BLA Clinical Review Memorandum

Application Type	Supplemental Biologics License Application
STN	103914/6290
CBER Received Date	4 January 2019
PDUFA Goal Date	4 November 2019
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name(s) Review Completion Date / Stamped Date	Yosefa Hefter, M.D. Susan K. Wollersheim, M.D.
Supervisory Concurrence	Maria Allende, M.D. Roshan Ramanathan, M.D., M.P.H.
Applicant	Sanofi Pasteur, Inc.
Established Name	Influenza Virus Vaccine
(Proposed) Trade Name	Fluzone High-Dose Quadrivalent
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Quadrivalent, split virion, inactivated influenza virus vaccine Each dose contains 60 µg of influenza hemagglutinin protein (240 µg total) from each of the following four influenza subtypes or lineages: • A/H1N1 • A/H3N2 • B Victoria • B Yamagata Other ingredients: • Octylphenol Ethoxylate • Buffered saline solution
Dosage Form(s) and Route(s) of Administration	Suspension for injection available in 0.7 mL single-dose, prefilled syringe
Dosing Regimen	A single 0.7 mL dose for intramuscular injection
Indication(s) and Intended Population(s)	Fluzone High-Dose is indicated for active immunization against influenza disease caused by influenza subtype A viruses and type B viruses contained in adults 65 years of age and older
Orphan Designated (Yes/No)	No

Table of Contents

Glossary 1

1. Executive Summary 2
1.1 Demographic Information: Subgroup Demographics and Analysis Summary 3
1.2 Patient Experience Data 4

2. Clinical and Regulatory Background 4
2.1 Disease or Health-Related Condition(s) Studied 4
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s) 5
2.3 Safety and Efficacy of Pharmacologically Related Products 5
2.4 Previous Human Experience with the Product (Including Foreign Experience) 6
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission 6
3.1 Submission Quality and Completeness 6
3.2 Compliance With Good Clinical Practices And Submission Integrity 7
3.3 Financial Disclosures 7

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines 7
4.1 Chemistry, Manufacturing, and Controls 7
4.2 Assay Validation 7
4.3 Nonclinical Pharmacology/Toxicology 8
4.4 Clinical Pharmacology 8
4.4.1 Mechanism of Action 8
4.5 Statistical 8
4.6 Pharmacovigilance 8

5. Sources of Clinical Data and Other Information Considered in the Review 8
5.1 Review Strategy 8
5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review 9
5.3 Table of Studies/Clinical Trials 10
5.5 Literature Reviewed 10

6. Discussion of Individual Studies/Clinical Trials 11
6.1 Trial #1 11
QHD00013 11
6.1.1 Objectives 11
6.1.2 Design Overview 12
6.1.3 Population 12
6.1.4 Study Treatments or Agents Mandated by the Protocol 13
6.1.6 Sites and Centers 14
6.1.7 Surveillance/Monitoring 14
6.1.8 Endpoints and Criteria for Study Success 15
6.1.9 Statistical Considerations & Statistical Analysis Plan 16
6.1.10 Study Population and Disposition 17
6.1.11 Efficacy Analyses 20
6.1.12 Safety Analyses 26
6.1.13 Study Summary and Conclusions 33

9. Additional Clinical Issues 34
9.1 Special Populations 34
9.1.2 Use During Lactation 34
9.1.3 Pediatric Use and PREA Considerations 34
9.1.4 Immunocompromised Patients 34

10. Conclusions 35

11. Risk-Benefit Considerations and Recommendations 36
11.1 Risk-Benefit Considerations 36
11.2 Risk-Benefit Summary and Assessment 36
11.4 Recommendations on Regulatory Actions 37
11.5 Labeling Review and Recommendations 37
11.6 Recommendations on Postmarketing Actions 37

GLOSSARY

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AESI	Adverse Events of Special Interest
AR	Adverse Reaction
BIMO	CBER Bioresearch Monitoring
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use (EMA)
CI	Confidence Interval
CFR	Code of Federal Regulations
CRF	Case Report Form
CSR	Clinical Study Report
dil	Dilution
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
GMTR	Geometric Mean Titer Ratio
HA	Hemagglutinin
HAI	Hemagglutination Inhibition Assay
ICH	International Conference on Harmonization
IND	Investigational New Drug application
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
NA	Neuraminidase
OBE	Office of Biostatistics and Epidemiology
OVRR	Office of Vaccines Research and Review
PeRC	Pediatric Review Committee
PI	Package Insert
PMC	Post marketing Commitment
PMR	Post marketing Requirement
PP	Per-protocol Analysis Set
PREA	Pediatric Research Equity Act
PT	Preferred Term
QIV	Quadrivalent influenza vaccine
QIV-HD	Fluzone High-Dose Quadrivalent
SAE	Serious Adverse Event
SAS	Safety Analysis Set
sBLA	Supplemental Biologics License Application
SCR	Seroconversion Rate
SOC	System Organ Class
STN	Submission Tracking Number
TIV	Trivalent influenza vaccine
TIV-HD	Fluzone High-Dose (trivalent)
US	United States
VRBPAC	Vaccines and Biological Products Advisory Committee
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Fluzone High-Dose is a trivalent, split-virion, inactivated, seasonal influenza virus vaccine (TIV-HD) containing 60 mcg hemagglutinin (HA) antigen per virus strain (for a total of 180 mcg HA antigen per dose) and is currently licensed for the prevention of influenza disease caused by influenza A subtype viruses and type B virus contained in the vaccine in persons 65 years of age and older. With this supplement, Sanofi Pasteur is seeking approval for the Fluzone High-Dose Quadrivalent Influenza Vaccine (QIV-HD), a quadrivalent, split-virion, inactivated, seasonal influenza vaccine containing 60 mcg hemagglutinin (HA) antigen per virus strain (for a total of 240 mcg HA antigen per dose) indicated for active immunization against influenza disease caused by influenza A subtypes and type B viruses contained in the vaccine. QIV-HD is manufactured using the same process as the currently licensed Fluzone High-Dose trivalent vaccine, with a type B strain of a second lineage added to the seasonal TIV formulation. QIV therefore contains antigens from two influenza A subtype viruses (representing the H1N1 and H3N2 subtypes) and two type B viruses (representing the B/Victoria and B/Yamagata lineages). The applicant is pursuing licensure of QIV-HD as a supplement to the existing Fluzone High Dose vaccine license based on demonstration of non-inferior immunogenicity and comparable safety with respect to TIV-HD. This supplement is intended to support the safety and effectiveness of QIV-HD in persons 65 years of age and older.

Summary of Clinical Findings

Study QHD00013 was a Phase III, randomized, modified double-blind, active-controlled, multi-center study in healthy adults 65 years of age and older to evaluate the safety and immunogenicity of Fluzone High-Dose Quadrivalent Influenza Vaccine (QIV-HD) compared to the licensed Fluzone High-Dose (Trivalent; TIV-HD1) or an investigational TIV-HD2 containing the alternate B strain. A total of 2,670 subjects were randomly assigned in 4:1:1 ratio to one of the three treatment arms.

The primary objective of the study was to demonstrate that QIV-HD induces an immune response (as assessed by hemagglutination inhibition [HAI] geometric mean titers [GMTs] and seroconversion rates) that is non-inferior to responses induced by the TIV HD1 and TIV-HD2 for the 4 virus strains at 28 days post-vaccination in all subjects. Non-inferiority was demonstrated if, for each of the common strains, the lower limit of the 2-sided 95% CI for the ratio of GMTs (QIV-HD/TIV-HD) was above 0.667 and the lower limit of the 2-sided 95% CI for the difference in seroconversion rates (QIV-HD minus TIV-HD) was above -10%. The non-inferiority criteria for the primary endpoint were met for all strains based on the ratios of GMTs and differences in seroconversion rates.

A secondary immunogenicity objective of the study was to demonstrate that each B strain in QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-HD that does not contain the corresponding B strain. Superiority of QIV-HD to each TIV-HD group was demonstrated if, for both B strains, the LL of the 2-sided 95% CI was above 1.5 for the ratios of GMTs and above 10% for seroconversion rates. The superiority criteria were met for the secondary endpoint demonstrating the superiority of QIV B strain responses compared to the cross-reactive responses generated by the TIV containing the non-corresponding B strain lineage for both B strains.

Safety data showed that solicited local adverse reactions and systemic adverse reactions occurred at similar rates between the study groups. No imbalances in the frequency or severity of unsolicited adverse events were observed between the treatment arms, and serious or uncommon conditions were not observed at unexpectedly high frequencies in any group.

