing.

The unsolicited non-serious AEs will be analyzed “Within 28 days”, which corresponds to AEs with a time of onset between 0 and 28 days after vaccination or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

Note: Unsolicited non-serious AE that occurred before the 1st vaccination (negative time of onset) or with a time of onset higher than 28 days will not be included in analysis and will be listed separately.

Time of onset will be categorized into and displayed as D0-D3, D4-D7, D8-D14, ≥ D15, and Missing.

4.4.1.2.5 Duration

Duration will be derived from the start and end dates of the unsolicited non-serious AE provided in the clinical database:

- end date of unsolicited non-serious AE - start date of unsolicited non-serious AE + 1.

The duration will be considered as missing only if one or both of the start and end dates of the unsolicited non-serious AE was missing or partially missing.

Duration will be categorized and displayed as 1-3 days, 4-7 days, 8-14 days, ≥ 15 days, and Missing.

4.4.1.3 SAEs

AESIs will be collected from inclusion until the end of the study as SAEs. AESIs are to be reported and analyzed as SAEs.

4.4.1.3.1 Last Vaccination

The last vaccination before an SAE is derived from the last visit numbers provided in the clinical database and is calculated as follows:

- If an SAE has a non-missing visit number, the visit number should be used to determine the last vaccination before the SAE
- If the visit number is missing, then the start date should be used to determine the last vaccination before the SAE

4.4.1.3.2 Time of Onset

Time of onset will be computed using the same methodology as for unsolicited non-serious AEs described in Section 4.4.1.2.4.

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

- Within 28 days after each and any injection
- Within 180 days from 28 days after the last injection
- During the study (ie, all SAEs occurred during the study)

An SAE with missing time of onset will be considered to have occurred just after the vaccination, indicated by the visit number, and will be included in these tables.

Note: SAEs that occurred before the 1st vaccination (ie, negative time of onset or with a time of onset higher than defined 28 days) will not be included in analysis but may be listed separately.

4.4.1.4 Other Safety Endpoints

4.4.1.4.1 AEs Leading to Study Discontinuation

A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- For subject disposition: if subject did not complete the study due to AE as recorded in Completion at End of Study form
- For safety overview: if subject did not complete the study due to AE as recorded in Completion at End of Study form or had any solicited or unsolicited AEs causing study discontinuation / termination as recorded in solicited reaction or unsolicited AE forms within the time period indicated

- For summary of unsolicited AEs by system organ class (SOC) / PT: An unsolicited AE causing study discontinuation as recorded in Unsolicited AE form within the time period indicated

4.4.1.4.2 Solicited Reactions after Any Doses

The rules for calculation are to select the worst case:

- Time period: At least one daily intensity Grade 1, Grade 2 or Grade 3 on the period and considered for at least one injection
- Maximum intensity: Select the maximum overall intensity for any injection
- Time of onset: Select the minimum time of onset for any injection

The worst case cannot be identified for number of days of occurrence and action taken. No tables after any dose will be produced for these endpoints.

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

For HAI, SN, and ELLA tests, in order to appropriately manage replicate values for analysis purposes, the individual geometric mean (GM) of all values will be computed for each blood sample after managing extreme values as described. The computed value is then considered the titer for that particular blood sample.

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

Duplicate records (per subject, antigen, and method) will be recorded for HAI and anti-NA titration. A GM of duplicate will be applied in order to obtain a unique value for the statistical analysis. Unique records will be recorded for SN titration.

Depending on titration method and time, the following computations will be applied:

- If detectable titers (≥ 10 [1/dilution (dil)]) at D0 and 28 days after the last vaccination (D28/D56) for HAI, SN, and anti-NA, the derived ≥ 10 (1/dl) indicator will be “Yes” for that test, otherwise ≥ 10 (1/dil) indicator will be “No”.
- If titer ≥ 40 (1/dil) on D0 and 28 days after the last vaccination (D28/D56) for HAI, the derived ≥ 40 (1/dil) indicator will be “Yes”, otherwise ≥ 40 (1/dil) indicator will be “No”.
- If titer ≥ 20, 40, and 80 (1/dil) at D0 and 28 days after last vaccination (D28/D56) for SN and anti-NA, the derived ≥ 20, 40 and 80 (1/dil) indicator will be “Yes” for that test, respectively, otherwise will be “No”.

4.4.2.2 Fold-rise

The derived endpoint fold-rise is driven by both baseline (D0) and post-baseline (D28/D56) computed values as described in Section 4.4.2.1 and is computed as individual titer ratio:

- 28 days after the last vaccination divided by D0 for HAI, SN, and anti-NA.

If the computed fold-increase ≥ 2 for SN and anti-NA, the derived ≥ 2-fold rises indicator will be "Yes" for that test, otherwise ≥ 2-fold rises will be "No".

If the computed fold-increase ≥ 4 for, HAI, SN and anti-NA, the derived ≥ 4-fold rises indicator will be "Yes" for that test, otherwise ≥ 4-fold rises will be "No".

Note: if pre-vaccination (D0) or post-vaccination (D28/D56) values is missing, the fold-rise is missing.

4.4.2.3 Seroconversion

Seroconversion for HAI is defined as a binary indicator. If a pre-vaccination (D0) titer < 10 (1/dil): post-vaccination titer ≥ 40 (1/dil) on 28 days after the last vaccination (D28/D56), or ≥ 4-fold-rise for subjects with a pre-vaccination titer ≥ 10 (1/dil), the derived seroconversion indicator will be "Yes", otherwise will be "No".

Note: if pre-vaccination (D0) or post-vaccination (D28/D56) values is missing, the seroconversion is missing.

4.4.3 Efficacy

For each subject, the efficacy endpoints will be derived based on a combination of the following items:

ILI occurrence: at each ILI visit, the occurrence of a temperature of ≥ 100.4°F (38°C), starting more than 14 days after the 1st vaccination for the Full Analysis Set for Efficacy (FASE) as defined in Section 5.2.1 and last vaccination for the Per-Protocol Analysis Set for Efficacy (PPASE) as defined in Section 5.2.2 and concurrent with at least one other symptom meeting the definition of an ILI[1] will be considered as an ILI occurrence.

Notes:

- The start date of the ILI is the start of fever ≥ 100.4°F (38°C)
- Start and end dates of fever are considered as the start and end date of the ILI (when the end date is unknown, the last date the fever is known to be present is used)
- The date of start / end of each symptom is used in comparison of start and end of fever ≥ 100.4°F (38°C) to define concurrent symptoms with ILI: when start and end dates for fever and one other protocol-defined symptom are not missing, the start date for fever is ≤ the end date for the symptom and the end date for fever is ≥ the start date for the symptom

[1] Cough, wheezing, difficulty breathing, nasal congestion, rhinorrhea, pharyngitis (sore throat), otitis, vomiting, diarrhea, shivering, fatigue, headache or myalgia

- After the end of an ILI episode, an interval of 2 days has to pass before a new ILI episode can be considered
- For the primary and secondary objectives, in case of more than one occurrence of the same efficacy endpoint for the same subject, only the first occurrence based on the start date of the fever (≥ 100.4°F [38°C]) is considered for the estimation of vaccine efficacy for the prevention of this endpoint

Modified CDC-defined ILI is the occurrence of a temperature of ≥ 100.4°F (38°C), starting more than 14 days after the first vaccination and concurrent with cough or pharyngitis (sore throat). The same derivation rules for ILI occurrence will be used.

PCR-confirmed influenza case: An ILI occurrence is PCR-confirmed as positive for influenza A or B types if the PCR result of the corresponding NP swab, recorded at the corresponding ILI visit in the database and taken within 10 days after the start of the ILI, is positive for influenza.

Culture-confirmed influenza case: An ILI occurrence is culture-confirmed as positive for influenza A or B types if the virology result of the corresponding NP swab, recorded at the corresponding ILI visit in the database and taken within 10 days after the start of the ILI, is positive for influenza.

Laboratory-confirmed influenza case: An ILI occurrence is laboratory-confirmed as positive for influenza A or B types if it is either PCR- or culture-confirmed (see above).

Strain: Virus strains used for sequencing and vaccine formulations for similarity assessment will be detailed in a separate Appendix to this Statistical Analysis Plan (SAP) when it is available and can be updated up to the database lock.

