Application Type	BLA Supplement
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Division / Office	DVRPA/OVRR
Committee Chair	Goutam Sen
Clinical Reviewers	Yosefa Hefter; Susan Wollersheim
Project Managers	Katherine Berkhousen; Rebekah Weismann
Priority Review	No
Reviewer Name	Jennifer L. Kirk
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lei Huang Concurring Reviewer, Viral and Bioassay Team, VEB/DB
	Tsai-Lien Lin Branch Chief, Vaccine Evaluation Branch, DB
Applicant	Sanofi Pasteur, Inc.
Established Name	Influenza Virus Vaccine
Proposed Trade Name	Fluzone High-Dose
Pharmacologic Class	Vaccine
Formulation	0.7ml suspension
Dosage Form and Route of Administration	Intramuscular injection of 0.7ml dose
Dosing Regimen	1 dose
Indication and Intended Population	Immunization for the prevention of influenza disease in persons aged 65 years and older

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GLOSSARY

AE	Adverse Event
AESI	Adverse Event of Special Interest
BLA	Biologics Licensing Application
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
FAS	Full Analysis Set
FDA	U.S. Food and Drug Administration
GMT	Geometric Mean Titer
GMTR	Geometric Mean Titer Ratio
HAI	Hemagglutination Inhibition
IM	Intramuscular
IND	Investigational New Drug Application
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PPAS	Per-Protocol Analysis Set
QIV	Quadrivalent Influenza Vaccine
QIV-HD	High-Dose Quadrivalent Influenza Vaccine
QIV-SD	Standard-Dose Quadrivalent Influenza Vaccine
SAE	Serious Adverse Event
SafAS	Safety Set
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SRID	Serial Radial Immunodiffusion
TIV	Trivalent Influenza Vaccine
TIV-HD	High-Dose Trivalent Influenza Vaccine
TIV-SD	Standard-Dose Trivalent Influenza Vaccine
ULOQ	Upper Limit of Quantitation
VRBPAC	Vaccines and Related Biologic Products Advisory Committee

1. Executive Summary

Sanofi Pasteur Inc. seeks to license their quadrivalent high-dose inactivated influenza vaccine (QIV-HD) for the prevention of influenza disease in persons aged 65 years and older. A trivalent high-dose inactivated influenza vaccine (TIV-HD) manufactured by Sanofi Pasteur Inc., was licensed for use in the United States on December 23, 2009 in adults aged 65 years and older.

This submission included the results from a single phase III study, QHD00013. QHD00013 was a multicenter, randomized, active-controlled, modified double-blind non-inferiority study of the immunogenicity and safety of QIV-HD, which was formulated with two A strain antigens and two B strain antigens. QIV-HD was compared to two different formulations of TIV-HD, TIV-HD1 and TIV-HD2, each with one of the QIV-HD B strain antigens. The primary objective of QHD00013 was to demonstrate that QIV-HD induces an immune response that is non-inferior to the immune response induced by TIV-HD1 and TIV-HD2 for all 4 influenza virus strains at 28 days post-vaccination in all subjects, as measured by hemagglutinin inhibition assay titers. Non-inferior immune response was assessed via geometric mean titer ratios (GMTRs) and the difference in seroconversion rates. QIV-HD was compared to the combined TIV-HD groups for the A strains and to the TIV-HD group with the corresponding B strain for the B strains. Non-inferiority was demonstrated if the two-sided, 95% confidence interval for the GMTRs exceeded 0.667 and the difference in seroconversion rates on the percent scale exceed -10% for all 4 strains.

QHD00013 enrolled 2,670 subjects who were randomized 4:1:1 to QIV-HD, TIV-HD1, and TIV-HD2. Subjects were predominantly white, and non-Hispanic, with a median age of approximately 72 in all study groups. GMTRs comparing QIV-HD to the relevant comparator vaccine at Day 28 ranged from 0.83–1.08, with lower 95% confidence bounds ranging from 0.74–1.08. Differences in seroconversion rates comparing QIV-HD to the relevant comparator ranged from -3.27% to -0.71% with lower 95% confidence limits ranging from -7.66% to -4.38%. The primary non-inferiority criteria were met for all 4 influenza strains.

QHD00013 had a small percent of subjects discontinue the study early for adverse events (0.1%), and a small percent of subjects who died during the study (0.2%). 4.6% of subjects experienced one or more non-fatal SAE, with a similar distribution between the QIV-HD and combined TIV-HD groups. The most frequent unsolicited non-serious adverse event in all study groups was cough. The rates of solicited AEs, including injection site reactions, were comparable between QIV-HD and the combined TIV-HD vaccines. These results suggest that QIV-HD has a safety profile that does not differ substantially from that of TIV-HD.

Overall, the results from QHD00013 suggest that QIV-HD generates a non-inferior immune response compared to TIV-HD for the shared strains and a superior response for the B strain not included in TIV-HD, and that QIV-HD has a safety profile that is similar to that of TIV-HD. Based on these results, I recommend approval of QIV-HD for immunization for the prevention of influenza disease in adults aged 65 years and older.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Conditions Studied

Please refer to the clinical review for further details.

2.2 Currently Available, Pharmacologically Unrelated Treatments/Interventions for the Proposed Indication

A trivalent high-dose (TIV-HD) inactivated influenza vaccine manufactured by Sanofi Pasteur Inc., Fluzone High-Dose, was licensed for use in the United States (US) on December 23, 2009 in adults aged 65 years and older. Fluzone High-Dose was licensed under accelerated approval based on a single study, FIM05, using hemagglutination inhibition (HAI) titers as a surrogate endpoint.

FIM05 was a multicenter, randomized, active-controlled, double-blind, phase III study conducted during the 2006–2007 US influenza season. A total of 3,875 adults aged 65 years and older were randomized 2:1 to receive TIV-HD or Fluzone standard dose trivalent influenza vaccine (TIV-SD). The primary objectives of FIM05 included demonstration of a superior immune response induced by TIV-HD relative to TIV-SD. The immune response was measured using geometric mean titers (GMTs) and seroconversion rates. Seroconversion was defined as a pre-vaccination titer < 1:10 and a post-vaccination titer > 1:40 or a pre-vaccination titer ≥ 1:10 and at least a four-fold increase post-vaccination. To demonstrate a superior immune response to TIV-HD for GMTs and seroconversion, at least two strains in TIV-HD needed to demonstrate a superior immune response, and if a strain failed to demonstrate superiority, then it had to demonstrate non-inferiority. In FIM05, TIV-HD demonstrated superior GMTs and seroconversion rates for both the A/H1N1 and A/H3N2 strains and non-inferior GMT and seroconversion rate for the B/Malaysia strain.

Because TIV-HD was initially licensed under accelerated approval, Sanofi Pasteur conducted a post-licensure efficacy study, FIM12. The primary objective of FIM12 was to compare the efficacy of TIV-HD for preventing laboratory-confirmed influenza to the efficacy of TIV-SD in adults from the US and Canada aged 65 years and older during the 2011–2012 and 2012–2013 influenza seasons. FIM12 demonstrated that TIV-HD had superior vaccine efficacy relative to TIV-SD.

A quadrivalent standard dose (QIV-SD) inactivated influenza vaccine manufactured by Sanofi Pasteur Inc., Fluzone, was licensed for use in the US on May 28, 2013 in adults aged 65 years and older.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Previous foreign experience with QIV-HD in adults aged 65 years and older includes study QHD00008, a phase I/II randomized, modified double-blind, active-controlled, multicenter study conducted in Japan during the 2017–2018 Northern Hemisphere

influenza season. In this study 175 subjects were randomized to receive a single dose of either QIV-HD by intramuscular route, QIV-HD by subcutaneous route, or QIV-SD. The first 10 subjects enrolled were randomized 1:1 to receive QIV-HD by subcutaneous (SC) or intramuscular route (IM). The remaining 165 subjects were randomized 1:1:1 to the three vaccines. The QIV-SD vaccine contained the influenza strains recommended by the Japanese National Institute of Infectious Diseases, while the other two vaccines contained the influenza strains recommended by the Vaccines and Related Biological Products Advisory Committee (VRBPAC). The influenza strains recommended by the Japanese National Institute of Infectious Diseases and VRBPAC were not the same. The immune responses were measured using GMTs and seroconversion rates. Seroconversion was defined as a pre-vaccination titer < 1:10 and a post-vaccination titer > 1:40 or a pre-vaccination titer ≥ 1:10 and at least a four-fold increase post-vaccination.