A total of 128 subjects experienced serious adverse events (SAEs) during the trial period: 80/1777 (4.5%) in the QIV-HD and 48/493 (5.4%) in the pooled TIV groups. One SAE in the QIV-HD group, a

small fiber inflammatory neuropathy, was considered related to vaccination by the investigator; however, because of the presence of alternative potential causes (vitamin B12 deficiency and concomitant viral illness), it was considered unlikely to be related to vaccination by the sponsor and the reviewer. Five deaths were reported in the trial; three in the QIV-HD group (myocardial infarction; sepsis; chronic obstructive pulmonary disease exacerbation), and two in the TIV-HD1 group (myocardial infarction; sepsis/cardiac arrest). No deaths were considered related to vaccination by the sponsor or the reviewer. The percentages of subjects who reported at least 1 solicited injection site reaction were 44.1% in the QIV-HD and 39.8% in the pooled TIV-HD groups, respectively. The most common reactions occurring after QIV-HD administration were injection-site pain (41.3%), myalgia (22.7%), headache (14.4%), and malaise (13.2%), comparable to those observed with the pooled TIV-HD group. Unsolicited non-serious adverse events were reported at the same rate the QIV-HD group and in the pooled TIV-HD (15.7% in each arm). The most commonly reported unsolicited adverse event was cough.

In conclusion, the data submitted by the applicant to sBLA 103914/6290 support the safety and effectiveness of Fluzone High-Dose Quadrivalent for active immunization against influenza disease in adults 65 years of age and older. The risks of vaccination with QIV-HD in adults 65 years of age and older were found to be comparable to those of the US-licensed comparator vaccine and consistent with those of other approved inactivated influenza vaccines. Thus, the overall risk-benefit profile of QIV-HD has been determined to be favorable.

Compliance with Pediatric Research Equity Act (PREA)
Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups must be submitted at the time an application for a new active ingredient is submitted, unless the requirement for assessment has been deferred or waived. A partial waiver for conducting studies with QIV-HD in children from birth to <6 months of age was granted because the necessary studies are impossible or highly impracticable to conduct in this age group [Section 505B(a)(4)(i)]. In children <6 months of age, a clinical endpoint study would be necessary to support licensure, because the association between hemagglutination inhibition (HI) titer and protection from influenza is not well-established in this age group and the presence of maternal antibodies would confound the interpretation of immunogenicity data without relying on clinical endpoints to assess efficacy. An efficacy study would be impracticable due to considerations such as need for large sample size, timely recruitment of infants in this age cohort, and the logistics of administering 2 doses of vaccine early in the influenza season in order to assess for efficacy during the remainder of season. A deferral was granted for children 6 months through 18 years of age [Section 505B(a)(3)].

Recommendation for Regulatory Action
The clinical data submitted by the Applicant support the approval of the 0.7 mL dose of Fluzone High-Dose Quadrivalent for active immunization of adults 65 years of age and older against influenza disease caused by the influenza subtypes A and type B viruses contained in the vaccine.

Recommendation on Postmarketing Action
No safety signals were identified in the pre-licensure data. Routine pharmacovigilance will be adequate.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The study was not powered to detect differences in immunogenicity or safety with regard to age, gender or geographical ancestry. Post hoc subgroup analyses of immunogenicity and safety were performed by age, gender, and ethnicity. The subgroup analyses of immunogenicity and safety by age,

gender, and ethnicity generally were shown to be consistent with the overall immunogenicity and safety results.

1.2 Patient Experience Data

Patient Experience Data Relevant to this Application.

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Influenza, a respiratory and systemic illness caused by influenza virus infection, is an important cause of infectious morbidity and mortality worldwide. Annual influenza epidemics are responsible for an estimated 3 to 5 million cases of severe respiratory illness and about 290,000 to 650,000 deaths worldwide each year (1). In the United States, an estimated 55,000 to 431,000 hospitalizations and 3,000 to 49,000 deaths are attributed to influenza each year (2, 3). Influenza causes morbidity in all ages, with the highest rates of serious morbidity and death among older adults and persons with specific underlying medical conditions, such as chronic pulmonary or cardiac disease (4, 5). During the past 4 influenza seasons in the United States, the cumulative hospitalization rate (per 100,000) for adults over 65 years of age was up to four times higher than that of adults 18-49 years of age (4,5).

Adults ≥65 years of age also account for the majority (90%) of deaths from seasonal influenza in the United States (4,5).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently, six FDA-licensed antiviral drugs are available for use in the United States [Tamiflu® (oseltamivir phosphate), Relenza® (zanamivir), Rapivab® (peramivir), Flumadine® (rimantidine), amantadine, and Xofluza® (baloxavir marboxil). Of these, only 4 are currently recommended for use by the Centers for Disease Control and Prevention: the neuraminidase inhibitors Tamiflu, Relenza, Rapivab, and the cap-dependent endonuclease inhibitor Xofluza, which was approved for use in October 2018. Although Xofluza is approved for use in persons 12 years of age and older, adults 65 years of age and older were not included in the intial published clinical trials (6). Use of adamantine class derivatives (amantadine and Flumadine) is no longer recommended because many strains of influenza, including the 2009 H1N1 influenza, are now resistant to this class of drugs. Although neuraminidase inhibitors are currently effective against most seasonal influenza viruses, resistance to drugs in this class has developed sporadically (7).

2.3 Safety and Efficacy of Pharmacologically Related Products

Inactivated whole-virus influenza vaccines have been commercially available since the 1940s. Fluzone High-Dose is currently the only licensed high-dose inactivated trivalent influenza vaccine available for use in adults 65 years of age and older. Currently, seven inactivated trivalent standard dose influenza vaccines are licensed in the U.S for use in adults 65 years of age and older. These include Fluzone®, Flucelvax®, Fluvirin®, FluLaval®, Fluarix®, Agriflu®, and Afluria®. Fluad® is an adjuvanted inactivated trivalent standard dose (15 µg hemagglutinin (HA)/strain) influenza vaccine licensed in the U.S for use in adults 65 years of age and older In addition, five standard dose, inactivated quadrivalent influenza vaccines are available for use in adults 65 years of age and older: Afluria® Quadrivalent, Fluarix Quadrivalent®, FluLaval Quadrivalent®, Fluzone Quadrivalent®, and Flucelvax Quadrivalent. Flublok® is a recombinant protein influenza vaccine that contains 45 µg HA/strain and is licensed in the U.S. for use in adults 28 years of age and older.

Although 5 licensed, standard dose, quadrivalent influenza vaccines are currently available to adults 65 years of age and older, immune responses to yearly influenza vaccination is substantially lower in this population, possibly due to decreased T-cell-dependent antibody responses, comorbidities, and functional disabilities observed in this population (8).

Fluzone High-Dose was initially licensed for use in adults ≧65 years of age in 2009 via accelerated approval based on antibody responses assessed by hemagglutinin inhibition (HAI) assay. Traditional approval was granted in 2014 following review of a large phase IIIb/IV, randomized, modified double-blind, multi-center trial (FIM12) in elderly adults (≧65 years of age) comparing efficacy of Fluzone HD (n=15,992) to Fluzone (n=15,991) in prevention of laboratory confirmed influenza disease. The study met pre-defined criteria for demonstration of superior efficacy with respect to prevention of laboratory-confirmed, protocol defined influenza-like illness (ILI) caused by any viral types/subtypes (relative VE 24.2%; 95%CI: 9.7; 36.5). A secondary endpoint of the study also demonstrated superiority of Fluzone HD compared to Fluzone with respect to prevention of culture-confirmed, modified CDC-defined ILI caused by viral types/subtypes similar to those contained in the vaccine (relative VE 51.1%; 95%CI 16.8; 72.0) (9).

Solicited injection-site reactions and systemic adverse reactions were more frequent after vaccination with Fluzone High-Dose compared to Fluzone. The most frequent adverse reactions (occurring in ≥ 10% of persons vaccinated) associated within 7 days of use of Fluzone High-Dose in adults 65 years of

age and older are: injection-site pain, injection-site erythema, myalgia, malaise and headache. Onset of symptoms was within the first 3 days after vaccination and the majority of the reactions resolved within 3 days. Less than 1.9% of these adverse reactions were severe. No differences in serious adverse events (SAEs) or deaths was associated with use of Fluzone High-Dose when compared to Fluzone. Data on SAEs, deaths and AESIs was collected in the large phase IIIb/IV multi-center, modified double-blind, efficacy trial (FIM12) comparing 15,992 Fluzone HD recipients to 15,991 Fluzone recipients and no differences were observed.

Evidence for a causal relationship of Guillain-Barré Syndrome (GBS) with inactivated influenza vaccines is inconclusive. If an excess risk exists, it is probably slightly more than 1 additional case per 1 million persons vaccinated (10). Anaphylaxis and other allergic/hypersensitivity reactions (including Stevens-Johnson syndrome, urticarial and angioedema) have been described in association with the use of Fluzone or Fluzone High-Dose. No clinically meaningful differences between Fluzone and Fluzone High-Dose in the rates of these less common AEs was apparent in the clinical data.

