Sponsor: Sanofi Pasteur **Drug substance(s):** Quadrivalent Influenza Vaccine (Split Virion, Inactivated) High-Dose (QIV-HD)	**Study Identifiers:** Eudra CT number: 2019-004721-24 WHO UTN: U1111-1243-5993 MX CTA: MX 203301410A0141/2021 BB-IND: 017556 **Study code:** QHD00014

Title of the study:
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

Study center(s):
Sentinel Safety Cohort was conducted at 10 sites in the US.

Study period:
Date first study participant enrolled: 15 Sep 2020
Date last study participant completed: 02 June 2021
Study Status: Terminated. The study was interrupted after the Sentinel safety cohort due to COVID-19 pandemic and was terminated due to new changes to the recommendations for flu vaccines.

Phase of development: Phase 3

Objectives:
Primary objectives:
Efficacy objective

- 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.

Secondary objectives:
Confirmatory Efficacy 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.

Methodology:
QHD00014 was planned to be a Phase III, randomized, modified double-blind, active-controlled, multi-center efficacy study to be conducted in children 6 months through 35 months. Subjects were to be enrolled in the following cohorts:
Sentinel Safety Cohort: The first 100 US subjects were enrolled during 2020-2021 NH influenza season in an open-label design without a comparator vaccine. All Sentinel subjects were assigned to receive QIV-HD according to their influenza vaccination history (described in Vaccination section below). The Sentinel Safety Cohort subjects did not provide blood samples and were not to be followed for influenza-like illness (ILI) surveillance The Sentinel Safety Cohort subjects were evaluated for safety prior to the enrollment of subjects in the Main Efficacy Cohort.
Main Efficacy Cohort: A total of 13 220 subjects were expected to be enrolled and randomized to receive either QIV-HD or QIV-SD. The study was terminated so the main cohort was not enrolled or vaccinated.
Enrollment of main cohort subjects was to be performed in a stepwise manner after the initial safety review of the Sentinel cohort.

Vaccination:

In the Sentinel Safety Cohort, all eligible subjects received 1 or 2 doses of QIV-HD according to their influenza vaccination history defined as follows:

- Subjects enrolled in the Sentinel Safety Cohort who were previously vaccinated against influenza were to receive 1 dose of the QIV-HD on Day (D) 0, with no comparator vaccine.
- Subjects enrolled in the Sentinel Safety Cohort who were not previously vaccinated against influenza were to receive 2 doses of the QIV-HD with no comparator vaccine. Each dose was to be administered 28 days apart (at D0 and D28).

Note: Previously unvaccinated subjects were defined as subjects who had not received at least 2 doses of seasonal influenza vaccine in a prior influenza season. These subjects were to receive 2 doses of study vaccine at least 28 days apart after enrolling in the study.

Previously vaccinated subjects were defined as subjects who had received at least 2 doses of seasonal influenza vaccine in prior influenza seasons. These subjects were to receive only 1 dose of study vaccine after enrolling in the study.

An unblinded administrator at each site were to administer the vaccine.

Following randomization and vaccination(s),Surveillance for influenza-like illness was planned for the Main Cohort only but did not occur as the study was terminated.:

Collection of safety data:

Enrollment in the Main Efficacy Cohort was not to begin until an IDMC reviewed the safety findings from the Sentinel Safety Cohort. If the IDMC determined that there was no significant safety issue during their review of the Sentinel Safety Cohort data, then subjects were to be subsequently enrolled in the Main Efficacy Cohort starting with Season 1).

All enrolled subjects were observed for 30 minutes after vaccination, and any unsolicited systemic adverse events (AEs) occurring during that time were to be recorded as immediate unsolicited systemic AEs .

For subjects enrolled in the Sentinel Safety Cohort, solicited reactions were to be collected through day 7 after each vaccination, and unsolicited AEs were to be collected through day 28 after each vaccination in all subjects. Serious adverse events (SAEs) and adverse events of special interest (AESIs) were to be collected in all subjects throughout the study (D0 through approximately 6 to 7 months after vaccination in each season). AESIs were to be captured as SAEs in this study

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

Staff were to review the safety data with subjects' parents / guardians at each visit.

Number of study participants (planned and analyzed):

A total of 13 320 subjects were planned to be enrolled in the study: 100 subjects in the Sentinel Safety Cohort and 13 220 in the main cohort.