At baseline, the GMTs for all influenza strains were comparable across study groups. Post-vaccination, the GMTs were higher in all three study groups, although QIV-HD IM had the highest GMTs, followed by QIV-HD SC. The GMT ratios comparing post-vaccination to pre-vaccination titers ranged from 7.51 with a 95% confidence interval (CI) of (4.93, 11.95) to 16.93 (95% CI: 10.99, 26.10) for QIV-HD IM; 4.68 (95% CI: 3.34, 6.56) to 9.25 (95% CI: 6.11, 14.00) for QIV-HD SC; and 2.67 (95% CI: 2.00, 3.57) to 6.56 (95% CI: 4.36, 9.86) for QIV-SD.

Seroconversion rates were higher post-vaccination for QIV-HD IM and QIV-HD SC compared to QIV-SD. The differences in seroconversion rates between each QIV-HD group and the QIV-SD group ranged from 17.9% (95% CI: 0.1%, 34.4%) to 42.9% (95% CI: 25.2%, 57.0%) for QIV-HD IM and 10.2% (95% CI: -8.1%, 27.6%) to 30.3% (95% CI: 11.6%, 46.2%) for QIV-HD SC among different strains. Seroconversion rates were higher for QIV-HD IM compared to QIV-HD SC.

2.5 Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission

On October 11, 2016, the Center for Biologics Evaluation and Research (CBER) received a request for a pre-IND meeting which included two clinical questions:

1. Sanofi Pasteur proposes a safety database of approximately 1700 QIV-HD adult recipients aged 65 years and older with supportive data of approximately 17,100 TIV-HD recipients from clinical studies FIM05 and FIM12 and an existing clinical safety database of TIV-HD for which the number of doses sold to-date is over (b) (4) million.

   Additionally, TIV-HD will have been on the market for over 10 years at the time of the QIV-HD BLA submission. Does CBER agree that the QIV-HD general investigational plan, including the QHD00013 pivotal trial, will be adequate for license registration in adults 65 years of age and older?

2. Does CBER agree with the proposed QHD00013 trial design?

The pre-meeting response to these questions indicated that the proposed general investigation plan appeared acceptable, given the information provided prior to the meeting, and that the proposed QHD00013 trial design was generally acceptable. Two specific comments were provided to Sanofi Pasteur about the QHD00013 trial design:

1. We note that you intend to break trial blinding at Visit 2 so that safety results and immunogenicity analyses can be performed. Please clarify who will have access to the unblinded data and analysis results and whether and how the staff involved in the trial conduct will be kept blinded until the end of the study.
2. You may wish to consider conducting a Phase 2 study with the QIV-HD clinical trial material formulated with drug substance produced by the TIV-HD licensed process prior to moving forward with this Phase III study.

Additional comments provided by the statistical reviewer about the proposed design of QHD00013 included: a recommendation to include subgroup analyses and the specification of the statistical model for the geometric mean titers. No meeting was held with Sanofi Pasteur after this response was sent. Both of these comments were addressed in the statistical analysis plan (SAP) submitted for QHD00013.

The protocol and SAP for QHD00013 were reviewed in IND 17556/0. Both the proposed study design and analysis plan were acceptable to the statistical reviewer. Comments were provided to the applicant requesting clarification of the randomization blocking and the proposal for a blinded statistical review of the data before database lock. In the response to the statistical reviewer's comments provided in IND 17556/1, Sanofi Pasteur Inc. clarified that the randomization was stratified only by site and that the blinded data review would not include any statistical analyses. The statistical reviewer found these responses acceptable.

Revised versions of the protocol and SAP were reviewed under IND 17556/1 and IND 17556/9, respectively. The revisions to the protocol submitted in IND 17556/1 consisted of changes in wording to clarify descriptions of study procedures and withdrawal criteria. These changes did not alter the statistical content of the protocol. Revisions to the SAP included changes in the adverse event data collected, which were acceptable. A supplemental SAP describing an exploratory analysis of neuraminidase titers from an (b) (4) assay were added. The proposed exploratory analysis was acceptable, although the statistical reviewer provided a comment to the applicant noting that no upper limit of quantitation was given and that the lower and upper limits of quantitation should be based on a well-designed validation study that demonstrates that the proposed assay has acceptable accuracy and precision at the lower and upper limits of quantitation.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

3.2 Compliance with Good Clinical Practices and Data Integrity

The conduct of QHD00013, the clinical trial included in this submission, was consistent with the Declaration of Helsinki and compliant with International Council for Harmonisation guidelines for good clinical practice.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

Please refer to the corresponding reviews for disciplines not addressed below.

4.1 Chemistry, Manufacturing, and Controls

Please see the CMC statistical review for details.

4.2 Assay Validation

The hemagglutination inhibition assay used to generate the HAI titers for the primary analysis was performed at (b) (4) facility. This assay was validated in a concordance study by comparison to Sanofi Pasteur's GCI facility, which was qualified in 2010. The concordance study was reviewed by a statistical reviewer in BLA 103914/6208, and the qualification of Sanofi Pasteur's GCI facility was reviewed by a statistical reviewer in BLA 103914/5574. Sanofi Pasteur's GCI facility was found acceptable, as was the (b) (4)

The assay used to generate seroneutralization results for QHD00013 was reviewed by the statistical reviewer in a separate CMC statistical memo.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review focuses on the single randomized study conducted in American adults, QHD00013, provided in this submission.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

This review refers to the documents and datasets from the BLA supplement (BLA 103914/6290) in Module 5.3.5.1 QHD00013 – QHD00013, as well as several documents from IND 17556:

- Amendment 0
  - QHD00013 Protocol, version 3.0
  - QHD00013 Statistical Analysis Plan, version 1.0
- Amendment 1
  - QHD00013 Protocol, version 4.0
  - Section 1.11.4 Multiple Module Information Amendments
- Amendment 9
  - QHD00013 Statistical Analysis Plan, version 4.0

6. Discussion of Individual Studies/Clinical Trials

6.1 QHD00013

QHD00013 was a randomized, active-controlled phase III study of the immunogenicity and safety of QIV-HD during the 2017–2018 Northern Hemisphere influenza season in the US.

6.1.1 Objectives

The primary objective of QHD00013 was to demonstrate that QIV-HD induces an immune response that is non-inferior to the immune response induced by TIV-HD1 and TIV-HD2 for all 4 influenza virus strains at 28 days post-vaccination in all subjects.

The secondary objectives were to:

- demonstrate for each influenza B strain that QIV-HD induces a superior immune response compared to a TIV-HD vaccine that does not include the corresponding B strain in all subjects
- describe the immune response, as measured by HAI, induced by QIV-HD, TIV-HD1, and TIV-HD2 in all subjects
- describe the immune response, as measured by seroneutralization, 28 days post-vaccination
- describe the safety profile of all subjects in each study group

6.1.2 Design Overview

QHD00013 was a multicenter, randomized, active-controlled, modified double-blind phase III non-inferiority study of the immunogenicity and safety of QIV-HD, a quadrivalent influenza vaccine formulated with two A strain antigens and two B strain antigens. QIV-HD was compared to two different formulations of TIV-HD, each with

one of the QIV-HD B strain antigens. The study was designed to enroll 2,616 US adults at approximately 35 sites between September 1, 2017 and April 4, 2018.

6.1.3 Population

QHD00013 enrolled adults 65 years and older. Potential subjects were excluded from trial participation if they had received a vaccine during the 4 weeks prior to study vaccination or planned to receive a vaccine within 28 days after study vaccine administration.

6.1.4 Study Treatments or Agents Mandated by the Protocol

The three study vaccines had different influenza strain antigen compositions which are indicated in Table 1. QIV-HD and TIV-HD1 contained the World Health Organization/VRBPAC recommendations for the 2017–2018 Northern Hemisphere influenza season. All study vaccines were administered in a single injection, with a higher volume for QIV-HD.

Table 1. Influenza Strain Antigen Composition of the Study Vaccines

Influenza Strain	QIV-HD	TIV-HD1	TIV-HD2
A/Michigan/45/2015	×	×	×
A/Hong Kong/4801/2014	×	×	×
B/Brisbane/60/2008	×	×	–
B/Phuket/3073/2013	×	–	×

Source: The reviewer created this table based on the QHD00013 final study report (pp. 51–53).

6.1.6 Sites and Centers

This study was conducted at 35 centers in the US. The study protocol originally stated that the trial would be conducted at approximately 36 sites, and 36 sites were opened. However, one site in Florida closed prior to the enrollment of any subjects because of a hurricane. The investigators at all sites were coordinated by the Coordinating Investigator at Vanderbilt Clinical Trials Center (Nashville, Tennessee).