Genetic similarity*:* Genetic similarity is defined when a laboratory-confirmed isolate is deemed similar to one of the viral strains contained in the vaccine formulations according to sequencing of full HA gene segments proteins. A strain is considered similar to one of the vaccine strains included in the formulation of the considered season if the sequence of full HA gene matches ≥ 99% with a strain known to be and pre-defined as vaccine-similar. This will be defined in a separate Appendix to this SAP when it is available and can be updated up to the database lock.

Antigenic similarity: Antigenic similarity is defined when a laboratory-confirmed isolate is deemed similar to one of the viral strains contained in the vaccine formulations according to Ferret Antigenicity testing (HAI against a panel of known standard ferret reference antisera).

Similarity to vaccine components: For prevention of laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine in subjects 6 months through 35 months of age, laboratory-confirmed isolate is deemed similar to one of the vaccine components based on antigenic similarity only. For all the other endpoints, similarity is based on antigenic similarity when available or based on genetic similarity otherwise.

Potentially, the same swab can be linked to several ILIs, and several swabs may be taken for the same ILI. Therefore, occurrences of positive swabs attached to an ILI are not necessarily equal to occurrences of ILIs with positive swab.

4.4.4 Derived Other Variables

4.4.4.1 Age for Demographics

The age of a subject in the study will be the calendar age in months at the time of inclusion.

For randomization stratification and subgroup analyses, the 2 following classes of age will be used: < 24 months and ≥ 24 months.

4.4.4.2 Breastfeeding

For subjects who have been breastfed, the duration of breastfeeding in weeks will be derived as:

(end date – start date + 1) / 7

If the end date is missing and the breastfeeding is ongoing at inclusion, the duration of breastfeeding in weeks will be derived as:

(first vaccination date – start date + 1) / 7

Missing or partially missing dates will not be imputed except for the missing day where for start date the missing day is replaced with the first day of the month and for end date the missing day is replaced with the last day of the month to derive the duration of breastfeeding.

4.4.4.3 Vaccine Formulation

The vaccine formulation will be derived as:

- Formulation = “Formulation 0” for all subjects in the Sentinel Safety Cohort
- Formulation = “Formulation 1” for all subjects included in Season 1
- Formulation = “Formulation 2” for all subjects included in Season 2
- Formulation = “Formulation 3” for all subjects included in Season 3

If the same formulation is used in 2 or more seasons, analyses per formulation will be performed by pooling seasons using the same formulations.

4.4.4.4 Occurrence of symptoms / events associated with ILI

For observational objectives, symptoms / events are considered to be associated with any ILI or laboratory-confirmed ILI including AOM, ALRI, medication use, hospitalization (recorded as Inpatient Hospitalization in Health Care Utilization form), emergency room visits (recorded as Outpatient Hospitalization in Health Care Utilization form), non-routine medical office visits (recorded as Outpatient Visit in Health Care Utilization form), absenteeism due to child sick days if the start date of the event is within 30 days after the start of the ILI (0 ≤ start date of symptom / event – start date of fever ≤ 30 days).

Duration of ILI symptoms is defined as end date – start date + 1.

4.4.4.5 Medical history of interest

Medical history of interest are those pre-listed in Chronic Medical History form: asthma, chronic lung disease, pulmonary hypertension, cystic fibrosis, congenital heart disease, cystic kidney disease, renal insufficiency, sickle cell trait, thalassemia major and minor, febrile seizure, egg allergy, eczema, and diabetes mellitus.

An indicator of baseline medical history of interest will be derived as "Yes" if a subject has at least one of the pre-defined medical history and "No" otherwise.

5 Statistical Methods and Determination of Sample Size

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

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

For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation (SD), quartiles (first quartile [Q1], median, third quartile [Q3]), minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% confidence intervals [CIs]) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
Immunogenicity results	**Categorical data (eg, seroconversion, cutoff, 4-fold-rise)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).
Efficacy results	**Categorical data**	Number and percentage (95% CIs) of subjects. Number of cases, relative vaccine efficacy (rVE) and 95% CIs

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (12), ie, using the inverse of the beta integral with SAS®.

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

Rounding rules on descriptive statistics will follow the Sanofi Pasteur standard. To present percentages (and 95% CI of percentages), one digit after the decimal place will be used by default (ie, for a large number of outputs). However, 2 digits may be used for some numbers, such as percentages of influenza cases (typically for relative vaccine efficacy [rVE]).

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objective

5.1.1.1 Hypotheses

Non-inferior efficacy hypotheses:

H_0: rVE $\leq$ -10%

H_A: rVE >-10%

Superior efficacy hypotheses:

H_0: rVE $\leq$ 5%

H_A: rVE > 5%

5.1.1.2 Statistical Methods

Efficacy

The rVE of QIV-HD relative to QIV-SD will be compared in a step-wise manner:

A non-inferiority testing approach will be applied first, using a non-inferiority margin of -10%. If non-inferiority is demonstrated, a superiority test will be applied using a superiority margin of 5%. Both tests will use a one-sided Type I error at 2.5% if the interim analysis at the end of Season 2 is not performed, and there is no need for multiplicity adjustment due to the step-wise approach.

The rVE of QIV-HD to QIV-SD will be estimated for primary endpoint as follows:

$$rVE = (1 - (C_{HD} / N_{HD}) / (C_{SD} / N_{SD})) \times 100\%$$

where:

- C_{HD} and C_{SD} are the numbers of influenza cases meeting the considered primary endpoint definition in the QIV-HD and QIV-SD groups, respectively.
- For analysis in PPASE, the first episode among those occurring more than 14 days after the last vaccination will be considered. For analysis in FASE, the first episode among those occurring more than 14 days after the first vaccination will be considered.
- If subject experiences multiple occurrences of the same endpoint, only the first episode will be considered
- N_{HD} and N_{SD} are the numbers of subjects in the QIV-HD and QIV-SD groups, respectively.

CIs for 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 rVE of QIV-HD will be considered as non-inferior to QIV-SD if the lower bound of the rVE is > -10%, and superior to QIV-SD if the lower bound of the CI for the rVE is > 5%. The PPASE will be used as the primary analysis set for the non-inferiority test and the FASE will be used as the primary analysis set for the superiority test.

If the interim analysis is conducted, an alpha spending method quoted by Lan and Demets (power family, phi=2) will be used to maintain an overall Type I error (the 'alpha') of 0.025 one-sided, considering that [redacted] of information time is reached at the time. Consequently, a one-sided nominal alpha of [redacted] will be used at interim and final analysis, respectively. This corresponds to [redacted] two-sided CIs to be used at interim and final analysis, respectively. If the interim analysis is not conducted or if the superior rVE is concluded at the interim analysis with the most stringent [redacted] threshold (ie, the stopping rule for superior efficacy is fulfilled), the final analysis will be performed with one-sided alpha of 0.025 without multiplicity adjustment.

A complementary analysis of comparing Kaplan-Meier curves between QIV-HD and QIV-SD groups for the primary endpoint will be performed for all subjects and stratified by age group and previous vaccination history:

- Start date: D0 (first vaccination date)
- Event date for subjects with a protocol-defined ILI is the start date of the first fever episode
- End date for subjects without a protocol-defined ILI is the last visit or contact date whichever is later

The non-inferiority test on the FASE and the superiority test on the PPASE will be performed as sensitivity analyses.