In the opinion of the clinical reviewer who reviewed Fluzone High-Dose at the time of its traditional approval, the adverse event profile of Fluzone High-Dose compared to standard dose Fluzone in older adults was outweighed by the clinical benefit as demonstrated in the evaluation of efficacy in study FIM12 (11).

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

Fluzone High-Dose was licensed on December 23, 2009. As of the most recent Development Safety Update Report for Fluzone High-Dose submitted by Sanofi Pasteur, Inc. on June 23, 2014, an estimated 25,090 subjects have received Fluzone High-Dose vaccine in clinical studies since the 2006-2007 influenza seasons. Since the 2006-2007 influenza season, a total of approximately (b) (4) doses of Fluzone High-Dose have been distributed worldwide. There has been no increase in reporting frequency or event severity of any identified or potential risks associated with Fluzone vaccines, including Fluzone High-Dose. Therefore, the benefit-risk balance remains unchanged based on the collective post-marketing experience to date.

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

Sanofi Pasteur first submitted background materials for a Pre-IND Meeting about Fluzone QIV-HD in November 2016, during which advice was provided from CBER for the product development. The original IND (17556) was submitted in June 2017 containing the study protocol for QHD00013 and CBER provided advice regarding the non-inferiority margins for the primary endpoint for this study.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

This submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

According to the applicant, the single study submitted with this supplement was conducted in accordance with the standards established by the Declaration of Helsinki and compliant with the International Conference on Harmonisation (ICH) guidelines for good clinical practice (GCP) as well as with all local and/or national regulations and directives.

No CBER Bioresearch Monitoring (BIMO) inspections were conducted for the trial included in this supplement. Please see the review memo by the Office of Compliance and Biologics Quality dated March 4, 2019.

3.3 Financial Disclosures

In accordance with 21 CFR 54, Sanofi Pasteur submitted FDA Form 3454 with this supplement, certifying that the applicant had not entered into any financial arrangement with any clinical investigators involved in the trials comprising this licensure application, whereby the value of compensation to the investigator could be affected by the outcome of the study, as defined in 21 CFR 54.2(a). The applicant also certifies that each listed clinical investigator required to disclose to the applicant whether the investigator had a proprietary interest in this product or a significant equity in the applicant as defined in 21 CFR 54.2(b) did not disclose any such interests. The applicant further certifies that no investigators were the recipients of significant payments as defined in 21 CFR 54.2(f).

Table 1. Financial Disclosures for Study QHD00013

Covered clinical study (name and/or number): Study QHD00013 (NCT 03282240)		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 472		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

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

4.1 Chemistry, Manufacturing, and Controls

Review of the chemistry, manufacturing, and controls data submitted in this supplement was conducted by Dr. Jackeline Soto, OVRR/Division of Viral Products. The processes for manufacturing Fluzone Quadrivalent are the same as those of licensed Fluzone, except that an additional B strain is included at the (b) (4) step. Please see the review memo from Dr. Soto for additional details.

4.2 Assay Validation

Review of the assay validation data submitted in this supplement was conducted by Dr. Jackeline Soto, OVRR/Division of Viral Products. Please see the review memo from Dr. Soto for additional details.

4.3 Nonclinical Pharmacology/Toxicology

Review of the nonclinical pharmacology/toxicology data submitted in this supplement was conducted by Dr. Joe Sun, OVRR/Division of Vaccines and Related Products Applications and concluded that the submission contained adequate nonclinical toxicology data to support the indication from a toxicological standpoint. Please see the review memo from Dr. Sun for additional details.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vaccination against influenza results in an immune response that can be quantified by elevation in serum HAI titers. Some studies and meta-analyses associate HAI titers ≥ 1:40 with 50% reduction in the risk of contracting influenza, based on controlled influenza challenge studies in adults (12). Because these studies were conducted in younger adults and used attenuated challenge viruses to assess protection, induction of HAI titer > 1:40, has not been proven to correlate with protection of older adults from illness due to wild type influenza viruses (13). Indeed, vaccine failures have been described in association with high HAI titers previously thought to be protective (14), indicating that continued work needs to done to establish correlates of protection to support licensure of novel influenza vaccines in all populations, but particularly in older adults and others at high risk for influenza infection. However, non-inferiority comparisons of HAI GMTs and seroconversion rates have regulatory precedent for immunobridging approaches to infer effectiveness of influenza vaccines following manufacturing changes within a platform, such as addition of a second B strain.

4.5 Statistical

Statistical review of the clinical data submitted in this supplement was conducted by Dr. Jennifer Kirk, OBE/Division of Biostatistics/Vaccine Evaluation Branch. Based upon an independent examination of the submitted datasets, the reviewer concluded that the study primary and secondary endpoints were met, in addition to confirming subpopulation analyses; no safety concerns were identified. Please see the review memo from Dr. Kirk for additional details.

4.6 Pharmacovigilance

Review of the pharmacovigilance plan for Fluzone Quadrivalent was conducted by Dr. Jane Woo, OBE/Division of Epidemiology/Vaccine Safety Branch. The recommendation is that the applicant should revise the pharmacovigilance plan statement as follows: “at this time, there is limited information regarding the safety of QIV HD among immunocompromised patients, individuals with chronic debilitating diseases, and those with chronic cardiac, pulmonary, renal, or metabolic disorders (e.g., diabetes).” Routine pharmacovigilance will be adequate. Please see the review memo from Dr. Woo for additional details.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

A single phase 3 Study, QHD00013, was submitted to this BLA to serve as the primary basis for licensure and is described in detail in Section 6.1.

The clinical review was undertaken jointly by two clinical reviewers. Dr. Wollersheim focused primarily on the efficacy analysis and Dr. Hefter reviewed focused primarily on the safety analysis. The two reviewers worked jointly on synthesis of the data and overall conclusions.

The following sections were deleted from this review as they were not applicable to this application: 4.4.2: Human Pharmacodynamics, 4.4.3: Human Pharmacokinetics, 5.4: Consultations, 6.1.5: Directions for Use, 6.1.10.1.2: Medical/Behavioral Characterization of the Enrolled Population, 6.1.11.5: Exploratory and Post Hoc Analyses, 6.1.12.6: Clinical Test Results, 7: Integrated Overview of Efficacy and 8: Integrated Overview of Safety.

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

The following files served as the basis for the clinical review of STN 103914/6208:

STN 103914/6290.0 modules:

- 1.3.4 Financial Disclosures
- 1.6.3 Correspondence Regarding Meetings
- 1.9.1 Pediatric Deferral Request
- 1.9.2 Pediatric Waiver Request
- 1.14 Labeling
- 2.5 Clinical Overview
- 2.7 Clinical Summaries
- 5 Clinical Study Reports
- Amendments 5001 through 5010 were reviewed for materials relevant to the clinical review process.

5.3 Table of Studies/Clinical Trials

Table 2. Clinical Study included in sBLA 103914/6290

Study Number; Population; Country; Start/End Dates	**Study Description**	**Study Objectives**	**Test Products**	**Number of Subjects**
QHD00013 Healthy adults 65 years of age and older United States 08 Sept 2017/ 19 April 2018	Phase 3, randomized, modified double-blind, active-controlled, multi-center study	Primary Objective: Non-inferiority of antibody responses to QIV-HD compared with TIV-HDs as assessed by HAI GMTs and seroconversion rates for the 4 virus strains at 28 days postvaccination. Secondary Objectives: 1) Superiority of antibody responses to each B strain in QIV-HD compared with those of each TIV-HD not containing the corresponding B strain. 2) Describe the immune response induced by QIV-HD, TIV-HD1, and TIV-HD2 by HAI measurement method in all subjects. 3) Describe the immune response 28 days after vaccination by virus SN measurement method in a randomized subset of subjects from each study group 4) Describe the safety profile of each study group	QIV-HD: Single intramuscular dose of 0.7 mL containing 60 µg of HA/strain (total 240 µg) TIV-HD1 (Licensed): Single intramuscular dose of 0.5 mL containing 60 µg of HA/strain (total 180 µg) TIV-HD2 (Investigational): Single intramuscular dose of 0.5 mL containing 60 µg of HA/strain (total 180 µg)	**QIV-HD:** Randomized: 1777 PPAS: 1680 FAS:1763 SafAS:1777 **TIV-HD1:** Randomized: 443 PPAS: 423 FAS: 439 SafAS: 443 **TIV-HD2:** Randomized: 450 PPAS: 430 FAS: 446 SafAS: 450