Statistical Reviewer's Comment: *The closure of a site before enrollment has begun is unlikely to have a significant impact on the results.*

6.1.8 Endpoints and Criteria for Study Success

The primary endpoints were HAI titers at study Day 28 and seroconversion status at Day 28, defined as a titer < 10 at Day 0 and ≥ 40 at Day 28 or a titer ≥ 10 at Day 0 and at least a 4-fold increase at Day 28. The secondary endpoints for immunogenicity measured by HAI assay included:

- titers at study Day 0 and Day 28;
- ratio of titers at Day 28 relative to Day 0;
- seroconversion status, defined as for the primary endpoint;

- seroprotection status, defined as a titer ≥ 40,

and the secondary endpoints for immunogenicity measured by seroneutralization assay included:

- titers at study Day 0 and Day 28;
- ratio of titers at Day 28 to Day 0;
- titers greater than 20, 40, and 80 at Day 28;
- 2- and 4-fold-rise in Day 28 titers relative to Day 0;
- detectable titers at Day 0 and Day 28, defined as titers ≥ 10.

Immunogenicity measurements less than the lower limit of quantitation (LLOQ) were replaced with one-half the LLOQ, and immunogenicity measurements greater than the upper limit of quantitation (ULOQ) were replaced with the ULOQ for calculation of GMTs.

Statistical Reviewer's Comment: *These endpoints were prespecified in the protocol and the primary endpoints are consistent with the U.S. Food and Drug Administration (FDA) guidance, "Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines." As noted in the statistical review of the protocol, these endpoints appear appropriate for the study objectives.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

The applicant planned to enroll 2,616 subjects; however, to compensate for the study site closure and the impact of a hurricane on other study sites, the applicant enrolled 2,670 subjects. Subjects were randomized 4:1:1 to QIV-HD, TIV-HD1, and TIV-HD2 using a permuted block design in blocks of 6 or 12 subjects within strata defined by site. Subjects, laboratory staff, and study staff assessing outcomes were blinded to treatment assignment, while study treatment administrators were not blinded.

Statistical Reviewer's Comment: *As noted in the statistical review of the protocol, the modified double-blind design is considered appropriate, because of the differences in the three study vaccines.*

No early review of safety data was planned or conducted. The final analyses for the primary and secondary endpoints, including safety analyses, were performed before the end of the 6-month follow-up period. Unblinded results from these analyses were available to the applicant but not to study staff or site monitors until after final database lock. No adjustment for multiplicity was made. After the end of the 6-month follow-up period, the final safety analyses were performed.

Statistical Reviewer's Comment: *The timing of the unblinded analyses is acceptable, as study staff and site monitors remained blinded. No adjustment for multiplicity is needed, as each analysis represents the final analysis of the endpoints collected at that time.*

For the primary immunogenicity analysis, the applicant calculated GMT ratios (GMTRs) with two-sided asymptotic 95% confidence intervals and differences in seroconversion rates with two-sided 95% confidence intervals using the Newcombe-Wilson score method without continuity correction.

Statistical Reviewer's Comment: *The asymptotic confidence intervals assume normally distributed titers (on the logarithmic scale) or a sufficiently large sample size for the central limit theorem to apply. Given the large sample size in each study group, this assumption is reasonable. However, asymptotic confidence intervals may not be appropriate for subgroup analyses if the subgroup sample sizes are small.*

The use of Newcombe-Wilson score confidence intervals without continuity correction for the difference in seroconversion rates is appropriate. Newcombe-Wilson score confidence intervals are an asymptotic method, and as noted above, may not be appropriate when the sample size is small, such as for subgroup analyses.

To demonstrate non-inferiority of the GMTs and seroconversion rates based on HAI titers, the applicant performed one-sided, non-inferiority hypothesis tests at a significance level of 0.025 comparing QIV-HD to a control group for each strain. For both A strains, the control group was the combined TIV-HD1 and TIV-HD2 groups. For B/Brisbane, the control group was TIV-HD1, and for B/Phuket, the control group was TIV-HD2.

The non-inferiority null hypotheses tested were:

$$H_0: \frac{\mu^s_{QIV-HD}}{\mu^s_C} \leq 0.667$$

and

$$H_0: \pi^s_{QIV-HD} - \pi^s_C \leq 0.1$$

where μ^s_{QIV-HD} is the QIV-HD GMT for strain *s*, μ^s_C is the comparator GMT for strain *s*, π^s_{QIV-HD} is the QIV-HD seroconversion rate for strain *s*, and π^s_C is the comparator seroconversion rate for strain *s*.

Post-vaccination GMTs for QIV-HD were considered non-inferior if the lower 95% confidence bound for the ratio of QIV-HD GMTs to the comparison group exceeded $1/1.5 \approx 0.667$. The post-vaccination seroconversion rates for QIV-HD relative to the comparison group were considered non-inferior if the lower 95% confidence bound for the difference in seroconversion rates exceeded -0.1 or -10% on the percent scale.

The overall non-inferiority objective was met if non-inferiority was demonstrated for all 4 strains for both GMTs and seroconversion rates. Because all 8 non-inferiority tests must be significant to meet the overall primary objective, no multiplicity adjustment was needed for the primary immunogenicity objective.

Statistical Reviewer's Comment: *The proposed statistical methods are appropriate for the study objectives and endpoints. As noted in the statistical review of the protocol, the hypothesis tests and non-inferiority margins are consistent with the FDA guidance, "Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines."*

No multiplicity adjustment is needed for the primary immunogenicity objective because the overall success criteria requires all 8 hypothesis tests to be rejected at 0.025 level. In this case, the overall type I error rate is controlled at 0.025.

For the primary immunogenicity analysis, descriptive analyses comprising HAI GMTs at Day 0 and Day 28 with asymptotic 95% CIs and HAI seroconversion rates at Day 28 with exact 95% confidence intervals were reported by strain. The primary immunogenicity analysis was performed on the Per-Protocol Analysis Set (PPAS), defined as all randomized subjects who received at least one vaccination, had a valid post-vaccination HAI titer for at least one strain, and had no major protocol deviations. Major protocol deviations included:

- a failure to meet all inclusion criteria, or meeting at least one exclusion criterion
- the receipt of protocol-prohibited therapy or medication
- a vaccine preparation or administration not done according to the protocol
- a Day 28 immunology sample that was not collected or collect outside the protocol-specified time-frame
- a mishandled immunology sample or
- an immunology sample that did not produce any valid HAI titers.

Subjects in the PPAS were analyzed according to the vaccine they actually received.

A supporting analysis using the Full Analysis Set (FAS), defined as all randomized subjects who had a post-vaccination HAI titer for at least one strain, was performed. A sensitivity analysis adjusted for pre-vaccination HAI titers was performed using an analysis of covariance model.

Descriptive subgroup analyses comprising HAI GMTs with asymptotic 95% CIs and HAI seroconversion rates with exact 95% confidence intervals were reported by sex, race (white or non-white), age group (65–<75 years old or ≥75 years old), baseline serostatus, and prior seasonal influenza vaccine exposure.

To demonstrate superiority of the GMTs and seroconversion rates based on HAI titers for the secondary objective, the applicant used hypothesis tests comparing QIV-HD to each TIV-HD group for the two B strains. For B/Brisbane, the control group was TIV-HD2, and for B/Phuket, the control group was TIV-HD1.

Post-vaccination GMTs for QIV-HD were considered superior if the lower 95% confidence interval bound for the ratio of QIV-HD GMTs to the comparison group exceeded 1.5. The differences in post-vaccination seroconversion rates for QIV-HD relative to the comparison group were considered superior if the lower 95% confidence interval bound for the difference in seroconversion rates exceeded 0.1. The overall

superiority objective was met if superiority was demonstrated for both B strains for both GMTs and seroconversion rates in the FAS. The applicant performed a supportive analysis using the PPAS.

For all immunogenicity analyses, subjects were excluded from any analyses for which they were missing the relevant data. No imputation or sensitivity analyses for missing data were performed.

The study was designed to have 90% power to demonstrate non-inferiority for the GMTs and seroconversion rates based on HAI titers comparing QIV-HD to the relevant TIV-HD groups for all vaccine strains. Assuming an attrition rate of 8% and the expected seroconversion rates and HAI GMT standard deviations given in Table 2, a total of 1,744 QIV-HD, 436 TIV-HD1, and 436 TIV-HD2 subjects yields the desired power.

Table 2. Assumed Seroconversion Rates and Hemagglutinin Inhibition (HAI) Geometric Mean Titer (GMT) Standard Deviations (SD) for Power Calculations

Strain	Seroconversion Rate	HAI GMT SD
A/Michigan	45%	0.63
A/Hong Kong	70%	0.63
B/Brisbane	40%	0.55
B/Phuket	40%	0.55

Source: The reviewer created this table based on the QHD00013 statistical analysis plan, version 4.0 (p. 31).