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

5.1.2.1 Hypotheses

Efficacy

Superior efficacy hypotheses for the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type using a more stringent margin threshold of [redacted] in subjects 6 months through 35 months of age (ie, the 1st secondary efficacy objective):

[redacted]

If all the above efficacy objectives are demonstrated, superior efficacy hypotheses for prevention of laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine in subjects 6 months through 35 months of age and the prevention of laboratory-confirmed influenza illness caused by any influenza A or B type in subjects 6 months through 23 months of age (ie, the 2nd and 3rd secondary efficacy objectives respectively):

H_0: rVE $\leq$ 0%

H_A: rVE > 0%

Immunogenicity

If all of the above confirmatory efficacy objectives are demonstrated, a superiority testing approach will be used to compare post-vaccination GMTs and seroconversion rates between QIV-HD and QIV-SD groups for each strain using a one-sided test with Type I error rate of 0.025 following the individual hypotheses:

Superiority for GMTs:

$$H_0^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{QIV-SD}} \leq 1 \Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{QIV-SD}) \leq 0$$

$$H_A^s : \frac{GMT^s_{QIV-HD}}{GMT^s_{QIV-SD}} > 1 \Leftrightarrow log_{10}(GMT^s_{QIV-HD}) - log_{10}(GMT^s_{QIV-SD}) > 0$$

Where: s is one strain in the quadravalent quadrivalent influezna vaccine (A/H1N1-like strain, A/H3N2-like strain, B/Victoria lineage-like strain, and B/Yamagata lineage-like stain)

$GMT_{QIV\text{-}HD}$ is the HAI GMT at 28 days after the last vaccination in QIV-HD group

$GMT_{QIV\text{-}SD}$ is the HAI GMT at 28 days after the last vaccination in QIV-SD group

Superiority for seroconversion where s is the strain:

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

Where: s is one strain in the quadravalent quadrivalent influenza vaccine (A/H1N1-like strain, A/H3N2-like strain, B/Victoria lineage-like strain, and B/Yamagata lineage-like stain)

π_{QIV-HD} is the seroconversion rate in QIV-HD group

π_{QIV-SD} is the seroconversion rate in QIV-SD group

5.1.2.2 Statistical Methods

Efficacy

If the primary objective is demonstrated, the secondary confirmatory objectives will be tested. A hierarchical testing combined with a graphical approach will be used to adjust the multiplicity of the 3 secondary confirmatory efficacy objectives, which prevents any inflation of the overall one-sided Type I error beyond 2.5%.

For the 1st secondary objective, a superiority test using a more stringent margin of [redacted] will be performed only after the primary objective is demonstrated. No multiplicity adjustment is needed, and the same nominal alpha levels for the primary objective being used in the interim analysis (ie, one-sided [redacted]) and in the final analysis (ie, one-sided [redacted] if the stopping rule for superior efficacy is not fulfilled at the interim analysis or one-sided 0.025 without adjustment if otherwise) will be used. The FASE will be used as the main analysis set and the same analysis on the PPASE will be performed as a sensitivity analysis.

Additional sensitivity analyses for the primary and 1st secondary objectives will be performed as follows using the same statistical method for the final analysis of the primary endpoint as detailed above:

- Excluding all siblings participating in the study to evaluate potential bias due to within-siblings flu contamination. For this, any subjects who had a sibling enrolled in this study will be excluded
- Considering the first ILI episode as defined in Section 4.4.3 but occurring from the first dose for the primary endpoint on the PPASE and FASE respectively

At the time of the final analysis, if superiority for the 1st secondary objective is demonstrated, a graphical approach of Holm with full alpha-propagation will be applied to control alpha within the 2nd and 3rd secondary efficacy objectives. If one of the 2nd and 3rd objectives is claimed for efficacy using a two-sided 97.5% CI, then the other one will be tested using a two-sided 95% CI to assess superiority. QIV-HD will be considered as superior to QIV-SD if the lower bound of the CI for the corresponding rVE is > 0%. Estimation of rVE for these two secondary efficacy objectives will be the same as those described for the primary objective above in Section 5.1.1.2. The FASE will be used as the main analysis set and the same analysis on the PPASE will be performed as a sensitivity analysis.

For the prevention of laboratory-confirmed influenza illness caused by viral strains similar to those contained in the vaccine in subjects 6 through 35 months of age, a secondary analysis using similarity based on genetic sequencing and an exploratory analysis using similarity based on antigenic similarity when available or genetic similarity otherwise will be performed.

For descriptive purposes, rVE and 95% CIs as calculated in Section 5.1.1.2 will be produced for each vaccine group for the following ILIs occurring ≥ 14 days after vaccination:

- laboratory-confirmed as positive for any influenza A or B type, in subjects according to their previous vaccination status
- laboratory-confirmed as positive for viral strains similar to those contained in the vaccine, in subjects according to their previous vaccination status
- laboratory-confirmed as positive for any influenza A or B type, and associated with AOM
- laboratory-confirmed as positive for viral strains similar to those contained in the vaccine, and associated with AOM
- laboratory-confirmed as positive for any influenza A or B type, and associated with ALRI
- laboratory-confirmed as positive for viral strains similar to those contained in the vaccine, and associated with ALRI
- PCR-confirmed as positive for any influenza A or B types
- PCR-confirmed as positive for viral strains similar to those contained in the vaccine
- culture-confirmed as positive for any influenza A or B types
- culture-confirmed as positive for viral strains similar to those contained in the vaccine
- laboratory-confirmed as positive for any influenza A or B type and associated with hospitalization
- laboratory-confirmed as positive for viral strains similar to those contained in the vaccine and associated with hospitalization

Immunogenicity

If the 3 secondary confirmatory efficacy objectives are demonstrated, superior immunogenicity will be considered. The ratios of HAI GMTs 28 days after last vaccination (D28/D56) will be obtained between vaccine groups with the two-sided 95% CIs calculated using normal approximation of log-transformed titers. The differences in the HAI seroconversion rates between vaccine groups will be computed along with the two-sided 95% CIs by the Wilson-Score method without continuity correction. If the superiority is demonstrated for post-vaccination GMTs and seroconversion rates for the 4 strains (ie, the two-sided 95% CIs all lie above 0), the immunogenicity of QIV-HD will be considered as superior to QIV-SD. The Full analysis set for immunogenicity (FASI) as defined in Section 5.2.5 will be used as the main analysis set.

For descriptive purposes, the statistics presented on **Error! Reference source not found.** will be produced for each vaccine group. All immunogenicity endpoints for HAI, SN and anti-NA will be summarized for each vaccine strain with 95% CIs in the Immunogenicity Analysis Set (IAS) as defined in Section 5.2.7 by season and by vaccine formulation if applicable.

The 95% CIs for the GMTs on D0 and 28 days after the last vaccination (D28/D56), and fold-rise as GM of Titers ratios (GMTRs) will be calculated using normal approximation of log-transformed titers.

The 95% CIs for the proportions (seroconversion rates and derived binary indicators) will be based on the Clopper-Pearson method.

Reverse cumulative distribution curves (RCDC) against each strain will be performed for baseline (D0) and post-vaccination immunogenicity (D28 or D56 as appropriate).

Subjects enrolled in both Season 1 and Season 3 (ie, the re-vaccination cohort) have 4 vaccine schedules: QIV-HD + QIV-HD, QIV-HD + QIV-SD, QIV-SD + QIV-HD and QIV-SD + QIV-SD. For re-vaccination response, immunogenicity endpoints based on HAI titers against the 4 strains used in Season 3 will be summarized descriptively in re-enrolled subjects in the Immunogenicity Subset in Season 3 (and by 4 vaccine schedules) and in subjects who are in the Immunogenicity Subset and only enrolled in Season 3 (and by each vaccine group).

Safety

Safety results will be described for each vaccine group with the statistics as presented on Table 5.1.

5.1.3 Statistical Methods for Observational Objectives

5.1.3.1 Observational efficacy endpoints

Estimation of efficacy for the observational objectives will be performed as described for the primary objective above, using the number of cases meeting each of the observational endpoint definitions; for each estimate of efficacy, a 95% CI will be calculated by an exact method conditional on the total number of cases in both groups.

5.1.3.2 ILI-associated with events and healthcare utilization

Events and healthcare utilization associated with cases of laboratory-confirmed influenza ILI caused by any viral type / subtype and with any ILI occurring within 30 days after the ILI onset will be presented for each vaccine group with statistics presented on Table 5.1.

5.1.3.3 [redacted]

[redacted]

[redacted]

5.1.3.4 Antibody persistence

For antibody persistence evaluation in the re-vaccination cohort, HAI titers against the 4 strains used in Season 1 will be summarized as described in Section 5.1.2.2 for immune response on HAI individual titer, titer ≥ 10 (1/dil), and ≥ 40 (1/dil) at D0 and 28 days after the last vaccination (D28/D56) of Season 1 and at D0 of Season 3. Seroconversion rate in Season 1 and individual titer ratio of D28/D56 over D0 in Season 1 and of D0 in Season 3 over D0 from Season 1 will be also presented.

5.1.4 Complementary analyses

5.1.4.1 Efficacy

The rVE will be displayed per factors such as by region / country, by sex, and by pre-defined baseline medical history (Yes or No), by breastfeeding (Yes or No) for subjects < 24 months of age and by vaccine formulation if applicable for the following efficacy endpoints:

- Primary endpoint: occurrence of ILI laboratory-confirmed as positive for any viral types / subtypes
- Occurrence of ILI laboratory-confirmed positive for viral strains similar to those contained in the vaccine (note: presented by age group and by season as well)

Similarity assessment and frequency distribution for laboratory-confirmed ILI based on ferret antigen and genetic sequencing will be summarized by vaccine group in the FASE.