Source: Adapted from STN 103914/6290: module 5.2 Tabular Listing of all Clinical Studies
FAS: full analysis set; GMT: geometric mean titer; HA: hemagglutinin; HAI: hemagglutination inhibition; PPAS: per-protocol analysis set; QIV-HD: high-dose quadrivalent influenza vaccine; SafAS: safety analysis set; SN: seroneutralization; TIV-HD: high-dose trivalent influenza vaccine

5.5 Literature Reviewed

1. World Health Organization. Influenza (Seasonal). WHO Fact Sheet. accessed October 2019 at: https://www.who.int/en/news-room/fact-sheets/detail/influenza-(seasonal)

2. Thompson, MG, et al. Influenza Div, National Center for Immunization and Respiratory Diseases, CDC. Estimate of Deaths Associated with Seasonal Influenza- United States, 1976-2007. MMWR August 27, 2010; 59(33);1057-1062. Retrieved from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5933a1.htm
3. Centers for Disease Control and Prevention (CDC). Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. Morb Mortal Wkly Rep. 2010 Aug 27;59(33):1057-62.
4. Epperson S, Blanton L, Kniss K, Mustaquim D, Steffens C, Wallis T, Dhara R, Leon M, Perez A, Chaves S, Abd Elall A, Gubareva L, Xu Xiyan, Villaneuva J, Bresse J, Cox N, Finelli L, Brammer L. Influenza Activity – United States, 2013-14 Season and Composition of the 2014-15 Influenza Vaccines. MMWR June 6, 2014, 63(22); 483-490. Retrieved from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6322a2.htm
5. Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, Fukuda K. Influenza-associated hospitalizations in the United States. JAMA. 2004 Sep 15;292(11):1333-40.
6. Hayden FG, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl Med 6 Sept 2018; 379:913-923.
7. Uyeki TM, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. CID, vol 68, Issue 6, 15 March 2019:e1-e47.
8. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. Ann Intern Med. 1995;123:518-27.
9. Fluzone High-Dose® [Package Insert]. Sanofi Pasteur Inc., Swiftwater, PA; March 2019. Accessed September 13, 2019. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM305079.pdf
10. Lasky T, Terracciano GJ, Magder L, et al. The Guillain-Barré Syndrome and the 199201993 and 1993-1994 influenza vaccines. N Engl J Medicine 1998; 339:1797-180.
11. Ramanathan, Roshan. Clinical Review, Fluzone High Dose STN 103914/5726, October 29, 2014.
12. Hobson D, Curry RL, Beare AS, Ward- Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. J. Hyg. (Lond.) 70(4),767–777 (1972).
13. Reber A, Immunological assessment of influenza vaccines and immune correlates of protection. Expert Rev Vaccines 12 (5):519-536 (2013).
14. Ohmit SE, Petrie JG, Cross RT, Johnson E, Monto AS. Influenza hemagglutination inhibition antibody titer as a correlate of vaccine-induced protection. J. Infect. Dis. 204(12), 1879–1885 (2011).

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

QHD00013

Title: Safety and Immunogenicity of High-Dose Quadrivalent Influenza Vaccine Administered by Intramuscular Route in Subjects Aged 65 Years and Older

6.1.1 Objectives

The purpose of this study was to assess immunogenicity and safety of high-dose quadrivalent influenza vaccine (QIV-HD) compared to the licensed high-dose trivalent influenza vaccine (TIV-HD1) and an investigational TIV-HD (TIV-HD2), containing the influenza B strain for the alternate lineage.

Primary Objective

To demonstrate that QIV-HD induces an immune response (as assessed by hemagglutination inhibition [HAI] geometric mean titers [GMTs] and seroconversion rates) that is non-inferior to responses induced by the TIV-HD1 and TIV-HD2 for the 4 virus strains at 28 days post-vaccination in all subjects

Secondary Objectives

Immunogenicity:

1. To demonstrate that each B strain in QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-HD that does not contain the corresponding B strain in all subjects
2. To describe the immune response induced by QIV-HD, TIV-HD1, and TIV-HD2 by HAI measurement method in all subjects
3. To describe the immune response 28 days after vaccination by virus SN measurement method in a randomized subset of subjects from each study group

Safety:

1. To describe the safety profile of all subjects in each trial group

6.1.2 Design Overview

QHD00013 was a randomized, modified double-blind, active-controlled, multi-center trial conducted in 2670 healthy subjects aged 65 years and older. Subjects were randomized into 3 groups in 4:1:1 ratio: QIV-HD, TIV-HD1, and TIV-HD2. An unblinded administrator at each site administered the vaccine. Subjects provided a pre-vaccination blood sample on Day 0 and a postvaccination blood sample on Day 28 for HAI testing. All subjects were observed for 30 minutes after vaccination, and any unsolicited systemic AEs occurring during that time were recorded as immediate unsolicited systemic AEs. Solicited reactions were collected for 7 days after vaccination, and unsolicited adverse events (AEs) were collected up to Day 28. Serious adverse events (SAEs) and adverse events of special interest (AESIs) were collected through Day 180 following vaccination.

6.1.3 Population

Inclusion Criteria

A potential subject had to meet all of the following criteria to be considered for trial enrollment:

1. Aged ≥ 65 years on the day of inclusion
2. Informed consent form has been signed and dated
3. Able to attend all scheduled visits and to comply with all trial procedures

Exclusion Criteria

A potential subject meeting any of the following criteria was ineligible for trial enrollment:

1. Participation at the time of trial enrollment (or in the 4 weeks preceding the trial vaccination) or planned participation during the present trial period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure
2. Receipt of any vaccine in the 4 weeks (28 days) preceding the trial vaccination or planned receipt of any vaccine prior to V02 (Day 28)
3. Previous vaccination against influenza (in the preceding 6 months) with either the trial vaccine or another vaccine
4. Receipt of immune globulins, blood or blood-derived products in the past 3 months
5. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months;

or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

6. Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the trial or to a vaccine containing any of the same substances
7. Thrombocytopenia or bleeding disorder, contraindicating IM vaccination based on investigator's judgment
8. Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily
9. Alcohol or substance abuse that, in the opinion of the investigator, might interfere with the trial conduct or completion
10. Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion
11. Identified as an Investigator or employee of the Investigator or trial center with direct involvement in the proposed trial, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed trial
12. Personal or family history of GBS
13. Neoplastic disease or any hematologic malignancy (except localized skin or prostate cancer that is stable at the time of vaccination in the absence of therapy and subjects who have a history of neoplastic disease and have been disease free for ≥ 5 years)
14. Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective subject should not be included in the trial until the condition has resolved or the febrile event has subsided

<u>Reviewer Comment:</u> Eligibility criteria were appropriate for this study and allow for generalizability to a population of adults aged <u>≥</u> 65 years.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects received one of the following products:

- QIV-HD: 0.7mL dose containing 60µg HA of each of the following strains (based on WHO/Vaccines and Related Biological Products Advisory Committee [VRBPAC] recommendations for the 2017-2018 northern hemisphere [NH] influenza season):
    - A/Michigan/45/2015 X-275 (H1N1) strain
    - A/Hong Kong/4801/2014 (NYMC X-263B) (H3N2) strain
    - B/Brisbane/60/2008 strain
    - B/Phuket/3073/2013 strain

  Excipients included buffered saline solution (quantity sufficient to appropriate volume) and Octylphenol Ethoxylate (Triton X-100® - not more than 350µg).
  Batch number: (b) (4)

- TIV-HD1 (Licensed Fluzone High-Dose Influenza Vaccine): 0.5mL dose containing 60µg HA of each of the following strains (based on WHO/VRBPAC recommendations for the 2017-2018 NH influenza season):
    - A/Michigan/45/2015 X-275 (H1N1) strain
    - A/Hong Kong/4801/2014 (NYMC X-263B) (H3N2) strain
    - B/Brisbane/60/2008 strain

  Excipients included buffered saline solution (quantity sufficient to appropriate volume) and Octylphenol Ethoxylate (Triton X-100®) (not more than 250µg).

Batch number: (b) (4)

- TIV-HD2: 0.5mL dose containing 60µg HA of each of the following strains (based on WHO/VRBPAC recommendations for the 2017-2018 NH influenza season):
    - A/Michigan/45/2015 X-275 (H1N1) strain
    - A/Hong Kong/4801/2014 (NYMC X-263B) (H3N2) strain
    - B/Phuket/3073/2013 strain

  Excipients were (b) (4) to TIV-HD1 product.
  Batch number: (b) (4)

Per standard practice for receipt of annual influenza vaccine, subjects received a single dose of vaccine. Vaccines were provided in pre-filled syringes and administered intramuscularly in the region of the deltoid muscle.

6.1.6 Sites and Centers

Study QHD00013 was conducted at 35 centers in the United States.

6.1.7 Surveillance/Monitoring

Study monitoring procedures are described in Table 3 below.