Statistical Reviewer's Comment: *The sample size calculations were confirmed in the statistical review of the original protocol (IND 17756/0) and did not change subsequently.*

For the safety analyses, Sanofi Pasteur calculated the frequency of solicited reactions, unsolicited adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) in the Safety Set (SafAS). The SafAS included all subjects who received a study vaccine. Subjects in the SafAS were analyzed by the vaccine they received. The applicant reported the proportions of subjects experiencing each event with two-sided exact 95% confidence intervals by study group and by Medical Dictionary for Regulatory Activity (MedDRA) preferred term, nature, duration, intensity, and relationship to the vaccines.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 3 shows the number of subjects enrolled by study group, and the number of subjects per population analysis group. All enrolled subjects were vaccinated according to the randomization.

Table 3. Analysis Population Sample Sizes for the Study Group and Combined

Population	QIV-HD	TIV-HD1	TIV-HD2	All
Enrolled	1777	443	450	2670
Safety Set	1777	443	450	2670
Full Analysis Set	1763	439	446	2648
Per-Protocol Analysis Set	1680	423	430	2533

Source: The reviewer created this table based on Figure 1 (p. 87) and Section 4.3 (p.90) from the QHD00013 final study report.

The number of subjects enrolled per site in the SafAS ranged from 61 to 96, with a median of 73 and a mean of 76. The number of subjects per site in the FAS and PPAS ranged from 49 to 95, with a median of 71 and a mean of 75.

6.1.10.1.1 Demographics

Table 4 shows the demographics of the SafAS by study group. The distributions of sex, race, and ethnicity across the QIV-HD, TIV-HD1, and TIV-HD2 groups are similar. TIV-HD1 has a slightly higher proportion of female and Black or African American subjects numerically. TIV-HD2 has a slightly lower proportion of non-Hispanic or Latino subjects numerically. Table 5 shows summary statistics for age at enrollment in the SafAS by study group. The distribution of ages is similar across the study groups. Table 6 shows the demographics for the PPAS by study group, and Table 7 shows the summary statistics for age at enrollment in the PPAS by study group. The demographics in the PPAS are similar to those in the SafAS.

Table 4. Safety Set: Demographics by Study Group; numbers in parentheses indicate the count as a percent of the study group total sample size.

Demographic	-	QIV-HD	TIV-HD1	TIV-HD2	TIV-HD
Sex	Female	1027 (57.8)	268 (60.5)	252 (56.2)	520 (58.2)
	Male	750 (42.2)	175 (39.5)	198 (44.0)	373 (41.8)
Race	AI/AL Native*	9 (0.51)	2 (0.45)	3 (0.67)	5 (0.56)
	Asian	13 (0.73)	2 (0.45)	3 (0.67)	5 (0.56)
	Black/AA†	123 (6.92)	41 (9.26)	35 (7.78)	76 (8.51)
	Native HI/PI‡	4 (0.23)	1 (0.23)	1 (0.22)	2 (0.22)
	White	1618 (91.1)	395 (89.2)	402 (89.3)	797 (89.3)
	Multiple	6 (0.34)	1 (0.23)	2 (0.44)	3 (0.34)
	Missing	4 (0.23)	1 (0.23)	4 (0.89)	5 (0.56)
Ethnicity	Hispanic/Latino	50 (2.81)	9 (2.03)	14 (3.11)	23 (2.58)
	Not Hispanic/Latino	1723 (97.0)	433 (97.7)	434 (96.4)	867 (97.1)
	Missing	4 (0.23)	1 (0.23)	2 (0.44)	3 (0.33)

*American Indian/Alaskan Native
†Black/African American
‡Native Hawaiian/Pacific Islander
Source: The reviewer created this table based on Table 9.19 (pp. 167–168) from the QHD00013 final study report.

Table 5. Safety Set: Age at Enrollment Summary Statistics by Study Group

Statistic	QIV-HD	TIV-HD1	TIV-HD2	TIV-HD
Minimum	65	65	65	65
Median	72	72	73	72
Maximum	100	94	95	95
Mean	72.9	72.8	73.2	73.0
Standard Deviation	5.6	5.8	5.5	5.7

Source: The reviewer created this table based on Table 9.19 (pp. 167–168) from the QHD00013 final study report.

Table 6. Per-Protocol Analysis Set: Demographics by Study Group; numbers in parentheses indicate the count as a percent of the study group total sample size.

Demographic	-	QIV-HD	TIV-HD1	TIV-HD2	TIV-HD
Sex	Female	977 (58.2)	251 (59.3)	239 (55.6)	490 (57.4)
	Male	703 (41.8)	172 (40.7)	191 (44.4)	363 (42.6)
Race	AI/AL Native*	9 (0.5)	2 (0.5)	3 (0.7)	5 (0.6)
	Asian	12 (0.7)	2 (0.5)	3 (0.7)	5 (0.6)
	Black/AA†	114 (6.8)	36 (8.5)	32 (7.4)	68 (8.0)
	Native HI/PI‡	3 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)
	White	1532 (91.2)	380 (89.8)	385 (89.5)	765 (89.7)
	Multiple	6 (0.4)	1 (0.2)	2 (0.5)	3 (0.4)
	Missing	4 (0.2)	1 (0.2)	4 (0.9)	5 (0.6)
Ethnicity	Hispanic/Latino	47 (2.8)	9 (2.1)	13 (3.0)	22 (2.6)
	Not Hispanic/Latino	1630 (97.0)	413 (97.6)	415 (96.5)	828 (97.1)
	Missing	3 (0.2)	1 (0.2)	1 (0.2)	2 (0.2)

*American Indian/Alaskan Native
†Black/African American
‡Native Hawaiian/Pacific Islander
Source: The reviewer created this table based on Table 4.3 (pp. 91–92) from the QHD00013 final study report.

Table 7. Per-Protocol Set: Age at Enrollment Summary Statistics by Study Group

Statistic	QIV-HD	TIV-HD1	TIV-HD2	TIV-HD
Minimum	65	65	65	65
Median	72	72	73	72
Maximum	100	94	95	95
Mean	72.9	72.8	73.2	73.0
Standard Deviation	5.6	5.8	5.5	5.7

Source: The reviewer created this table based on Table 4.3 from the QHD00013 final study report (pp. 91–92).

Statistical Reviewer's Comment: *I have verified the demographics and age summary statistics for the SafAS and PPAS using R 3.5.3 and the dm.xpt dataset.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Prior exposure to a seasonal influenza vaccine was defined as receipt of an influenza vaccine since August 1, 2016. Table 8 shows the frequency of prior seasonal influenza exposure among the PPAS. The distributions across study groups are generally similar, although exposure to prior seasonal vaccines was slightly less frequent among TIV-HD1 subjects. The distributions across study groups in the SafAS are similar to these distributions (not shown).

Table 8. Per-Protocol Analysis Set: Number and Percent of Subjects with Prior Seasonal Influenza Vaccine Exposure by Study Group; numbers in parentheses indicate the count as a percent of the study group total sample size.

Vaccine Exposure	QIV-HD	TIV-HD1	TIV-HD2	TIV-HD	All
Yes	1265 (75.3)	296 (70.0)	320 (74.4)	616 (72.2)	1881 (74.3)
No	393 (23.4)	124 (29.3)	104 (24.2)	228 (26.7)	621 (24.5)
Unknown	22 (1.3)	3 (0.7)	6 (1.4)	9 (1.1)	31 (1.2)

Source: The reviewer created this table based on Table 9.22 (p. 172) from the QHD00013 final study report.

Statistical Reviewer's Comment: *I have confirmed the applicant's results shown in Table 8, as well as the prior seasonal influenza exposure frequencies in the SafAS*

(QHD00013 final study report, Table 9.21, p. 171). I have also confirmed that the frequency of prior seasonal influenza exposure across study groups is similar in the SafAS, FAS, and PPAS.

Prior seasonal influenza vaccine exposure was recorded in two different ways on the case report forms: as a yes, no, or unknown response to "Seasonal Influenza Vaccination Since August 1, 2016?" and as the date of last administration of a seasonal influenza vaccine. 24 subjects gave incomplete or inconsistent responses to these two questions: 22 subjects indicated "yes" to receipt of a seasonal influenza vaccine since August 1, 2019 but provided a date of last administration of "2016" and 2 subjects indicated "yes" to receipt of a seasonal influenza vaccine since August 1, 2016 but provided no date of last administration. The applicant classified these subjects as having prior vaccine exposure. As shown in Table 9, reclassification of these subjects as unknown does not substantially change the percent of subjects with prior vaccine exposure in each study group in the PPAS. The results from the SafAS and FAS are similar (not shown).