5.1.4.2 Immunogenicity

For HAI immunogenicity endpoints as listed below per strain, analyses will be displayed per factors such as by region / country, by age group, by sex, by baseline serostatus (< 10 vs ≥ 10 [1/dil]), by previous influenza vaccination history, by vaccine formulation if applicable, and by baseline medical history.

- Individual HAI titer on D0 and 28 days after the last vaccination (D28/D56).
- Seroconversion
- Individual titer ratio: 28 days after the last vaccination (D28/D56) / D0.
- Subjects with titer ≥ 10 and ≥ 40 (1/dil) on D0 and 28 days after the last vaccination (D28/D56)

5.1.4.3 Safety

Solicited reactions within 7 days, unsolicited AEs within 28 days and SAEs including AESIs within 28 days after each vaccination and any vaccination as well as SAEs including AESI within 180 days from 28 days after the last injection will be presented by age group, by season, by region / country, by sex, by vaccine formulation if applicable, and by pre-defined baseline medical history.

5.2 Analysis Sets

Seven analysis sets will be used: the FASE, the PPASE, the Safety Analysis Set (SafAS), the ESafAS, the FASI, the Per-Protocol Analysis Set for Immunogenicity (PPASI), and the IAS.

5.2.1 Full Analysis Set for Efficacy

The FASE will be used for the analysis of all efficacy objectives and is defined as the subset of randomized subjects who received at least 1 dose of the study vaccine. Subjects will be analyzed as randomized.

5.2.2 Per-Protocol Analysis Set for Efficacy

- The PPASE is a subset of the FASE and will be used for primary and secondary efficacy objectives. The subjects presenting with at least one of the following conditions will be excluded from the PPASE:
- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule according to their previous vaccination history
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol

- For previously unvaccinated subjects, subject did not receive the 2nd injection in the proper time window (28 days to 38 days after first injection)
- Subject received non-study influenza vaccine between the 1st study vaccine and the end of surveillance
- Subject did not have at least one contact point more than 14 days after last vaccination and before the end of the surveillance period
- Any other deviation identified during the study conduct and identified as relevant by the clinical team during data review, eg, indicated as excluding subjects from this analysis set in the manual deviations dataset.

Of note, any cases between dose 1 and dose 2 for subjects receiving 2 doses will not be considered in the PPASE analysis.

In the event of a local or national immunization program with a pandemic influenza vaccine or other vaccine, subjects who receive 1 or more doses of pandemic influenza vaccine or other vaccine at any time during the study will not be withdrawn from the study.

Subjects will be analyzed as treated.

5.2.3 Safety Analysis Set

The SafAS will be used for SAEs / AESIs analyses and is defined as those subjects who have received at least one dose of the study vaccine(s). Of note, subjects in the Sentinel Safety Cohort and the Re-vaccination Cohort will be included in SafAS.

All subjects will be analyzed after each dose according to the vaccine they actually received, and after any dose according to the vaccine received at the 1st dose.

5.2.4 Expanded Safety Analysis Set

The ESafAS will be used for the analysis of solicited and unsolicited AEs. Subjects who received at least 1 dose of the study vaccine in the Sentinel Safety Cohort, all subjects in Season 1, subjects in Season 2 and 3 who are randomized into the ESafAS, and the Re-vaccination Cohort in Season 3 will be included in the ESafAS.

All subjects will have their safety analyzed after each dose according to the vaccine they actually received, and after any dose according to the vaccine received at the first dose.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

5.2.5 Full Analysis Set for Immunogenicity

The FASI will be used as the main analysis set for secondary superior immunogenicity objective and is defined as the subjects randomized in the Immunogenicity Subset in Season 1 who received at least one dose of the study vaccine and had one post-vaccination blood sample. Subjects will be analyzed as randomized.

5.2.6 Per-Protocol Analysis Set for Immunogenicity

The PPASI is a subset of the FASI and will be used for secondary superior immunogenicity objective as a sensitivity analysis. The subjects presenting with at least one of the following conditions will be excluded from the PPASI:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule according to their previous vaccination history
- Subject received a vaccine other than the one that he / she was randomized to receive
- Preparation and / or administration of vaccine was not done as per-protocol
- For previously unvaccinated subjects, subject did not receive the 2nd injection in the proper time window (28 days to 38 days after first injection)
- Subject did not provide post-dose serology samples in the proper time window (28 days to 38 days after last vaccination)
- Subject received concomitant treatment that may affect the immunogenicity[1] or a non-study influenza vaccine prior to the post-vaccination blood sample
- Any other deviation identified during the study conduct and identified as relevant by the clinical team during data review, eg, indicated as excluding subjects from this analysis set in the manual deviations dataset.

In the event of a local or national immunization program with a pandemic influenza vaccine or other vaccine, subjects who receive 1 or more doses of pandemic influenza vaccine or other vaccine at any time during the study will not be withdrawn from the study.

Subjects will be analyzed as treated.

5.2.7 Immunogenicity Analysis Set

The IAS will be used for all descriptive immunogenicity objectives and is defined as the subjects in the main cohort randomized in the Immunogenicity Subset in Seasons 1, 2, and 3 and the subjects in the Re-vaccination Cohort in Season 3 who received at least one dose of the study vaccine and had one post-vaccination blood sample. Subjects will be analyzed as treated.

For analysis of immunogenicity by SN and ELLA methods, the subset of IAS with available results on the considered serological method will be used.

For correlate of protection assessment, subjects who are part of both the IAS and the FASE will be considered.

[1] other vaccines, blood products, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors

5.2.8 Other Analysis Set(s)

Randomized subjects

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

Subjects with data in CRF

Subjects with data in CRF are subjects for whom data were recorded at a visit (except screening).

5.2.9 Populations Used in Analyses

The primary and secondary efficacy analyses with hypotheses tests will be performed on the PPASE and all the efficacy analyses will be performed on the FASE. The PPASE will be the main analysis set for the non-inferior efficacy analysis and the FASE will be the main analysis for all the superior efficacy analyses.

The secondary immunogenicity analysis for superiority testing will be performed on the FASI and will be confirmed on the PPASI. The secondary analyses for the immunogenicity descriptive assessment will be performed on the IAS.

The analyses of efficacy endpoints for observational objectives and ILI-associated symptoms / events will be performed on the FASE. Analyses of antibody persistence and re-vaccination response will be performed on a subset of IAS enrolled in Seasons 1 and 3 and with blood samples drawn in both seasons.

In addition to the ones above, other analysis sets will be taken into account in the description of the population (eg, the disposition, the demographic, or baseline characteristics).

5.3 Handling of Missing Data and Outliers

Kaplan-Meier plots of the dropouts across time will be provided by vaccine groups and reason for the drop-out for each season on the randomized subjects to explore the missing frequency and pattern due to early withdrawal.

5.3.1 Efficacy

Subjects who discontinued from the study without developing an ILI will be included number of subjects in each vaccine group (ie, N_{HD} or N_{SD}) for the calculation of rVE and its CI for all efficacy objectives. To assess the impact of missing data due to early withdrawal on number of cases in each vaccine group (ie, C_{HD} and N_{SD}), the tipping point analysis (17) will be performed in the FAS. The considered approach will analyze all possible combinations of missing cases that may occur in both vaccine groups

In addition, for primary endpoint if the attrition rate for PPASE is > 10%, a time-to-event analysis will be conducted to address the possible imbalance in the drop-out rates between vaccine groups. Cox proportional hazards model will be used for the comparison of the hazard rates between the 2 vaccine groups. If the assumption of proportional hazards (based on Schoenfeld residuals) is violated, a stratified Cox model by season and age group will be computed.

5.3.2 Immunogenicity

For the secondary confirmatory immunogenicity objective, the missing immunogenicity data will not be imputed. If the degree of missing immunogenicity data in the FASI is unexpectedly high (more than 10%) on HAI data for at least one strain, a sensitivity analysis with multiple imputation methods will be performed. For each missing value, a set of 5 plausible values will be produced based on their predicted distribution, using D0 titer, previous vaccination history against influenza, site and age (as a continuous variable) as covariates.

Number of available subjects for the descriptive summary of immunogenicity response for each strain will be calculated as number of subjects who are in the IAS with available HAI titers, or as number of a subset of the IAS who are randomized to have SN assay or ELLA with available SN or anti-NA titers respectively at the timepoint indicated. No imputation will be performed.