Table 3. Schedule of Events

Visit/Contact	Visit 1 (V1) Day 0	Day 8 (+2D) Telephone Call	Visit 2 (V2) Day 28 +7D	Day 180 (+14D) Safety Follow-Up Telephone Call
Informed Consent	X			
Inclusion/exclusion criteria	X			
Demographic data	X			
History of seasonal influenza vaccination	X			
Medical history	X			
Reportable concomitant medications	X			
Physical examination	X			
Randomization/allocation of subject number and unique dose number	X			
Blood Sampling (10mL)	X (prior to vaccination)		X	
Vaccination	X			
Immediate Surveillance (30 min)	X			
Diary Card Provided	X			
Recording of solicited injection site & systemic reactions	D0-D7			
Follow-up phone call		X		X
Collection of unsolicited AEs	V1-V2	V1-V2	V1-V2	
Diary card collected and reviewed			X	
Memory aid provided			X	
Memory aid reviewed				X
Trial active phase termination record			X	
Reporting of SAEs and AESIs	Any time	Any time	Any time	Any time

Source: Adapted from STN 103914/6290. QHD00013 Clinical Study Report Table 3.1.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint

Immunogenicity:

- HAI antibody (Ab) titers obtained on day 28 (D28)
- Seroconversion (titer < 10 [1/dil] at day 0 (D0) and post-injection titer ≥ 40 [1/dil] at D28, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold increase in titer [1/dil] at D28

Secondary Endpoints

Immunogenicity:

- HAI Ab titers obtained on D0 and D28
- Individual HAI titers ratio D28/D0
- Seroconversion (titer < 10 [1/dil] at D0 and post-injection titer ≥ 40 [1/dil] at D28, or titer ≥ 10 [1/dil] at D0 and a ≥ 4-fold increase in titer [1/dil] at D28)
- Seroprotection (titer ≥ 40 [1/dil]) at D0 and D28

Safety:

- Occurrence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term [PT]), duration, intensity, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after vaccination
- Occurrence, time to onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the trial, of solicited (prelisted in the subject's diary card and CRB) injection site reactions and systemic reactions occurring up to 7 days after vaccination
- Occurrence, nature (MedDRA PT), time to onset, duration, intensity, relationship to vaccination (for systemic AEs only), and whether the event led to early termination from the trial, of unsolicited AEs up to 28 days after vaccination
- Occurrence, nature (MedDRA PT), time to onset, seriousness criteria, relationship to vaccination, outcome, and whether the SAE led to early termination from the trial, of SAEs throughout the trial
- Occurrence, nature (MedDRA PT), and relationship to vaccination of AESIs throughout the trial

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical Methods for Primary Endpoint

Immunogenicity of QIV-HD was compared to that of TIV-HD1 and TIV-HD2. For the A strains, the comparison was made using the pooled TIV-HD groups. For each B-strain, the comparison was made with the TIV-HD strain containing the corresponding B strain.

For each strain, post-vaccination HAI GMTs and seroconversion rates were compared using a non-inferiority approach. The margins used for non-inferiority hypothesis testing were 1.5 for GMTs and 10% for seroconversion rates. The non-inferiority of QIV-HD to each TIV-HD group was demonstrated if, for each of the 3 common strains, the lower limit of the 2-sided 95% CI for the ratio of GMTs (QIV-HD/TIV-HD) was above 0.667 and the lower limit of the 2-sided 95% CI for the difference in seroconversion rates (QIV-HD minus TIV-HD) was above -10%. The non-inferiority objective was achieved if it was demonstrated for all 4 strains and for both GMTs and seroconversion rates in the per-protocol analysis set (PPAS). Analysis was also performed on the Full Analysis Set (FAS).

Statistical Methods for Secondary Endpoints

Superiority analyses were conducted for each B strain by comparing the immunogenicity of QIV-HD to the TIV-HD group not containing the corresponding B strain. Superiority of QIV-HD to each TIV-HD group was demonstrated if, for both B strains, the 2-sided 95% CI lie above 1.5 for the ratios of GMTs and above 10% for seroconversion rates. The superiority objective was achieved if superiority was demonstrated for both B strains and for both GMTs and seroconversion rates. Analyses were performed for both Full Analysis Set (FAS) and Per-Protocol Analysis Set (PPAS) but the conclusion was made from FAS results. See Section 6.1.10.1 below for definitions of analysis sets.

Safety results were analyzed descriptively for subjects in safety analysis set (SafAS) who received QIV-HD, TIV-HD1, and TIV-HD2. Solicited reactions (solicited injection site and systemic reactions),

unsolicited AEs, SAEs, and AESIs were summarized. The main parameters were described with 95% CIs (Clopper-Pearson method).

Sample Size and Power Calculation

A sample size of 2616 was determined based on an overall power of 90% for demonstrating non-inferiority for both the HAI GMTs and seroconversion rates comparing QIV-HD vs TIV-HD1 and / or TIV-HD2 for all 4 virus strains. The non-inferiority margins were defined as 1.5 for GMTs and 10% for seroconversion rates.

Assumptions for the above calculations were:

- The expected seroconversion rates for the 4 strains: 45% for A/H1N1 strain, 70% for A/H3N2 strain, and 40% for both B (B1 and B2) strains
- Assumed standard deviations for HAI GMTs: 0.63 for both A (A/H1N1 and A/H3N2) strains and 0.55 for both B strains
- An 8% attrition rate which provided approximately 2407 evaluable adults for immunogenicity analysis

Based on the planned sample size of 2616, there was 55.4% power to conclude the superiority of each B strain comparing QIV-HD groups versus either the TIV-HD1 or TIV-HD2 group in the secondary objective. This was based on an assumption of expected GMT ratio of 1.8 with a standard deviation of 0.55, seroconversion rate of 8% in the group without the B strain and 22% increase in the group with the B strain, and a 5% attrition rate in FAS.

Handling of Missing Data and Outliers

No replacement of missing data was done. For safety data, missing relationships were considered "related."

For immunogenicity data, extreme values below the lower limit of quantification (LLOQ) and above the upper limit of quantification (ULOQ) were managed as follows:

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is ≥ ULOQ (or > ULOQ), then use the computed value ULOQ

Please refer to the Statistical Review for further details of the statistical considerations and the statistical analysis plan.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Full Analysis Set (FAS)

The FAS was defined as the subset of randomized subjects who received at least 1 dose of a trial vaccine and had a post-vaccination blood sample HAI result for at least 1 strain. Subjects were analyzed according to the vaccine group to which they were randomized.

Per-Protocol Analysis Set (PPAS)

The PPAS was a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations were excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not receive vaccine
- 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
- Subject did not provide the post-dose serology sample in the proper time window (ie, 28 to 35 days after vaccination) or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited therapy/medication/vaccine
- Subject's post-dose serology sample did not produce a valid HAI assay result for any strain (ie, HAI results for all antigens were missing)
- Subject's sample was handled incorrectly during collection, processing, storage, or shipment

All protocol deviations were reviewed, and the list of the subjects excluded from the PPAS was finalized before the first database lock and unblinding of subjects' data.

Safety Analysis Set (SafAS)

The SafAS was defined as those subjects who have received study vaccine. All subjects had their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design were excluded from the analysis.

6.1.10.1.1 Demographics

Demographics of the SafAS which included all 2670 subjects in the study is summarized in Table 4 below.

Table 4. Demographics of SafAS

	QIV-HID group n (%)	TIV-HD1 group n (%)	TIV-HD2 group n (%)	All n (%)
All randomized subjects	1777	443	450	2670
Sex: n (%)				
Male	750 (42.2)	175 (39.5)	198 (44.0)	1123 (42.1)
Female	1027 (57.8)	268 (60.5)	252 (56.0)	1547 (57.9)
Missing	0	0	0	0
Sex ratio: Male/Female	0.73	0.65	0.79	0.73
Age				
M	1777	443	450	2670
Mean (SD)	72.9 (5.63)	72.8 (5.79)	73.2 (5.49)	73.0 (5.64)
Min; Max	65; 100	65; 94	65; 95	65; 100
Median	72	72	73	72
Q1;Q3	69; 77	68; 76	69; 77	69; 77
Age subgroup: n (%)				
≥65	1777 (100.0)	443 (100.0)	450 (100.0)	2670 (100.0)
66-74	1144 (64.4)	296 (66.8)	279 (62.0)	1719 (64.4)
≥75	633 (35.6)	147 (33.2)	171 (38.0)	951 (35.6)
Racial origin: n (%)				
American Indian or Alaska Native	9 (0.5)	2 (0.5)	3 (0.7)	14 (0.5)
Asian	13 (0.7)	2 (0.5)	3 (0.7)	18 (0.7)
Black or African American	123 (6.9)	41 (9.3)	35 (7.8)	199 (7.5)
Native Hawaii or other Pacific Islander	4 (0.2)	1 (0.2)	1 (0.2)	6 (0.2)
White	1618 (91.1)	395 (89.2)	402 (89.3)	2416 (90.4)
Multiple	6 (0.3)	1 (0.2)	2 (0.4)	9 (0.3)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not reported	3 (0.2)	1 (0.2)	1 (0.2)	5 (0.2)
Ethnicity				
Hispanic or Latino	50 (2.8)	9 (2.0)	14 (3.1)	73 (2.7)
Not Hispanic or Latino	1723 (97.0)	433 (97.7)	434 (96.4)	2590 (97.0)
Unknown	1 (<0.1)	0 (0.0)	1 (0.2)	2 (<0.1)
Not reported	3 (0.2)	1 (0.2)	1 (0.2)	5 (0.2)
BMI categories				
Underweight (<18.5)	18 (1.0)	0 (0.0)	1 (0.2)	19 (0.7)
Normal weight (18.5-24.9)	378 (21.3)	92 (20.8)	86 (19.1)	556 (20.8)
Overweight (25.-29.9)	592 (33.3)	162 (36.6)	160 (35.6)	914 (34.2)
Obese (≥30)	734 (41.3)	176 (39.7)	190 (42.2)	1100 (41.2)
Missing	55 (3.1)	13 (2.9)	13 (2.9)	81 (3.0)