Table 9. Per-Protocol Analysis Set: Number of Subjects with Revised Prior Seasonal Influenza Vaccine Exposure by Study Group; numbers in parentheses indicate the count as a percent of the study group total sample size.

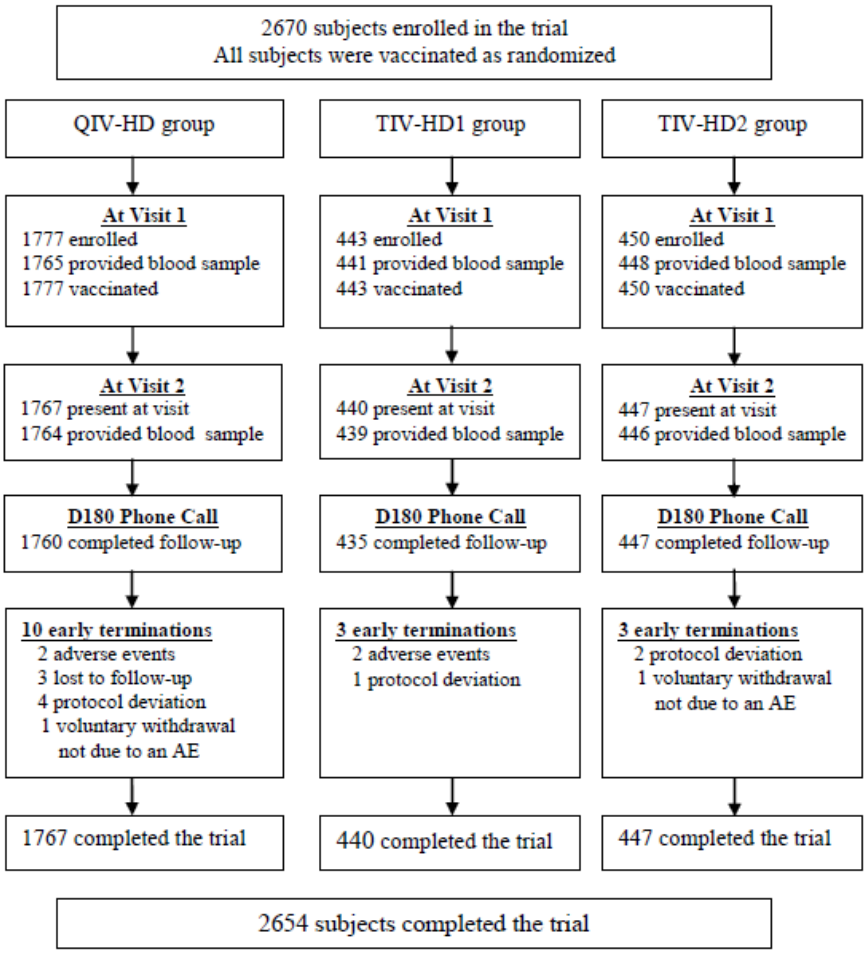
Vaccine Exposure	QIV-HD	TIV-HD1	TIV-HD2	TIV-HD	All
Yes	1249 (74.4)	292 (69.0)	317 (73.7)	609 (71.4)	1858 (73.4)
No	393 (23.4)	124 (29.3)	104 (24.2)	228 (26.7)	621 (24.5)
Unknown	38 (2.3)	7 (1.7)	9 (2.1)	16 (1.9)	54 (2.1)

Source: The reviewer created this table in R 3.5.3 using the datasets cm.xpt and demo.xpt.

6.1.10.1.3 Subject Disposition

Figure 1 shows the disposition of subjects in QHD00013 by study group. Rates of visit completion, early termination, and trial completion were similar across the study groups. Subjects in the TIV-HD1 and TIV-HD2 were slightly more likely to terminate study participation early.

Figure 1. Study QHD00013 Subject Disposition Flowchart



Source: The reviewer adapted this figure from Figure 1 (p. 87) in the QHD00013 final study report.

Statistical Reviewer's Comment: *I have verified the number and rate of early terminations in each study group for the reasons given in R 3.5.3 using the ds.xpt dataset. The rates of early termination for adverse events are extremely small: TIV-HD1: 0.5%, TIV-HD2: 0.0%, QIV-HD: 0.1%. Because the sample sizes are much smaller in the TIV-HD1 and TIV-HD2 groups, we expect the observed rates in these two study groups to be much more variable than the rate in the QIV-HD group. Given this expectation and that the absolute number of early terminations in all study groups is very small, I do not consider the numerical differences in early termination rates across treatment groups to be meaningful.*

Table 10 shows the number and percent of enrolled subjects per study group who were excluded from the FAS by exclusion reason. Rates of exclusion by reason were similar across study groups, as was the total percent of subjects excluded per group (approximately 1%), with the majority of subjects excluded because they failed to provide an immunogenicity sample at one or more study visits.

Table 10. Reasons Enrolled Set Subjects were Excluded from the Full Analysis Set by Study Group; the number of subjects excluded for each reason is shown with the percent of subjects excluded from the Enrolled Set in parentheses.

Reason for Exclusion	QIV-HD (N = 1777)	TIV-HD1 (N = 443)	TIV-HD2 (N = 450)
No Immunogenicity Sample(s)	13 (0.7)	4 (0.9)	4 (0.9)
Missing All HAI Data	1 (0.1)	0 (0.0)	0 (0.0)

Source: The reviewer created this table in R 3.5.3 based on the dv.xpt, ds.xpt, and dm.xpt datasets.

Table 11 shows the number of FAS subjects per study group who were excluded from the PPAS with percentages relative to the Enrolled Set sample sizes for each study group. Rates of exclusion by reason were similar across study groups, as was the total percent of enrolled subjects excluded from the PPAS but not the FAS (approximately 4–5%). All subjects excluded from the PPAS for multiple protocol deviations had at least one deviation that was either an immunogenicity sample taken out of the protocol-defined time-frame or the receipt of a protocol-prohibited therapy. The percentages of subjects in the FAS excluded from the PPAS for each reason, as a percent of the FAS, were similar (not shown).

Table 11. Reasons Full Analysis Set Subjects were Excluded from the Per-Protocol Set by Study Group; the number of subjects excluded for each reason is shown with the percent of subjects excluded from the Enrolled Set in parentheses.

Reason for Exclusion	QIV-HD (N = 1777)	TIV-HD1 (N = 443)	TIV-HD2 (N = 450)
Immunogenicity Sample Taken Out of Window	49 (2.8)	11 (2.5)	10 (2.2)
Prohibited Therapy Received	15 (0.8)	3 (0.7)	1 (0.2)
Neoplastic Disease/Hematologic Malignancy	1 (0.1)	0 (0.0)	1 (0.2)
Immunodeficiency/Immunosuppression	1 (0.1)	0 (0.0)	0 (0.0)
Participated in Another Clinical Trial	1 (0.1)	0 (0.0)	0 (0.0)
Immunogenicity Sample Handled Incorrectly	0 (0.0)	0 (0.0)	1 (0.2)
Multiple Protocol Deviations	16 (0.9)	2 (0.5)	3 (0.7)

Source: The reviewer created this table in R 3.5.3 based on the dv.xpt, ds.xpt, and dm.xpt datasets.