No test or search for outliers will be performed.

5.3.3 Safety

No search for outliers will be performed. In all subject listings, partial and missing data will be clearly indicated as missing.

5.3.3.1 Immediate

Generally, no replacement will be done unless specified otherwise. For unsolicited systemic AEs, a missing response to the “Immediate” filed is assumed to have occurred after the 30-minutes surveillance period and will not be imputed.

5.3.3.2 Causality

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions. Missing relationship to vaccine for unsolicited AEs will be considered at the time of analysis as related.

5.3.3.3 Measurements

Partial missing temperatures and measurements too large to measure will be handled as described in Section 4.4.1.1.1.

5.3.3.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

5.3.3.5 Start Date and End Date

Missing or partially missing start dates for unsolicited AEs (including SAEs) will remain missing and not be imputed, and the time of onset will be considered as missing. Nevertheless unsolicited AEs with missing time of onset will be included in analyses according to the visit collected.

Missing or partially missing end dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

5.4 Interim / Preliminary Analysis

5.4.1 Early Safety Data Review

An initial safety review is planned when the first 100 subjects are enrolled in a sentinel safety cohort. All 100 participants will receive QIV-HD (in this open-label cohort, no comparator vaccine will be administered). After the sentinel safety cohort has been vaccinated and has provided safety data for D0-D7 post-vaccination, an IDMC will convene and review the safety data. During this review, enrollment will be paused. Following a satisfactory safety review by the IDMC, enrollment of subjects will resume in Season 1 (2021-2022 NH).

The safety data collected will be entered into the CRB and will be summarized and reviewed by the Sponsor in a blinded manner. It is understood that this review is based on preliminary data that have not been subject to validation and database lock. The usual and ongoing process of monitoring safety signals outside of those specified in the protocol-defined early safety data review (ESDR) will continue unchanged. No hypothesis testing will be performed for the ESDR therefore the adjustment for alpha is not necessary.

The following safety parameters will be assessed as part of the ESDR review of the sentinel safety cohort in an unblinded manner by the IDMC. They will be collected during a period of 7 days after the vaccination:

- Immediate reactions
- Solicited injection site and systemic reactions
- Unsolicited AEs
- SAEs (including AESIs)

Enrollment will be paused during the IDMC review, and the data will be examined for the following occurrences:

- An SAE (including AESIs) considered as related to the vaccination by the Investigator and Sponsor
- > 10% of subjects experiencing Grade 3 fever within 7 days after vaccination

If any of the above criteria are met, a decision will be made by the IDMC as to whether enrollment in the study will be allowed to resume.

5.4.2 Safety Review at the End of Season 1

At the completion of the collection of safety data at the end of Season 1, the IDMC will be convened to review the safety data of participants in Season 1. Unblinding will be performed by

an independent statistician for the IDMC. Enrollment will not be paused during this IDMC review. Details of safety analyses will be in a separate interim SAP.

No statistical adjustment for alpha is necessary as no hypotheses will be tested.

5.4.3 Trigger for Planning of Extension to Season 4

The likelihood of achieving the expected [redacted]per-protocol lab-confirmed influenza cases for the primary endpoint at the end of the Season 3 will be assessed using the weekly number of reported ILI in the CRB (laboratory positivity for influenza need not have been confirmed yet) available in Season 3. It is assumed that after the peak number in the same season occurs the weekly number of reported ILI is exponentially distributed in a monotonically decreasing manner. An exponential regression curve will be plotted to forecast the weekly number of reported ILI until the end of the surveillance period in Season 3. Then, the predicted number of per-protocol cases for the primary endpoint at the end of Season 3 will be calculated as follows:

1) Calculate the total number of future ILI until the end of Season 3 based on weekly number of future ILI as forecast above
2) Multiply the positivity factor estimated from Season 1 to obtain the total number of future cases for the primary endpoint where the positivity factor is the number of cases for the primary endpoint divided by the number of ILI (Note: Season 2 data may be considered for a more conservative prediction)
3) Multiply the per-protocol factor estimated from the observed cases (ie, the number of per-protocol cases divided by the total number of cases for the primary endpoint)
4) Add the number of per-protocol cases already observed in the study

If laboratory results are available during this analysis, then observed cases for the primary endpoint in Season 3 will be used directly for the prediction using exponential regression.

Epidemiological data of influenza occurrence may be taken into count for the prediction of weekly number of reported influenza cases for the remaining season.

If the predicted total number of per-protocol cases for the primary endpoint is no less than [redacted] cases, there is still an [redacted] power to demonstrate the superior efficacy using the [redacted] threshold based on a one-sided alpha of 2.5%. If the predicted number is less than [redacted]cases, then the planning of a study extension to Season 4 is triggered. If this were to occur, then the total number of subjects needed to demonstrate superior efficacy based on the [redacted] superiority threshold, assuming [redacted] rVE of QIV-HD to QIV-SD, will be calculated using the overall attack rate observed in 3 seasons (if needed, the attack rate based on the predicted number of case in Season 3 can be used) .

Since this blinded sample size re-estimation is based on the total number of evaluable cases in both vaccine groups without using vaccine assignment, no bias can be introduced and the Type I error is well-controlled at the nominal value.

5.4.4 Interim Analysis for Efficacy

Following the end of Season 2, if the predicted total number of per-protocol cases for the primary endpoint as estimated in Section 5.4.3 is less than [redacted] cases, and if at least [redacted] per-protocol influenza cases meeting the primary endpoint have occurred (ie, at least [redacted] information time), an interim analysis for efficacy is planned to be conducted by an independent statistician and reviewed by the IDMC during Season 3.

If either of the 2 conditions is not met, the proposed interim analysis for efficacy will not be performed and the alpha will be not be adjusted at the final analyses.

The data cleaning for this interim analysis if conducted will focus on critical data for vaccine efficacy assessment involved in analysis sets and primary endpoint definitions: protocol deviations, ILI occurrence, and laboratory results.

At the interim analysis, the primary objective and first secondary objective will be assessed using

- the statistical methods described in Section 5.1.1.2 to demonstrate the primary and first secondary objectives. Note: fixed one-sided alpha of [redacted] will be used regardless of the observed total number of evaluable cases at the time of interim analysis, and the overall Type I error is not inflated (Appendix 1. Overall Type I error using a fixed alpha value for interim efficacy analysis).
- the predictive power as described below in Section 5.4.4.1 for the probability to demonstrate these objectives at the end of the ongoing Season 3 based on the and at the end of the study (ie, with [redacted] evaluable cases for the primary endpoint).

The IDMC may recommend stopping the study at the end of Season 3 if the primary and first secondary objectives are demonstrated (ie, the stopping rule for superior efficacy is fulfilled), if there is a high probability to demonstrate these objectives at the end of Season 3, or for futility if the probability to demonstrate the primary objective at the end of study is too low. In any case, the study will not stop before the 3 influenza seasons are completed. The IDMC will inform the Sponsor Executive Board of the recommendation, and then the Executive Board makes decision for stopping or not, taking the epidemiology data and relevant external data if available into account. In particular, a stopping for futility recommendation from the IDMC is a guideline that may or may not be followed depending on the totality of the available interim results. Therefore, the futility rule is not binding to the conduct and conclusion of the study (18).

The clinical study team will not be made aware of the IDMC's recommendations until the final database lock and unblinding at the end of Season 3. The clinical study team, the investigators, and study subjects will remain blinded until the end of the study. In addition, no modification will be allowed to the study conduct after this interim analysis. Information on organizational aspects, roles, responsibilities, data flow, and communication with the IDMC will be detailed in the IDMC charter.

In addition, at the time of the interim analysis, other efficacy and safety objectives may be assessed on the available data for information. These will be detailed in a separate SAP for the IDMC.

5.4.4.1 Predictive Power

Bayesian predictive power (19) with the non-informative uniform prior [Uniform (0, 1)] will be used for the calculation of the probability, conditional on the interim results, to conclude at the end of Season 3 and at the end of study. The Bayesian posterior distribution is determined using the results of interim analysis (likelihood data assuming the number of cases in QIV-HD group is binomially distributed conditional to the total number of cases in both vaccine groups) combined with the uniform prior distribution. Detailed statistical method for the predictive power is in Appendix 2. Bayesian Predictive Power.