Source: Adapted from STN 103914/6290. QHD00013 Clinical Study Report Table 9.19.
M: number of subjects with available data for the relevant endpoint
n: number of subjects fulfilling the item listed
The age of a subject in the study was the calendar age in years only.
Q1; Q3: first quartile; third quartile

Reviewer Comment: ***Subject demographics were balanced between study groups.***

6.1.10.1.3 Subject Disposition

Table 5. Subject Disposition

	QIV-HID group n (%)	TIV-HD1 group n (%)	TIV-HD2 group n (%)	All n (%)
All randomized subjects	1777	443	450	2670
Vaccinated subjects	1777 (100.0)	443 (100.0)	450 (100.0)	2670 (100.0)
Provided blood sample at visit 1	1765 (99.3)	441 (99.5)	448 (99.6)	2654 (99.4)
Present at visit 2	1767 (99.4)	440 (99.3)	447 (99.3)	2654 (99.4)
Provided blood sample at visit 2	1764 (99.3)	439 (99.1)	446 (99.1)	2649 (99.2)
D180 Follow-up phone call completed	1760 (99.0)	435 (98.2)	447 (99.3)	2642 (99.0)
Early terminations				
Total	10 (0.6)	3 (0.7)	3 (0.7)	16 (0.6)
Adverse events	2 (0.1)	2 (0.5)	0 (0.0)	4 (0.1)
Lost to follow-up	3 (0.2)	0 (0.0)	0 (0.0)	3 (0.1)
Protocol deviation	4 (0.2)	1 (0.2)	2 (0.4)	7 (0.3)
Voluntary withdrawal not due to AE	1 (0.1)	0 (0.0)	1 (0.2)	2 (0.1)
Completed trial	1767 (99.4)	440 (99.3)	447 (99.3)	2654 (99.4)

Source: Adapted from STN 103914/6290. QHD00013 Clinical Study Report, Figure 1.
n: number of subjects fulfilling the item listed

The FAS included 2648 subjects (99.2%) and excluded 22 subjects (0.8%) who had no valid post-dose serology for HAI for any strain.

The PPAS included 2533 subjects (94.9%) and excluded 137 subjects (5.1%) who had at least 1 protocol deviation. The protocol deviations were as follows:

- Post-dose serology at visit 2 not collected between days 28 and 35 post-vaccination (101 subjects (3.8%))
- Receipt of protocol prohibited therapy/medication/vaccine (30 subjects (1.1%))
- Failure to meet all inclusion and exclusion criteria (9 subjects (0.3%))
- Post-dose serology at visit 2 that did not provide valid HAI result for any strain (1 subject (<0.1%))
- Incorrectly handled sample during collection, processing, storage and shipment (1 subject (<0.1%))

The SafAS included all 2670 vaccinated subjects.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary objective of the study was to describe the antibody responses to Fluzone QIV-HD compared to the antibody responses induced by TIV-HD1 and TIV-HD2 for the four common influenza virus strains as assessed by HAI geometric mean titers (GMTs) and seroconversion rates 28 days post-vaccination. For each comparison, non-inferiority was demonstrated if the lower limit of the two-sided

95% confidence interval (CI) of the GMT ratio was > 0.67 and if the lower limit of the 2-sided 95% CI of the difference in seroconversion rates was > -10%. Analyses of the primary objective were based on the per protocol analysis set (PPAS) using pooled data from TIV-HD1 and TIV-HD2 for the A strains and data from each of the TIV-HD that contains the corresponding B strain. See Tables 6 and 7 for results.

Table 6. Post-vaccination HAI Antibody Geometric Mean Titers (GMTs) and Analyses of Non-inferiority of Fluzone High-Dose Quadrivalent Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set.

Influenza Strain	GMT	GMT	GMT	GMT Ratio	Met Predefined Noninferiority Criteria[d]
	QIV-HD N[a]=1679-1680	TIV-HD1[b] (B1 Victoria) N[a]=423	TIV-HD2[c] (B2 Yamagata) N[a]=430	QIV-HD over TIV-HD (95% CI)	
A (H1N1)[e]	312	374	374	0.83 (0.744; 0.932)	Yes
A (H3N2)[e]	563	594	594	0.95 (0.842; 1.066)	Yes
B1 (Victoria)	516	476	--	1.08 (0.958; 1.224)	Yes
B2 (Yamagata)	578	--	580	1.00 (0.881; 1.129)	Yes

Source: Adapted from sBLA 103914/6290, CSR Table 9.64.

[a] N is the number of vaccinated participants with available data for the immunologic endpoint listed

[b] TIV-HD1 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008 (B1, Victoria lineage)

[c] TIV-HD2 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Phuket/3073/2013 (B2, Yamagata lineage)

[d] Predefined noninferiority criterion for the GMT ratio: the lower limit of the 95% CI of the GMT ratio (QIV-HD divided by TIV-HD) is >0.667

[e] Pooled TIV-HD group includes subjects vaccinated with either TIV-HD1 or TIV-HD2 for the A strain comparison

Table 7. Post-vaccination Seroconversion Rates (SCR) and Analyses of Non-inferiority of Fluzone High-Dose Quadrivalent Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set.

Influenza Strain	SCR (%)[a]	SCR (%)[a]	SCR (%)[a]	Difference of Seroconversion Rates	Met Predefined Noninferiority Criteria[e]
	QIV-HD N[b]=1668-1669	TIV-HD1[c] (B1 Victoria) N[b]=420-421	TIV-HD2[d] (B2 Yamagata) N[b]=428	QIV-HD minus TIV-HD (95% CI)	
A (H1N1)[f]	50.4	53.7	53.7	-3.27 (-7.37; 0.86)	Yes
A (H3N2)[f]	49.8	50.5	50.5	-0.71 (-4.83; 3.42)	Yes
B1 (Victoria)	36.5	39.0	--	-2.41 (-7.66; 2.70)	Yes
B2 (Yamagata)	46.6	--	48.4	-1.75 (-7.04; 3.53)	Yes

Source: Adapted from sBLA 103914/6290, CSR Table 9.68

[a] Seroconversion Rates: For subjects with a pre-vaccination titer <10 (1/dil), proportion of subjects with a post-vaccination titer ≥40 (1/dil) and for subjects with a pre-vaccination titer ≥10 (1/dil), proportion of subjects with a ≥four-fold increase from pre-vaccination to post-vaccination titer

[b] N is the number of vaccinated participants with available data for the immunologic endpoint listed

[c] TIV-HD1 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Brisbane/60/2008 (B1, Victoria lineage)

[d] TIV-HD2 contained A/Michigan/45/2015 (H1N1), A/Hong Kong/4801/2014 (H3N2), and B/Phuket/3073/2013 (B2, Yamagata lineage)

[e] Predefined noninferiority criterion for seroconversion: the lower limit of the two-sided 95% CI of the difference of the seroconversion rates (QIV-HD minus TIV-HD) is > -10%

[f] Pooled TIV-HD group includes subjects vaccinated with either TIV-HD1 or TIV-HD2 for the A strain comparison

Reviewer Comment: The pre-specified noninferiority criteria for each strain were met in terms of both GMT ratios and seroconversion rates.