6.1.11 Efficacy Analyses

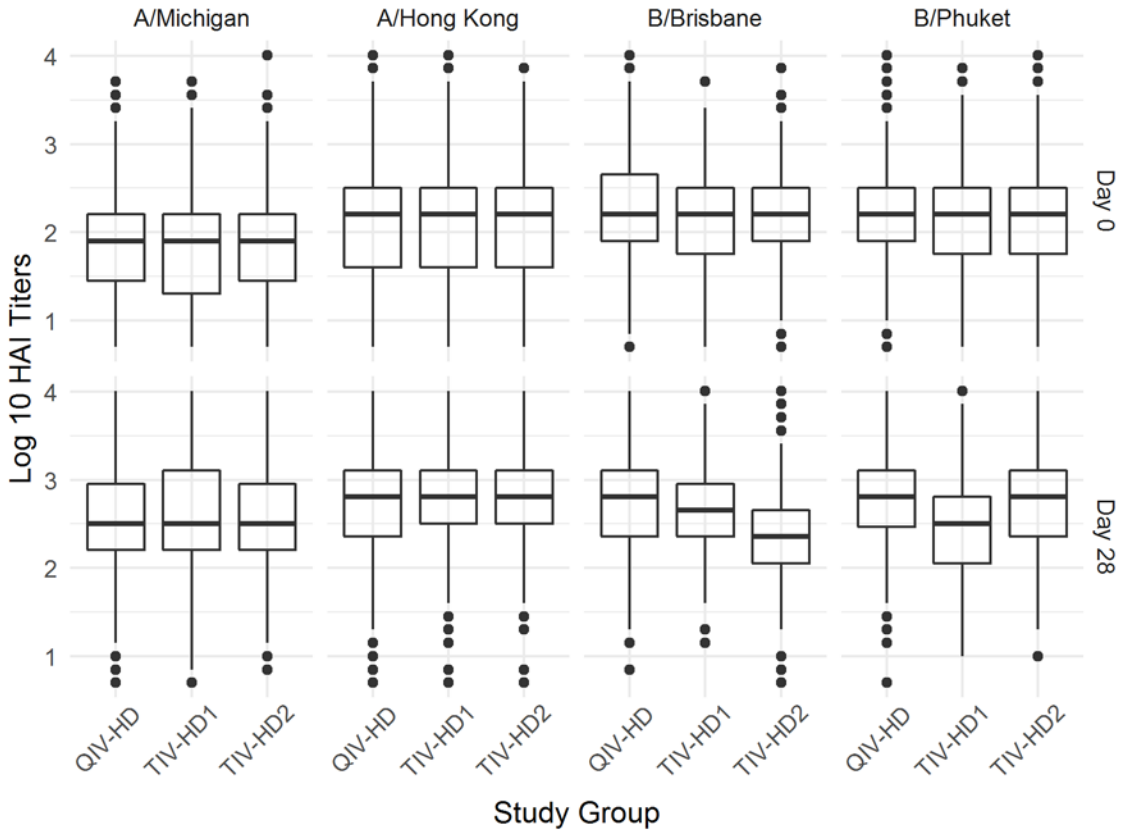
6.1.11.1 Analyses of Primary Endpoints

Figure 2 shows the distribution of HAI titers (log_{10} scale) by strain and study group at baseline (Day 0) and 28 days after vaccination (Day 28) in the PPAS. The log_{10} HAI titers fall between 0 and 4. The distribution of baseline HAI titers are similar across study groups for all 4 influenza strains. The distribution of post-vaccination (Day 28) HAI titers for A/Michigan and A/Hong Kong are similar across all 3 study groups, and all 3 study groups have higher median titers. For B/Brisbane, the titer distributions for QIV-HD and TIV-HD1 are similar with a slightly higher median for QIV-HD. Both QIV-HD and TIV-HD1 have median Day 28 titers greater than at baseline. The distribution of B/Brisbane titers for TIV-HD2, which did not contain B/Brisbane antigen, is similar to the TIV-HD2 baseline titer distribution. For B/Phuket, the titer distributions for QIV-HD and TIV-HD2 are similar and have higher medians than at baseline. The B/Phuket titer distribution for

TIV-HD1, which did not contain any B/Phuket antigen, is similar to the baseline TIV-HD1 titer distribution.

Table 12 shows the results of the primary immunogenicity analysis of the GMTRs in the PPAS: GMTRs with 95% confidence intervals comparing QIV-HD to the relevant comparator by strain. GMTRs ranged from 0.83 to 1.08, with higher GMTRs for B strains. The pre-specified non-inferiority criterion, a lower 95% confidence interval bound > 0.667, was met for all 4 strains.

Figure 2. Boxplots of Hemagglutinin Inhibition (HAI) Titers on the Log_{10} Scale by Study Group and Influenza Strain at Baseline (Day 0) and 28 Days After Vaccination (Day 28) in the Per-Protocol Analysis Set



Source: The reviewer created this figure in R 3.5.3 using the adis.xpt dataset.

Table 12. QIV-HD Post-Vaccination Geometric Mean Titer Ratios Relative to the Non-Inferiority Comparator Group by Influenza Strain with 95% Confidence Intervals Based on the Per-Protocol Analysis Set

Strain	Geometric Mean Titer Ratios*	95% Confidence Interval
A/Michigan	0.83	0.74, 0.93
A/Hong Kong	0.95	0.84, 1.01
B/Brisbane	1.08	0.96, 1.22
B/Phuket	1.00	0.88, 1.13

**QIV-HD/TIV-HD for A/Michigan and A/Hong Kong; QIV-HD/TIV-HD1 for B/Brisbane; QIV-HD/TIV-HD2 for B/Phuket*
Source: The reviewer created this table based on Table 5.1 (p. 94) from the QHD00013 final study report.

Table 13 shows the percent of subjects in the PPAS who seroconverted with 95% confidence intervals for each strain by study group. Seroconversion rates were highest for the A strains, with slightly higher seroconversion rates for A/Michigan than for A/Hong Kong. Seroconversion rates for QIV-HD were slightly lower than the rates for the relevant comparators for all 4 strains. Table 14 shows the difference in seroconversion rates between the QIV-HD and comparator groups, relative to the comparator. All four strains met the pre-specified non-inferiority success criterion.

Table 13. Percent of Per-Protocol Analysis Set Subjects Who Seroconverted at 28 Days After Vaccination with 95% Confidence Intervals by Study Group and Strain; 95% confidence intervals are indicated in parentheses.

Strain	QIV-HD	TIV-HD1	TIV-HD2	TIV-HD*
A/Michigan	50.4 (48.0, 52.8)	56.2 (51.3, 61.0)	51.2 (46.3, 56.0)	53.7 (50.2, 57.1)
A/Hong Kong	49.8 (47.3, 52.2)	52.9 (48.0, 57.7)	48.1 (43.3, 56.0)	50.5 (47.1, 53.9)
B/Brisbane	36.5 (34.2, 38.9)	39.0 (34.3, 43.8)	---	---
B/Phuket	46.6 (44.2, 49.0)	---	48.4 (43.5, 53.2)	---

*TIV-HD: combined TIV-HD1 and TIV-HD2 groups
Source: The reviewer created this table based on Table 5.2 (p. 95) from the QHD00013 final study report.

Table 14. Differences in Seroconversion Rates Between QIV-HD and the Non-Inferiority Comparator Group in the Per-Protocol Analysis Set by Influenza Strain with 95% Confidence Intervals

Strain	Difference in Seroconversion Rates*	95% Confidence Interval
A/Michigan	-3.27	-7.37, 0.86
A/Hong Kong	-0.71	-4.38, 3.42
B/Brisbane	-2.41	-7.66, 2.70
B/Phuket	-1.75	-4.83, 3.42

**QIV-HD - TIV-HD for A/Michigan and A/Hong Kong; QIV-HD - TIV-HD1 for B/Brisbane; QIV-HD - TIV-HD2 for B/Phuket*
Source: The reviewer created this tabled based Table 5.2 (p. 95) from the QHD00013 final study report.

The primary analyses were repeated using the FAS as a sensitivity analysis. The results of the primary non-inferiority analysis using the FAS (Table 15 and Table 16) are similar to the results from the analysis using the PPAS, with all 4 strains meeting the non-inferiority criteria for both the GMTs and seroconversion rates. The magnitude of the difference in A/Hong Kong seroconversion rates based on the FAS is slightly larger than that of the difference in seroconversion rates based on the PPAS, although the 95% confidence intervals from both the PPAS and FAS are consistent. This difference appears driven by a slightly lower A/Hong Kong seroconversion rate for the QIV-HD in the FAS and a slightly higher A/Hong Kong seroconversion rate for TIV-HD in the FAS, compared to the PPAS.

Table 15. QIV-HD Post-Vaccination Geometric Mean Titer Ratios Relative to the Non-Inferiority Comparator Group by Influenza Strain with 95% Confidence Intervals in the Full Analysis Set

Strain	Geometric Mean Titer Ratio*	95% Confidence Interval
A/Michigan	0.84	0.75, 0.94
A/Hong Kong	0.94	0.83, 1.05
B/Brisbane	1.07	0.95, 1.21
B/Phuket	0.98	0.87, 1.11

**QIV-HD/TIV-HD for A/Michigan and A/Hong Kong; QIV-HD/TIV-HD1 for B/Brisbane; QIV-HD/TIV-HD2 for B/Phuket*
Source: The reviewer created this table based on Table 9.65 (p. 273) of the QHD00013 final study report.

Table 16. Differences in Seroconversion Rates Between QIV-HD and the Non-Inferiority Comparator Group by Influenza Strain with 95% Confidence Intervals in the Full Analysis Set

Strain	Difference in Seroconversion Rates*	95% Confidence Interval
A/Michigan	-3.84	-7.86, 0.21
A/Hong Kong	-1.14	-5.18, 2.91
B/Brisbane	-2.58	-7.73, 2.43
B/Phuket	-1.31	-6.51, 3.86

**QIV-HD - TIV-HD for A/Michigan and A/Hong Kong; QIV-HD - TIV-HD1 for B/Brisbane; QIV-HD - TIV-HD2 for B/Phuket*
Source: The reviewer created this table based on Table 9.69 (p. 277) of the QHD00013 final study report.