If the superiority based on the [redacted] margin is not demonstrated at the interim analysis, the predictive power at the end of Season 3 will be calculated based on the predicted total number of per-protocol cases for the primary endpoint at the end of Season 3 using the available data at the time of interim analysis (Note: this total number of cases may be different from the trigger for the planning of extension to Season 4), the lower bound of the CI of rVE for the primary endpoint > [redacted] and one-sided alpha of [redacted]:

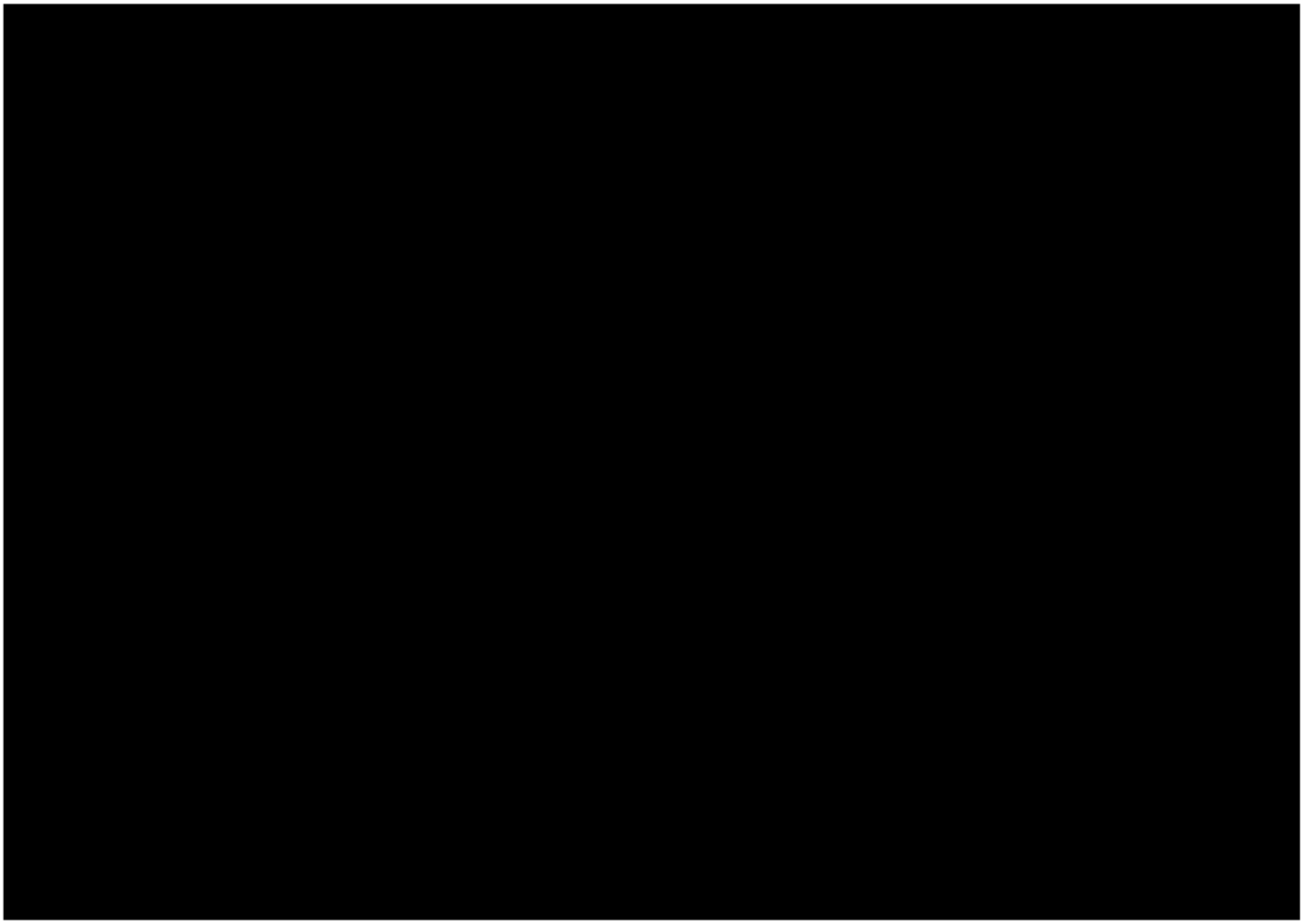
[redacted]

The thresholds above have been selected to limit the risk to stop the study by chance and to avoid study extension in case the primary and first secondary objectives cannot be demonstrated at interim analysis or the planned [redacted] evaluable cases for the primary endpoint cannot be achieved in 3 seasons.

5.4.4.2 IDMC Recommendation

Figure 5.1 illustrates the rules for IDMC recommendation based on the results of interim analyses and Sponsor's action upon the recommendation. More details will be made available in a separate SAP for IDMC and IDMC charter.

Figure 5.1: [redacted]



5.5 Determination of Sample Size and Power Calculation

A total of approximately 13,320 subjects will be enrolled: 100 subjects will be enrolled in the 2020-2021 NH influenza season in the open-label Sentinel Safety Cohort and 13,220 subjects in the main cohort will be enrolled over 3 subsequent influenza seasons with a randomization ratio of 1:1 for QIV-HD to QIV-SD.

Table 5.2: Planned sample size by vaccine and influenza season

Vaccine	Number of Subjects		
QIV-HD for open-label, Sentinel Safety Cohort	**100**		
Vaccine	**Season 1 (NH)**		
	Randomized	**Immunogenicity Subset**	**Expanded safety analysis set (ESafAS)**
QIV-HD	[redacted]		
QIV-SD			
Total			
Vaccine	**Season 2 (SH)**		
	Randomized	**Immunogenicity**	**Expanded safety AS)**
QIV-HD	[redacted]		
QIV-SD			
Total			
Vaccine	**Season 3 (NH)**		
	Randomized	**Immunogenicity Subset**	**Expanded safety analysis set (ESafAS)**
QIV-HD	[redacted]		
QIV-SD			
Total			
Vaccine	**Season 3 (NH) Re-vaccination Cohort†**		
	Randomized	**Immunogenicity**	**Expanded safety S)**
QIV-HD	[redacted]		
QIV-SD			
Total			
Overall Total	**13,320 subjects with [redacted] tested for immunogenicity*, [redacted] for expanded safety, and 100 sentinel safety cohort subjects**		

Abbreviations: NH, Northern Hemisphere; QIV-HD, high-dose quadrivalent influenza vaccine ; QIV-SD, standard-dose quadrivalent influenza vaccine ; SH, Southern Hemisphere

* Number of subjects who provide blood samples in Season 1 (NH) is greater than in Season 2 (SH) or Season 3 (NH) because unlike the Season 2 and 3 sera, which will be used for the descriptive immunogenicity results and [redacted], Season 1 (NH) sera will also be used to demonstrate immunogenicity superiority.

† Approximately [redacted] subjects from the Immunogenicity Subset of Season 1 (NH) will re-enroll in Season 3 (NH) to be evaluated for antibody persistence and re-vaccination immunogenicity endpoints. These subjects will not be part of the approximately [redacted] subjects in Season 3 who are being followed for ILI surveillance and efficacy.

Table 5.3: Samples sizes for evaluation based on assessment method

Assessment Method	Number of Subjects
hemagglutination inhibition (HAI)	approximately [redacted] subjects (all subjects in the Immunogenicity Subset)
seroneutralization (SN)	approximately [redacted] subjects in Season 1's Immunogenicity Subset
enzyme-linked lectin assay (ELLA)	Approximately [redacted] subjects in Season 1's Immunogenicity Subset

5.5.1 For efficacy assessments:

The sample size needed for the assessment of the primary objective of the study is expected to be approximately [redacted] subjects and may be adjusted based on the blinded number of cases in order to maintain the likelihood of achieving approximately [redacted] evaluable influenza cases from the PPASE meeting the primary endpoint.