6.1.11.2 Analyses of Secondary Endpoints

The main secondary objective was to demonstrate that each B strain in QIV-HD induced an immune response (as assessed by HAI GMTs and seroconversion rates) that was superior to the response induced by the TIV-HD that does not contain the corresponding B strain. The superiority of QIV-HD to each TIV-HD group in terms of GMTs was demonstrated if, for each B strain (compared to the TIV-HD group not including the corresponding B strain), the lower limit of 2-sided 95% CI for the ratio of post-vaccination was > 1.5. The superiority of QIV-HD to each TIV-HD group in terms of seroconversion rates was demonstrated if, for each B strain (compared to the TIV-HD group not including the corresponding B strain), the lower limit of the 2-sided 95% CI for the difference of seroconversion rates was > 10%. Analyses of the secondary objective of superiority were based on the full analysis set (FAS).

The B/Brisbane/60/2008 GMTs of QIV-HD and TIV-HD2 were 515 and 253, respectively. The GMT ratio was 2.03; and the lower limit of the 95% CI was 1.802, which is above the preestablished superiority threshold of 1.5. The B/Phuket/3073/2013 GMTs of QIV-HD and TIV-HD1 were 573 and 280, respectively. The GMT ratio was 2.04; and the lower limit of the 95% CI was 1.804, which is above the preestablished superiority threshold of 1.5.
The B/Brisbane/60/2008 seroconversion rates for QIV-HD and TIV-HD2 were 36.3% and 15.5%, respectively. The percent difference in seroconversion rates was 20.78%; and the lower limit of the 95% CI was 16.5%, which is above the pre-established superiority threshold of 10%. The B/Phuket/3073/2013 seroconversion rates for QIV-HD and TIV-HD1 were 46.7% and 17.4%, respectively. The percent difference was 29.27%; and the lower limit of the 95% CI was 24.78%, which is above the pre-established superiority threshold of 10%

Reviewer Comment: ***The superiority criteria for the B strains were met in analysis of both the FAS and PPAS.***

6.1.11.3 Subpopulation Analyses

Subgroup analyses of the immunogenicity data were assessed by age (65 to < 75 years of age and ≥75 years of age), gender, and ethnicity (Caucasian and non-Caucasian), previous influenza vaccination status, and baseline seropositivity status. There were no clinically significant differences in immunogenicity results seen in these subgroup analyses. See Tables 8 and 9 for results of the age, gender and ethnicity subgroups.

Table 8. Subgroup Analyses of Post-vaccination HAI Antibody Geometric Mean Titers (GMTs) of Fluzone High-Dose Quadrivalent Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set.

Influenza Strain	Subgroup	QIV-HD M	QIV-HD GMT	TIV-HD1 M	TIV-HD1 GMT	TIV-HD2 M	TIV-HD2 GMT	GMT Ratio QIV-HD over TIV-HD* (95% CI)
A (H1N1)	Age: 65 through < 75 yrs	1086	351	282	450	266	395	0.83 (0.72; 9.95)
A (H1N1)	Age: ≥75 years	594	251	141	286	164	315	0.83 (0.69; 1.01)
A (H1N1)	Gender: Female	977	341	251	444	239	399	0.81 (0.70; 0.94
A (H1N1)	Gender: Male	703	275	172	316	191	321	0.86 (0.721; 1.030)
A (H1N1)	Ethnicity: Caucasian	1532	295	380	375	385	340	0.83 (0.736; 0.932)
A (H1N1)	Ethnicity: Non-Caucasian	144	547	42	521	41	662	0.93 (0.647; 1.346)
A (H3N2)	Age: 65 through < 75 yrs	1086	620	282	614	266	669	0.97 (0.837; 1.123)
A (H3N2)	Age: ≥75 years	593	470	141	539	164	503	0.91 (0.743; 1.103)
A (H3N2)	Gender: Female	976	631	251	652	239	639	0.98 (0.839; 1.141)
A (H3N2)	Gender: Male	703	479	172	506	191	555	0.9 (0.752; 1.084)
A (H3N2)	Ethnicity: Caucasian	1531	540	380	578	385	581	0.93 (0.823; 1.054)
A (H3N2)	Ethnicity: Non-Caucasian	144	881	42	701	41	784	1.19 (0.793; 1.785)
B1 (Victoria)	Age: 65 through < 75 yrs	1086	518	282	519	266	237	1 (0.860; 1.162)
B1 (Victoria)	Age: ≥75 years	594	510	141	401	164	281	1.27 (1.029; 1.572)
B1 (Victoria)	Gender: Female	977	499	251	475	239	212	1.05 (0.896; 1.231)
B1 (Victoria)	Gender: Male	703	540	172	478	191	315	1.13 (0.931; 1.372)
B1 (Victoria)	Ethnicity: Caucasian	1532	496	380	447	385	247	1.11 (0.976; 1.263)
B1 (Victoria)	Ethnicity: Non-Caucasian	144	782	42	861	41	328	0.91 (0.625; 1.317)
B2 (Yamagata)	Age: 65 through < 75 yrs	1086	643	282	288	266	671	0.96 (0.821; 1.121)
B2 (Yamagata)	Age: ≥75 years	594	476	141	271	164	458	1.04 (0.849; 1.270)
B2 (Yamagata)	Gender: Female	977	618	251	286	239	588	1.05 (0.892; 1.236)
B2 (Yamagata)	Gender: Male	703	528	172	276	191	570	0.93 (0.764; 1.121)
B2 (Yamagata)	Ethnicity: Caucasian	1532	558	380	278	385	555	1.01 (0.882; 1.146)
B2 (Yamagata)	Ethnicity: Non-Caucasian	144	863	42	325	41	860	1 (0.683; 1.471)

Source: Adapted from STN 103914/6290/5010. Efficacy Information Amendment, Table 1.
M: number of subjects with available data for the considered endpoint
CI: Confidence Interval
2-sided 95% CI is based on the Student t-distribution of logarithmic transformation of the individual titers. Antilog transformations will be applied to the results.
*For A1, A2 strains, QIV-HD will be compared with TIV-HD pooled groups. For B1 strain, QIV-HD will be compared TIV-HD1 group. For B2 strain, QIV-HD will be compared TIV-HD2 group.
Subjects with 'Nor reportable' or 'unknown' racial origin will be excluded from the analyses.

Table 9. Subgroup Analyses of Post-vaccination Seroconversion Rates (SCR) of Fluzone High-Dose Quadrivalent Relative to Fluzone High-Dose, Adults 65 Years of Age and Older, Per-Protocol Analysis Set.

Influenza Strain	Subgroup	QIV-HD n/M	QIV-HD SCR (%)	TIV-HD1 n/M	TIV-HD1 SCR (%)	TIV-HD2 n/M	TIV-HD2 SCR (%)	Difference in SCRs QIV-HD minus TIV-HD* (95% CI)
A (H1N1)	Age: 65 through < 75 yrs	583/1079	54.0	173/281	61.6	139/265	52.5	-3.11 (-8.17,2.01)
A (H1N1)	Age: ≥75 years	258/590	43.7	63/139	45.3	80/163	49.1	-3.62 (-10.50,3.25)
A (H1N1)	Gender: Female	545/971	56.1	159/248	64.1	141/237	59.5	-5.73 (-10.98,-0.35)
A (H1N1)	Gender: Male	296/698	42.4	77/172	44.8	78/191	40.8	-0.29 (-6.58,5.91)
A (H1N1)	Ethnicity: Caucasian	759/1523	49.8	210/377	55.7	191/383	49.9	-2.93 (-7.25,1.42)
A (H1N1)	Ethnicity: Non-Caucasian	80/142	56.3	25/42	59.5	25/41	61.0	-3.9 (-16.73,9.43)
A (H3N2)	Age: 65 through < 75 yrs	568/1079	52.6	155/281	55.2	133/265	50.2	-0.11 (-5.22,5.03)
A (H3N2)	Age: ≥75 years	262/589	44.5	67/139	48.2	73/163	44.8	-1.88 (-8.77,4.98)
A (H3N2)	Gender: Female	521/970	53.7	135/248	54.4	126/237	53.2	-0.1 (-5.50,5.33)
A (H3N2)	Gender: Male	309/698	44.3	87/172	50.6	80/191	41.9	-1.74 (-8.04,4.53)
A (H3N2)	Ethnicity: Caucasian	749/1522	49.2	197/377	52.3	177/383	46.2	0 (-4.34,4.34)
A (H3N2)	Ethnicity: Non-Caucasian	79/142	55.6	25/42	59.5	26/41	63.4	-5.81 (-18.55,7.54)
B1 (Victoria)	Age: 65 through < 75 yrs	447/1079	41.4	124/282	44.0	49/265	18.5	-2.54 (-9.06,3.86)
B1 (Victoria)	Age: ≥75 years	163/590	27.6	40/139	28.8	16/163	9.8	-1.15 (-9.88,6.68)
B1 (Victoria)	Gender: Female	391/971	40.3	112/249	45.0	38/237	16.0	-4.71 (-11.63,2.10)
B1 (Victoria)	Gender: Male	219/698	31.4	52/172	30.2	27/191	14.1	1.14 (-6.82,8.43)
B1 (Victoria)	Ethnicity: Caucasian	541/1523	35.5	144/378	38.1	53/383	13.8	-2.57 (-8.10,2.77)
B1 (Victoria)	Ethnicity: Non-Caucasian	68/142	47.9	20/42	47.6	11/41	26.8	0.27 (-16.46,16.70)
B2 (Yamagata)	Age: 65 through < 75 yrs	543/1079	50.3	60/282	21.3	134/265	50.6	-0.24 (-6.91,6.44)
B2 (Yamagata)	Age: ≥75 years	235/590	39.8	14/139	10.1	73/163	44.8	-4.95 (-13.54,3.48)
B2 (Yamagata)	Gender: Female	499/971	51.4	53/249	21.3	125/237	52.7	-1.35 (-8.36,5.73)
B2 (Yamagata)	Gender: Male	279/698	40.0	21/172	12.2	82/191	42.9	-2.96 (-10.90,4.78)
B2 (Yamagata)	Ethnicity: Caucasian	694/1523	45.6	61/378	16.1	179/383	46.7	-1.17 (-6.76,4.37)
B2 (Yamagata)	Ethnicity: Non-Caucasian	83/142	58.5	13/42	31.0	25/41	61.0	-2.52 (-18.22,14.59)