Statistical Reviewer's Comment: *I have confirmed the results of primary analysis in the FAS.*

6.1.11.2 Analyses of Secondary Endpoints

Table 17 shows the GMT superiority results for each B strain. The results are similar in the FAS and the PPAS, and in both populations, the secondary superiority criteria were met for both strains. Table 18 shows the superiority results for the difference in seroconversion rates for each B strain. The results are similar in the FAS and the PPAS, and in both populations, the secondary superiority criteria were met for both strains.

Table 17. QIV-HD Post-Vaccination Geometric Mean Titer Ratios (GMTR) Relative to the Superiority Comparator Group by Influenza Strain and Analysis Set with 95% Confidence Intervals (CI) in the Full Analysis Set and Per-Protocol Analysis Set

Strain	Full Analysis Set: GMTRs (95% CI)*	Per-Protocol Analysis Set: GMTRs (95% CI)*
B/Brisbane	2.03 (1.80, 2.29)	2.04 (1.81, 2.31)
B/Phuket	2.04 (1.80, 2.32)	2.05 (1.81, 2.33)

**QIV-HD/TIV-HD2 for B/Brisbane; QIV-HD/TIV-HD1 for B/Phuket*
Source: The reviewer created this table based on Table 5.3 (p. 98) in the QHD00013 final study report.

Table 18. Differences in Seroconversion Rates Between QIV-HD and the Superiority Comparator Group by Influenza Strain and Analysis Set with 95% Confidence Intervals

Strain	Full Analysis Set: Seroconversion Rates Difference* (95% Confidence Intervals)	Per-Protocol Analysis Set: Seroconversion Rates Difference* (95% Confidence Intervals)
B/Brisbane	20.78 (16.50, 24.61)	20.78 (16.5, 24.61)
B/Phuket	29.27 (24.27, 33.29)	29.27 (24.78, 33.29)

**QIV-HD - TIV-HD2 for B/Brisbane; QIV-HD - TIV-HD1 for B/Phuket*
Source: The reviewer created this table based on Table 5.4 (p.98) in the QHD00013 final study report.

Statistical Reviewer's Comment: *I have confirmed the secondary analysis results for superiority.*

6.1.11.3 Subpopulation Analyses

Subgroup analyses included the primary analyses stratified by age group, sex, race, baseline serostatus, and prior exposure to seasonal influenza vaccines.

The distributions of HAI titers were similar across strains and timepoints for subjects 65–<75 and ≥ 75 years old in each study group. Subjects aged 75 years and older had post-vaccination GMTs and seroconversion rates that were lower compared to subjects aged 65-<75 years old, except for each B strains not included in TIV-HD1 and TIV-HD2. Seroprotection rates were similar across age groups for all strains at Day 28.

The distributions of HAI titers were similar across strains and timepoints for female and male subjects in each study group. Female subjects had somewhat higher baseline GMTs than male subjects for all strains and study groups, except in the QIV-HD group for A/Hong Kong. Female subjects had post-vaccination GMTs and seroconversion rates that were numerically higher than those for male subjects for all strains. Seroprotection rates were similar across both sexes for each study group and strain.

The distributions of HAI titers were similar across strains and timepoints for White and non-White subjects in each study group. Non-White subjects had post-vaccination GMTs and seroconversion rates that were numerically higher than White subjects. Seroprotection rates were similar for Whites and non-Whites for each study group and strain.

The distributions of HAI titers were similar across strains and timepoints for subjects with and without a prior seasonal influenza vaccine in each study group. Subjects who did not receive a prior influenza vaccine (since August 1, 2016) had higher point estimates than subjects who recently received a prior seasonal influenza vaccine for post-vaccination GMTs and seroconversion rates. Seroprotection rates were similar across subjects with and without prior seasonal influenza vaccination for each study group and strain.

There were relatively few seronegative subjects at baseline in each study group (QIV-HD: 298, TIV-HD1: 75, TIV-HD2: 61 subjects), leading to highly uncertain estimates of GMTs, seroconversion rates, and seroprotection rates. Because of the limited sample size

of seronegative subjects, no firm conclusions can be drawn about the differential effect of QIV-HD among seronegative and seropositive subjects.

Statistical Reviewer's Comment: *The applicant only presented GMTs, seroconversion rates, and seroprotection rates with 95% confidence intervals at each visit for the subgroup analyses. I have confirmed the GMTs and seroconversion rates, as well as their corresponding confidence intervals.*

None of the subgroup results presented suggest substantial differences in the immunogenicity between subgroups.

6.1.11.4 Missing Data

Subjects who discontinued were not included in any final immunogenicity analyses for which they did not have data. One QIV-HD subject (b) (6) was missing all of their Day 28 HAI data and was excluded from the FAS but did not have a protocol deviation indicating that they were lost to follow up or that they did not have a sample taken at Day 28. Two subjects, one each from the QIV-HD and TIV-HD1 groups, were each missing two HAI titers.

Statistical Reviewer's Comment: *Excluding subjects from analyses for which they are missing data assumes that their data is missing completely at random. There was no apparent evidence contradicting this assumption. In addition, the consistency between the primary immunogenicity results based on the PPAS and FAS, as well as the small number of subjects excluded from each of these sets, suggests that the results are reasonably robust to missing data.*

6.1.12 Safety Analyses

6.1.12.1 Solicited and Unsolicited Adverse Events

Solicited injection site reactions (bruising, erythema, induration, pain, swelling) and solicited systemic reactions (fever, headache, malaise, myalgia, and shivering) were collected within 7 days of vaccination. Unsolicited adverse events, including serious adverse events, were collected throughout the 28 days post-vaccination and the 6-month follow-up period, respectively. For a detailed description of the safety data collection, please refer to the clinical review.

Table 19 shows the number and percent of subjects reporting each solicited adverse event of any grade by study group. Rates were similar across study groups, with subjects most frequently reporting injection site pain and myalgia. Table 20 shows the number and percent of subjects reporting grade 3 solicited adverse events by study group. Rates were similar across the study groups, with slightly higher rates in the QIV-HD study group. Subjects most frequently reported injection site pain and myalgia.

Table 19. Number and Percent of Subjects Reporting at Least One Solicited Event of Any Grade in the 7 Days After Vaccination by Study Group

Solicited Event	QIV-HD n/N (%)	TIV-HD n/N (%)	TIV-HD1 n/N (%)	TIV-HD2 n/N (%)
Pain	731/1768 (41.3)	324/889 (36.4)	172/440 (39.1)	152/449 (33.9)
Erythema	110/1768 (6.2)	51/889 (5.7)	30/440 (6.8)	21/449 (4.7)
Swelling	86/1766 (4.9)	42/887 (4.7)	23/439 (5.2)	19/448 (4.2)
Induration	66/1766 (3.7)	31/887 (3.5)	17/439 (3.9)	14/448 (3.1)
Bruising	23/1756 (1.3)	10/887 (1.1)	6/439 (1.4)	4/448 (0.9)
Myalgia	402/1768 (22.7)	168/889 (18.9)	80/440 (18.2)	88/449 (19.6)
Headache	254/1768 (14.4)	121/889 (13.6)	63/440 (14.3)	58/449 (12.9)
Malaise	233/1768 (13.2)	119/889 (13.4)	52/440 (11.8)	67/449 (14.9)
Shivering	95/1768 (5.4)	42/889 (4.7)	20/440 (4.5)	22/449 (4.9)
Fever	7/1761 (0.4)	8/889 (0.9)	3/437 (0.7)	5/448 (1.1)

n: number of subjects reporting the event

N: total number of Safety Set subjects who are not missing data for the event

%: percent of Safety set subjects reporting the event relative to the total number of Safety Set subjects not missing data for the event

Source: The reviewer created this table based on Table 6.3 (p. 122) and Table 6.4 (p. 125) from the QHD00013 final study report.