These required numbers of evaluable influenza cases would provide at least [redacted] power at final analysis to conclude on the primary objective under the following assumptions:

- The true rVE of QIV-HD to QIV-SD is [redacted]
- An overall one-sided Type I error rate 0.025 ([redacted] spent at interim and final analysis, respectively)
- The lower bound of the CI of rVE should be > 5%
- An allocation ratio of QIV-HD to QIV-SD of 1:1
- An overall influenza attack rate of [redacted] for the occurrence of an influenza case in the QIV-SD group (equivalent to an attack rate of [redacted] across QIV-HD and QIV-SD groups in the PPASE given total number of evaluable cases is [redacted])
- [redacted] of enrolled subjects evaluable for the primary endpoint

Based on the same assumptions and using a more stringent [redacted] threshold, the power for the first secondary objective at final analysis is expected at approximately [redacted]

If there is a need to extend the study to Season 4, number of subjects required will be re-calculated in a blinded manner. By way of illustration,

> If the overall attack rate across 2 vaccine groups is [redacted], to demonstrate the superior efficacy of QIV-HD over QIV-SD with the lower bound of [redacted] CIs > [redacted] and approximately [redacted] power assuming the true rVE of QIV-HD to QIV-SD is [redacted], 1:1 allocation ratio and [redacted] of enrolled subjects evaluable the total number of subjects required is [redacted] Additional [redacted] subjects will be enrolled in Season 4. At the end of Season 4, [redacted] cases would be expected to have occurred.

At least [redacted] evaluable laboratory-confirmed influenza cases will be required for the interim analysis to be conducted. Such a number of cases would provide a power of approximately [redacted],

[redacted] to demonstrate up to the first secondary objective if the vaccine efficacy is [redacted] respectively, using one-sided alpha of [redacted].

For the assessment of the 2nd and 3rd confirmatory secondary efficacy objectives, the assumptions will be similar to those for primary objective except

- The lower bound of the CI for the corresponding rVE will be superior to 0%.
- The true rVE of QIV-HD to QIV-SD is [redacted] for each subset (ie, subjects 6 through 35 months of age against similar strains and subjects 6 through 24 months of age against any strains)
- [redacted] evaluable influenza cases ([redacted] of total cases) from each subset

For each objective, a [redacted] power will be achieved with a two-sided 97.5% CI and an [redacted] power will be achieved with a two-sided 95% CI.

5.5.2 For the immunogenicity assessments:

Approximately [redacted] subjects will be assessed for HAI immunogenicity in Season 1. Based on Phase II immunogenicity results from QHD04 and assuming [redacted] of non-evaluable subjects, with [redacted] evaluable subjects ([redacted] in each vaccine group), the study will have an overall [redacted] power to demonstrate the superiority for both HAI GMTs and seroconversion rates comparing QIV-HD to QIV-SD for all 4 strains with 1:1 allocation ratio (Table 5.4). The superiority margin is defined as 1 for GMTR and 0 for seroconversion rates for all 4 strains. The adjustment for alpha is not needed as the superiority for immunogenicity is concluded only when the superiority is demonstrated in both HAI GMTs and seroconversion rates for all 4 strains.

Table 5.4: Power to demonstrate superiority for immunogenicity

Strain	Endpoint	Estimates		Power (%)
		Expected seroconversion rate in QIV-HD	Expected seroconversion rate in QIV-SD	
A/(H1N1)-like strain	Seroconversion rate	[redacted]		
A/(H3N2)-like strain	Seroconversion rate			
B/(Victoria lineage)-like strain	Seroconversion rate			
B/(Yamagata lineage)-like strain	Seroconversion rate			
		Expected GMT ratio (QIV-HD/QIV-SD)	Expected SD (log10 titer)	
A/(H1N1)-like strain	GMT	[redacted]		
A/(H3N2)-like strain	GMT			
B/(Victoria lineage)-like strain	GMT			
B/(Yamagata lineage)-like strain	GMT			
Overall power				[redacted]

5.6 Data Review for Statistical Purposes

A blind review of the data is anticipated through the data review process led by data management before database lock. This review of the data includes a statistical review.

Number of evaluable cases for the hypothesis tests to demonstrate primary and secondary objectives will be closely monitored in a blinded manner throughout the study, and exclusion from the FASE, PPASE, FASI, and PPASI will be summarized in an aggregated way and reviewed by the clinical study team.

5.7 Changes in the Conduct of the Study or Planned Analyses

Not applicable.

6 References List

1. Munoz FM. The impact of influenza in children. Semin Pediatr Infect Dis. 2002;13(2):728.
2. Peltola V, Ziegler T, Ruuskanen O. Influenza A and B virus infections in children. Clin Infect Dis. 2003;36(3):299-305.
3. Antonova EN, Rycroft CE, Ambrose CS, Heikkinen T, Principi N. Burden of paediatric influenza in Western Europe: a systematic review. BMC Public Health. 2012;12:968.
4. World Health Organization 2012 Vaccines against influenza WHO position paper - November 2012. Wkly Epidemiol Rec. 87 461-76.
5. World Health Organization. (2019). Global influenza strategy 2019-2030. World Health Organization. https://apps.who.int/iris/handle/10665/311184.
6. Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev. 2018;(2):CD004879.
7. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA. 2003;289(2):179-86.
8. Chang LH, Meng Y, Jasosczyk H, Landolfi V, Talbot HK, QHD00013 Study Group. Safety and immunogenicity of high-dose quadrivalent influenza vaccine in adults greater than or equal to 65 years of age: A phase 3 randomized clinical trial. Vaccine. 2019;37(39):5825-34.
9. Halasa NB, Gerber MA, Berry AA, Anderson EL, Winokur P, Keyserling H, et al. Safety and immunogenicity of dull-dose trivalent inactivated influenza vaccine (TIV) compared with half-dose TIV administered to children 6 through 35 months of age. J Pediatric Infect Dis Soc. 2015;(3):214-24.
10. Safety and Immunogenicity of Fluzone® Quadrivalent Vaccine Administered to Healthy Children. [homepage on the Internet]. U.S. National Library of Medicine; [updated 2018 April 03; cited 2019 Oct 26] Available from https://clinicaltrials.gov/ct2/show/NCT02915302.
11. An Efficacy Study of GlaxoSmithKline (GSK) Biologicals' Candidate Influenza Vaccine GSK2321138A in Children [homepage on the Internet]. U.S. National Library of Medicine; [updated 2018 September 26; cited 2019 Oct 26] Available from https://clinicaltrials.gov/ct2/show/NCT01439360.
12. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat in Med. 1998;17:857-72
13. Qin L, Gilbert PB, Corey L, McElrath MJ, Self SG. A framework for assessing immunological correlates of protection in vaccine trials. J Infect Dis 2007;196:1304-12
14. Huang J, Huang B. Evaluating the proportion of treatment effect explained by a continuous surrogate marker in logistic or probit regression models. Stat Biopharm Res 2010; 2:229-38
15. Hosmer DW, Lemeshow S. Applied Logistic Regression. New York: Wiley. 2013, Third edition
16. Barlow WE. Robust variance estimation for the case-cohort design. Biometrics. 1994;50:1064–72

17. Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. J Biopharm Stat. 2009;19:1085-98.
18. Adaptive designs for clinical trials of drugs and biologics guidance for industry. US FDA Nov 2019
19. Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. Chapman and Hall/CRC. 2000.

7 Appendices

Appendix 1. Overall Type I error using a fixed alpha value for interim efficacy analysis

An alpha spending method quoted by Lan and Demets (power family, phi=2) is used to maintain an overall Type I error (the 'alpha') of 0.025 one-sided, assuming [redacted] of information time is reached at the time of interim analysis. Consequently, one-sided nominal alpha values of [redacted] at interim and [redacted] at final analysis (corresponding to [redacted] two-sided CIs respectively) are used for the sample size calculation as detailed in Section 5.5.1.

At the time of interim analysis if conducted, fixed one-sided alpha value of [redacted] will be used regardless of the observed total number of evaluable cases. The overall Type I error is not inflated using fixed alpha value at interim analysis as demonstrated in the following.