The IDMC reviewed safety data from the Sentinel Safety Cohort following both the first and second vaccinations. The committee confirmed that no safety concerns were identified and recommended continuing the study without modifications. However, this study was prematurely terminated following a global shift in the influenza vaccine composition from quadrivalent to trivalent formulation for 2024-2025 season. Hence, main efficacy cohort was not conducted, and the safety analysis of the 100 sentinel cohort participants in the Safety Analysis Set (SafAS) and ESafAS, is presented in Table 1.

Table 1 –Number of Subjects (planned and analyzed)

Timepoint		**QIV-HD (N=100) n (%)**
V01 (D0)	**Planned**	100
	Enrolled	100 (100)

	Randomized **Vaccinated**	0 100 (100)
V02 (D28)	**Present at visit** **Vaccinated**	100 (100) 41 (41.0)
V03 (D56)	**Present at visit**	41 (41.0)
Early termination	**Discontinued** **Adverse event** **Lost to follow-up** **Protocol deviation** **Withdrawal by subject**	0 0 0 0 0

Abbreviations: V, visit; D, day
Source: modified from Table 1

Diagnosis and criteria for inclusion:

The study was conducted in healthy children 6 months through 35 months of age on the day of inclusion.

Study products

Investigational medicinal product(s):

Identity of Study Product

The investigational QIV-HD was a quadrivalent influenza vaccine (split virion, inactivated) (60 µg HA/strain) containing virus strains chosen by the WHO (and recommended by VRBPAC in the US and EMA in the European Union) for the respective influenza season.

Composition

Each 0.7 mL dose of vaccine contained the following components:

Strains were based on WHO recommendations for the considered influenza season

Active Substances:

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

Identity of Control Product

No control product was used during the sentinel safety cohort (uncontrolled).

Duration of study intervention:

The duration of each subject's participation was approximately 6 to 7 months.

Criteria for evaluation:

Primary endpoints:

Efficacy endpoint

- Occurrence of laboratory-confirmed† influenza illness (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a protocol-defined ILI.

Secondary endpoints:

Confirmatory Efficacy Endpoints:

The following endpoints will be used for efficacy comparisons:

- Occurrence of laboratory-confirmed influenza illness (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes, in association with a protocol-defined ILI.
- Occurrence of an ILI starting ≥ 14 days after vaccination, laboratory-confirmed as positive for viral strains similar to those contained in the vaccine

- Occurrence of an ILI starting ≥ 14 days after vaccination, laboratory-confirmed as positive in subjects 6 through 23 months of age for any influenza A or B type

Statistical methods:

No statistical hypotheses were tested for this Sentinel Safety Cohort analysis. Statistics were descriptive. For the analysis presented, for the Sentinel Safety Cohort, the ESafAS is the same as the SafAS. The analysis set included participants who received at least 1 dose of the study vaccine in the sentinel safety cohort.

Changes in the planned analyses

The study was discontinued, so the analysis was limited to the safety evaluation of the Sentinel Cohort.

Summary Results:

Population characteristics:

Demographic and other baseline characteristics:

There were 54femaleand 46male participants in the sentinel group. The mean age was 1.7 years (SD 0.43)

Overall, most subjects were White (71.0%) and not of Hispanic or Latino ethnicity (78.0%).

Exposure:

A total of 100 subjects were enrolled in the Sentinel Safety Cohort and received the initial dose of QIV-HD on Day 0. All subjects (100%) completed the scheduled Visit 2 on Day 28. At Visit 2, 41 subjects, identified as previously unvaccinated, received a second dose of the vaccine in accordance with the study protocol. Subsequently, all 41 subjects (100%) who received the second dose attended Visit 3 on Day 56, which occurred 28 days after their second vaccination.

Efficacy/immunogenicity results:

No efficacy/immunogenicity data were obtained in this study.

Safety results:

No immediate unsolicited AEs were reported within 30 minutes of any injection.

The proportion of subjects with at least 1 solicited injection site reaction reported after any vaccination was 51.0% (51 subjects).

The proportion of subjects with at least 1 solicited systemic reaction reported was 46.0% (46 subjects).

The proportion of subjects with at least 1 unsolicited AE was 25.0% (25 subjects).

There were no AEs that caused subjects to discontinue from the study within 28 days of vaccination.

During the study, there was 1 unrelated SAE reported in 1 subject (1.0%) which occurred within 28 days of vaccination.

No deaths were reported during the study.

There were no AESIs within 28 days of vaccination or during the study.

Issue date: 27-February-2026