Table 20. Number and Percent of Subjects Reporting at Least One Grade 3 Solicited Event in the 7 Days After Vaccination by Study Group

Solicited Event	QIV-HD n/N (%)	TIV-HD n/N (%)	TIV-HD1 n/N (%)	TIV-HD2 n/N (%)
Pain	12/1768 (0.7)	2/889 (0.2)	1/440 (0.2)	1/449 (0.2)
Erythema	11/1768 (0.6)	2/889 (0.2)	1/440 (0.2)	1/449 (0.2)
Swelling	5/1766 (0.3)	1/887 (0.1)	0/439 (0.0)	1/448 (0.2)
Induration	3/1766 (0.2)	1/887 (0.1)	0/439 (0.0)	1/448 (0.2)
Bruising	0/1756 (0.0)	0/887 (0.0)	0/439 (0.0)	0/448 (0.0)
Myalgia	16/1768 (0.9)	6/889 (0.7)	3/440 (0.7)	3/449 (0.7)
Malaise	13/1768 (0.7)	4/889 (0.4)	3/440 (0.7)	1/449 (0.2)
Headache	11/1768 (0.6)	4/889 (0.4)	2/440 (0.5)	2/449 (0.4)
Shivering	5/1768 (0.3)	3/889 (0.3)	3/440 (0.7)	0/449 (0.0)
Fever	3/1761 (0.2)	2/889 (0.2)	1/437 (0.2)	1/448 (0.2)

n: number of subjects reporting the event

N: total number of Safety Set subjects who are not missing data for the event

%: percent of Safety set subjects reporting the event relative to the total number of Safety Set subjects not missing data for the event

Source: The reviewer created this table based on Table 6.3 (p. 122) and Table 6.4 (p. 125) from the QHD00013 final study report.

Statistical Reviewer's Comment: *I have confirmed the results in Tables 19 and 20, other than the total number of subjects in each study group with non-missing data for Fever. Table 19 and Table 20 have the following numbers of subjects with non-missing fever data: 1761 QIV-HD, 437 TIV-HD1, and 450 TIV-HD2 subjects. However, I found the following number of subjects with non-missing fever data: 1767 QIV-HD, 439 TIV-HD1, and 449 TIV-HD2. I confirmed the number of subjects reporting any grade fevers and grade 3 fevers as shown in Table 19 and Table 20, as well as the percentages. This discrepancy does not change the safety profile because the numerical changes are minimal.*

I confirmed the number and frequency of Grade 1 and Grade 2 solicited events shown in Table 6.3 (p. 122) and Table 6.4 (p.125) of the QHD00013 final study report, as well as the confidence intervals displayed in these tables.

Unsolicited non-serious AEs were reported by 279 (15.7%) of QIV-HD subjects and 140 (15.7%) of TIV-HD subjects. The most frequently reported unsolicited non-serious AE was cough, which was reported with similar rates in the QIV-HD and TIV-HD groups.

Statistical Reviewer's Comment: *I have not confirmed the number or frequency of subjects reporting unsolicited non-serious adverse events in the QIV-HD and TIV-HD study groups. Using the adae.xpt dataset and R 3.5.3, I find that 294 (16.5%) QIV-HD subjects and 144 (16.8%) TIV-HD subjects reported unsolicited non-serious AEs. I confirmed that the most frequently reported unsolicited non-serious AE was cough.*

6.1.12.3 Deaths

There were 5 deaths reported during the study: 3 QIV-HD subjects and 2 TIV-HD1 subjects. The causes of death reported for the 3 QIV-HD subjects were prostate cancer, natural causes, and acute respiratory infection. The causes of death reported for the two TIV-HD1 subjects were brain injury following pneumonia and myocardial infarction. Two deaths occurred within 28 days of vaccination: the QIV-HD death due to natural causes occurred 6 days after vaccination and the TIV-HD1 death due to myocardial infarction occurred 25 days after vaccination. The subjects who died within 28 days of vaccination were discontinued from the study early. The three other deaths occurred during the 6-month follow-up period. All deaths were deemed unrelated to the study vaccination.

Statistical Reviewer's Comment: *I have confirmed the number of reported deaths per study group and their timing based on the adae.xpt dataset.*

6.1.12.4 Nonfatal Serious Adverse Events

124 subjects experienced 157 nonfatal SAEs during the study. Table 21 shows the number and percent of SafAS subjects who experienced a nonfatal serious adverse event by study group and time period. The rates of nonfatal SAEs are similar between the QIV-HD and TIV-HD groups.

Two subjects who experienced non-fatal SAEs were discontinued early from the study: one TIV-HD1 subject who was hospitalized for a fractured rib and diagnosed with worsening left hip osteoarthritis 21 days after vaccination and one QIV-HD subject who experienced post cardiotomy syndrome and was hospitalized 39 days after vaccination. These SAEs resolved and are not considered related to the study vaccine.

Table 21. Number of Subjects Reporting Non-Fatal Serious Adverse Events by Follow-Up Period and Study Group; numbers in parentheses are percentages of the Safety Set in each study group.

Post-Vaccination Follow-Up Period	QIV-HD (N = 1777)	TIV-HD (N = 893)
Day 0–Day 28	17 (0.96)	11 (1.23)
Day 29–6 Months	60 (3.38)	39 (4.37)
Day 0–6 Months	77 (4.33)	47 (5.62)

Source: The reviewer created this table in R 3.5.3 using the adae.xpt dataset.

Statistical Reviewer's Comment: *I have confirmed the number of subjects experiencing nonfatal SAEs and the total number of nonfatal SAEs.*

6.1.12.5 Adverse Events of Special Interest (AESI)

During the 6 months of post-vaccination follow-up, 3 subjects reported 3 AESIs: 1 in the QIV-HD study group and 2 in the TIV-HD2 study group. One subject in the QIV-HD group was diagnosed with Bell's palsy 60 days after vaccination and hospitalized. The subject recovered 2 days later. Two TIV-HD2 subjects were diagnosed with Bell's palsy at 31 and 171 days after vaccination. The subject diagnosed 31 days after vaccination was recovering by the end of the 6-month follow-up period. The subject diagnosed 171 days after vaccination had not recovered by the end of the 6-month follow-up period.

6.1.12.7 Dropouts and/or Discontinuations

All enrolled subjects were included in the SafAS. Three subjects with SAEs within 28 days of vaccination withdrew early from the study: the QIV-HD subject who died of natural causes, the TIV-HD1 subject who died of myocardial infarction, and a TIV-HD1 subject who experienced rib fracture. All three were determined unrelated to the study vaccine. One QIV-HD subject experience an SAE after 28 days that led to early withdrawal from the study: small fiber inflammatory neuropathy 40 days after vaccination, which the investigator considered related to the vaccine.

Among subjects who terminated the study early for reasons other than SAEs, there were three subjects, all in the QIV-HD group, who experienced at least one SAE. Two of these subjects were discontinued for protocol deviations, including no completion of the Day 28 visit, and one subject voluntarily withdrew from the study. No other subjects who withdrew early from the study reported any unsolicited AEs or SAEs.

Statistical Reviewer's Comment: *While the QHD00013 final study report states that a subject* (b) (6) *discontinued the study early because of an SAE (small fiber neuropathy), this subject appears to have completed all visits per the ds.xpt dataset. The QIV-HD subject who discontinued the study early, according to the ds.xpt dataset, was the subject with post-cardiotomy syndrome.*

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This BLA includes the results from QHD00013, a phase III, randomized, modified double-blind, active-controlled non-inferiority study of immunogenicity and safety of QIV-HD compared to two TIV-HD vaccines to support an indication of the prevention of influenza. QHD00013 met the pre-specified primary immunogenicity endpoint of demonstrating non-inferior HAI GMTs and seroconversion rates compared to the relevant TIV-HD comparator for all 4 influenza strains. QHD00013 also met the pre-specified secondary immunogenicity endpoints to demonstrate superior GMTs and seroconversion rates compared to the relevant TIV-HD comparator for both B strains. In QHD00013, very few subjects discontinued the study early, and the percent of subjects excluded from both the FAS and PPAS were small. Together, these results provide high-quality evidence of the non-inferiority immunogenicity of QIV-HD relative to the TIV-HD vaccines.

QHD00013 had a small percent of subjects discontinue the study early for adverse events, and the overall rates of deaths and SAEs were small. The most frequent unsolicited non-serious adverse event in all study groups was cough. The rates of solicited AEs, including injection site reactions, were comparable between QIV-HD and the TIV-HD vaccines. These results suggest that QIV-HD has a safety profile that does not differ substantially from that of TIV-HD.

10.2 Conclusions and Recommendations

In conclusion, there were no major statistical issues observed with this submission. The pre-specified immunogenicity non-inferiority criteria in QHD00013 were met and support the immunogenicity of Sanofi Pasteur Inc.'s quadrivalent high-dose influenza vaccine for the proposed indication in adults aged 65 years and older. The safety results do not suggest that Sanofi Pasteur Inc.'s quadrivalent high-dose influenza vaccine has a safety profile that differs substantially from the safety profile of TIV-HD. Based on these results, I recommend approval of QIV-HD for immunization for the prevention of influenza disease in adults aged 65 years and older.