Let x_v^1, x_c^1, x_T^1 denote the observed number of cases at interim analysis in vaccine, control and both groups ($x_T^1 = x_v^1 + x_c^1$) and let n_v^1, n_c^1 denote the number of subjects in vaccine and control groups at interim analysis. Similarly, let x_v^2, x_c^2, x_T^2 denote the future number of new cases to be observed in the remaining part of the study and let n_v^2, n_c^2 denote the number of subjects in vaccine and control groups in the remaining part of the study. Assuming the number of cases in vaccine group is binomially distributed conditionally on the total number of cases at the interim analysis and for the remaining of the study, ie, $X_v^1 \sim B(q, x_T^1)$, $X_v^2 \sim B(q, x_T^2)$

Given that $VE = 1 - \frac{x_v^1/n_v^1}{x_c^1/n_c^1} = 1 - \frac{(x_v^1+x_v^2)/(n_v^1+n_v^2)}{(x_c^1+x_c^2)/(n_c^1+n_c^2)}$, and in this study $n_v^1 = n_c^1$, $n_v^2 = n_c^2$, $q = \frac{x_v^1}{x_v^1+x_c^1} = \frac{x_v^1+x_v^2}{x_v^1+x_v^2+x_c^1+x_c^2} = \frac{1-VE}{2-VE}$

$$Pr(X_v^1 = x_v^1 | q, x_T^1) = C_{x_T^1}^{x_v^1} q^{x_v^1} (1-q)^{x_c^1} \quad (1)$$

$$Pr(X_v^2 = x_v^2 | q, x_T^2) = C_{x_T^2}^{x_v^2} q^{x_v^2} (1-q)^{x_c^2}$$

$$Pr(X_v^1 + X_v^2 = x_v^1 + x_v^2 | q, x_T^1 + x_T^2) = C_{x_T^1}^{x_v^1} q^{x_v^1} (1-q)^{x_c^1} C_{x_T^2}^{x_v^2} q^{x_v^2} (1-q)^{x_c^2} \quad (2)$$

Based on the above formula, the overall Type I error to reject the null hypothesis (H_0: rVE ≤ VE_0) at the interim analysis and at the end of the trial where VE_0 is the pre-specified superiority margin, is obtained as follow:

1. Compute [redacted] two-sided confidence interval of rVE (ie, one-sided alpha of [redacted] for the interim analysis) for every combination of (x_v^1, x_c^1).
2. If the lower bound of the confidence interval of rVE is greater than VE_0, for the considered combination the null hypothesis is rejected.
3. The Type I error at the interim analysis is then the sum of the probability calculated in equation (1) over the set of all combination of cases for which the null hypothesis is rejected.
4. Compute [redacted] two-sided confidence interval of rVE (ie, one-sided alpha of [redacted] for the final analysis at the end of the study) for every combination of $(x_v^1 + x_v^2, x_c^1 + x_c^1)$.

5. If the lower bound of the confidence interval of rVE as calculated in step 1 is less than or equal to VE_0 and the lower bound of the confidence interval as calculated in step 4 is greater than the pre-specified margin, for the considered combination of $(x_v^1,\ x_c^1,\ x_v^2,\ x_c^2)$ the null hypothesis is rejected.
6. The Type I error at the final analysis is then the sum of the probability calculated in equation (2) over the set of all combination of cases for which the null hypothesis is rejected as in step 5.
7. The overall Type I error for the study is the sum of Type I error at the interim and final analyses.

Table 7.1 details the calculated overall Type I error for the study using fixed alpha values of [redacted] at the interim analysis and [redacted] at the final analysis based on total number of evaluable cases available at interim analysis increasing from [redacted]

Table 7.1: The overall Type I error using fixed alpha values

Total number of cases at interim	Information time (%)	Overall Type I error [redacted]	Overall Type I error rVE=5% and VE_0=5%
[redacted]			

Appendix 2. Bayesian Predictive Power

One method to perform the futility analysis is the Bayesian predictive power which can be interpreted as the probability of rejecting the null hypothesis at the end of the trial conditional on the interim data.

Let x_v^1, x_c^1, x_T^1 denote the observed number of cases at interim in vaccine, control and both group ($x_T^1 = x_v^1 + x_c^1$). Similarly, let x_v^2, x_c^2, x_T^2 denote the future number of new cases to be observed in the remaining part of the trial.

Bayesian posterior distribution

Assuming the number of cases in vaccine group is binomially distributed conditionally on the total number of cases in both group, the likelihood of the data at interim is:

$$f(x_v^1|P, x_T^1) = C_{x_T^1}^{x_v^1} P^{x_v^1}(1-P)^{x_c^1}$$

Based on Bayes's theorem, the Bayesian posterior distribution is then determined using the results of the interim analysis (likelihood data) combined with the prior (generally uniform) as follows:

$$f(P|x_v^1, x_T^1) = \frac{f(x_v^1|P, x_T^1)f(P)}{f(x_v^1|x_T^1)}$$

where $f(P) = 1$ (prior uniform) for $P \in [0,1]$;

$$f(x_v^1|x_T^1) = \int_0^1 f(x_v^1|P, x_T^1)f(P)dP = \int_0^1 C_{x_T^1}^{x_v^1} P^{x_v^1}(1-P)^{x_c^1}\, dP = C_{x_T^1}^{x_v^1} \frac{\Gamma(x_v^1+1)\Gamma(x_c^1+1)}{\Gamma(x_T^1+2)}$$

Therefore,

$$f(P|x_v^1, x_T^1) = \frac{f(x_v^1|P, x_T^1)f(P)}{f(x_v^1|x_T^1)} = \frac{\Gamma(x_T^1+2)}{\Gamma(x_v^1+1)\Gamma(x_c^1+1)} P^{x_v^1}(1-P)^{x_c^1}$$

Predictive distribution

The predictive distribution gives the probability distribution of the future cases in vaccine group occurring until the end of the trial:

$$Pr(X_v^2 = x_v^2|x_v^1, x_T^1) = \int_0^1 Pr(X_v^2, P|x_v^1, x_T^1)dP = \int_0^1 Pr(X_v^2 = x_v^2|P)\, f(P|x_v^1, x_T^1)dP$$

where $Pr(X_v^2 = x_v^2|P)$ is the likelihood of the future data:

$$Pr(X_v^2 = x_v^2|P) = C_{x_T^2}^{x_v^2} P^{x_v^2}(1-P)^{x_c^2}$$

$f(P|x_v^1, x_T^1)$ is the posterior distribution previously defined:

$$f(P|x_v^1, x_T^1) = \frac{\Gamma(x_T^1+2)}{\Gamma(x_v^1+1)\Gamma(x_c^1+1)} P^{x_v^1}(1-P)^{x_c^1}$$

Put everything together, the predictive distribution of the future cases in vaccine group occurring in the trial conditional on the observed interim data is:

$$Pr(X_v^2 = x_v^2 | x_v^1, x_T^1) = \int_0^1 Pr(X_v^2 = x_v^2 | P)\, f(P | x_v^1, x_T^1) dP$$
$$= \int_0^1 C_{x_T^2}^{x_v^2} P^{x_v^2} (1-P)^{x_c^2} \frac{\Gamma(x_T^1 + 2)}{\Gamma(x_v^1 + 1)\Gamma(x_c^1 + 1)} P^{x_v^1} (1-P)^{x_c^1} dP$$
$$= C_{x_T^2}^{x_v^2} \frac{\Gamma(x_T^1 + 2)}{\Gamma(x_v^1 + 1)\Gamma(x_c^1 + 1)} \int_0^1 P^{x_v^2 + x_v^1} (1-P)^{x_c^2 + x_c^1} dP$$
$$= C_{x_T^2}^{x_v^2} \frac{\Gamma(x_T^1 + 2)}{\Gamma(x_v^1 + 1)\Gamma(x_c^1 + 1)} \frac{\Gamma(x_v^1 + x_v^2 + 1)\Gamma(x_c^1 + x_c^2 + 1)}{\Gamma(x_T^1 + x_T^2 + 2)}$$

Bayesian predictive power

Based on the above formula, the predictive probability of rejecting the null hypothesis at the end of the trial, the Bayesian predictive power, is then obtained by integrating the predictive distribution over a pre-defined region of future cases, on which the overall data will lead to reject the null hypothesis, as follow:

- To obtain x_T^f ($x_T^f = x_T^1 + x_T^2$) (a total number of cases for the final analysis) from x_T^1 (the total cases are observed at interim), and x_T^2 (the total future new cases are needed during remaining part of the trial)
- The future cases x_T^2 are split into the vaccine and placebo group (x_v^2, x_c^2), all combinations of (x_v^2, x_c^2) are determined with the associated predictive probability.
- The cases in each group obtained at the interim look are pooled with the future cases given the following combination ($x_v^1 + x_v^2,\ x_c^2 + x_c^2$), the vaccine efficacy and the associated confidence interval is determined for each combination. For the considered combination the null hypothesis (H_0: rVE≤ VE_0) is rejected if the lower bound of the confidence interval is greater than VE_0 where VE_0 is the pre-specified superiority margin.
- The Bayesian predictive power is then the sum of the predictive probability over the set of all combination of cases for which the null hypothesis is rejected at end of the trial.