Source: Adapted from STN 103914/6290/5010. Efficacy Information Amendment, Table 2.
M: number of subjects with available data for the relevant endpoint
n: number of subjects fulfilling the item listed
CI: Confidence Interval
2-sided 95% CI for the difference is based on the Wilson score method without continuity correction.
*For A1, A2 strains, QIV-HD will be compared with TIV-HD pooled groups. For B1 strain, QIV-HD will be compared TIV-HD1 group. For B2 strain, QIV-HD will be compared TIV-HD2 group.
Subjects with 'Nor reportable' or 'unknown' racial origin will be excluded from the analyses.

***Reviewer Comment*: Subgroup analyses of the immunogenicity results did not reveal any clinically significant differences based on age, sex, or ethnicity. While there are numerical trends between the demographic subgroup immunogenicity results, all of the 95% CIs for GMT ratios and difference in seroconversion rates are overlapping. These trends do not raise a significant concern with respect to the efficacy of Fluzone-HD QIV within each of these subgroups.**

6.1.11.4 Dropouts and/or Discontinuations

Out of the 2670 randomized subjects, 16 (0.6%) subjects did not complete the study: 10 (0.6%), 3 (0.7%), and 3 (0.7%) subjects in the QIV-HD, TIV-HD1, and TIV-HD2 groups, respectively. Analyses using the Final Analysis Set demonstrated essentially the same results as the PPAS, so the final outcomes were not affected by subject dropouts or discontinuations.

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety analysis was conducted on the SafAS which included all 2670 vaccinated subjects. Subjects were analyzed according to the vaccine received. Subjects were observed for immediate systemic adverse events (AEs) for 30 minutes following vaccination. Solicited local and systemic adverse reactions (ARs) were collected within the first 7 days following vaccination. Unsolicited AEs were collected within the first 28 days following vaccination. Diary cards were used for collection of both ARs and AEs in the first 28 days. Serious adverse events (SAEs) and adverse events of special interest (AESIs) were collected for 180 days following vaccination.

6.1.12.2 Overview of Adverse Events

There were no significant safety imbalances between the QIV-HD group and pooled TIV-HD group. Solicited adverse reactions, both local and systemic, occurred in 53.1% of subjects in the QIV-HD group and 49.7% of subjects in the pooled TIV-HD group. In the QIV-HD and pooled TIV-HD groups, 16.4% vs. 16.5% of subjects, respectively, experienced unsolicited AEs. SAEs and deaths were uncommon. SAEs during the entire trial period occurred in 4.5% of subjects in the QIV-HD group and 5.4% of subjects in the pooled TIV-HD groups. A total of 5 deaths were reported during the trial; 3 in the QIV-HD group and 2 in the pooled TIV-HD group, representing <0.1% of subjects in each group.

Deaths, SAEs and AESIs are summarized below in Table 10.

Table 10. Serious Adverse Events throughout Trial Period

Subjects experiencing at least one SAE	**QIV-HD N=1777**	**TIV-HD1 N=443**	**TIV-HD2 N=450**	**Pooled TIV-HD N=893**
All SAEs (entire trial period) – n (%)	80 (4.5)	29 (6.5)	19 (4.2)	48 (5.4)
SAEs within 7 days	5 (0.3)	2 (0.5)	2 (0.4)	4 (0.4)
Deaths	1 (<0.1)	0 (0.0)	0 (0.0)	0 (0.0)
SAEs within 28 days	19 (1.1)	7 (1.6)	5 (1.1)	12 (1.3)
Deaths	1 (<0.1)	1 (<0.1)	0 (0.0)	1 (<0.1)
All Deaths	3 (<0.1)	2 (<0.1)	0 (0.0)	2 (<0.1)
All AESIs	1 (<0.1)	0 (0.0)	2 (0.4)	2 (0.2)

Source: Adapted from STN 103914/6290. QHD00013 Clinical Study Report, Table 9.24, 9.53
n: number of subjects experiencing the endpoint listed in the first column

Solicited Adverse Reactions

Injection site reactions and systemic ARs occurred in 53.1% of subjects in the QIV-HD group and 49.7% of subjects in the pooled TIV-HD group. Subjects in the QIV-HD group had slightly higher injection site reactions than those in pooled TIV-HD group, 44.1% vs. 39.8%. The most common local reaction was pain, occurring in 41.4% of subjects in the QIV-HD group and 36.4% of subjects in the pooled TIV-HD group. Systemic ARs were balanced between the groups, occurring in in 31.0% of subjects in the QIV-HD group and 29.7 of subjects in the pooled TIV-HD group. The most common

systemic ARs were myalgia, headache and malaise. Grade 3 solicited reactions occurred in 2.5% of subjects in the QIV-HD group and 1.5% of subjects in the pooled TIV-HD group. Solicited reactions are summarized below in Table 11.

Table 11. Subjects experiencing solicited reactions with 7 days after vaccination

Subjects who experienced at least one:	**QIV-HD N=1777**	**TIV-HD1 N=443**	**TIV-HD2 N=450**	**Pooled TIV-HD N=893**
All solicited reactions – n/M (%)	938/1768 (53.1)	235/440 (53.4)	207/449 (46.1)	442/889 (49.7)
All injection site reactions	779/1768 (44.1)	189/440 (43.0)	165/449 (36.7)	354/889 (39.8)
Pain, Any	731/1768 (41.3)	172/440 (39.1)	152/449 (33.9)	324/889 (36.4)
Pain, Grade 3	12/1768 (0.7)	1/440 (0.2)	1/449 (0.2)	2/889 (0.2)
Erythema, Any	110/1768 (6.2)	30/440 (6.8)	21/449 (4.7)	51/889 (5.7)
Erythema, Grade 3	11/1768 (0.6)	1/440 (0.2)	1/449 (0.2)	2/889 (0.2)
Swelling, Any	86/1766 (4.9)	23/439 (5.2)	19/448 (4.2)	42/887 (4.7)
Swelling, Grade 3	5/1766 (0.3)	0/439 (0)	1/448 (0.2)	1/887 (0.1)
Induration, Any	66/1766 (3.7)	17/439 (3.9)	14/448 (3.1)	31 (3.5)
Induration, Grade 3	3/1766 (0.2)	0/439 (0)	1/448 (0.2)	1/887 (0.1)
Bruising, Any	23/1765 (1.3)	6/439 (1.4)	4/448 (0.9)	10/887 (1.1)
Bruising, Grade 3	0/1765 (0)	0/439 (0)	0/448 (0)	0/887 (0)
All systemic reactions	548/1768 (31.0)	132/440 (30.0)	132/449 (29.4)	254/889 (29.7)
Myalgia, Any	402/1768 (22.7)	80/440 (18.2)	88/449 (19.6)	168/889 (18.9)
Myalgia, Grade 3	16/1768 (0.9)	3/440 (0.7)	3/449 (0.7)	6/889 (0.7)
Headache, Any	254/1768 (14.4)	63/440 (14.3)	58/449 (12.9)	121/889 (13.6)
Headache, Grade 3	11/1768 (0.6)	2/440 (0.5)	2/449 (0.4)	4/889 (0.4)
Malaise, Any	233/1768 (13.2)	52/440 (11.8)	67/449 (14.9)	119/889 (13.4)
Malaise, Grade 3	13/1768 (0.7)	3/440 (0.7)	1/449 (0.2)	4/889 (0.4)
Shivering, Any	95/1768 (5.4)	20/440 (4.5)	22/449 (4.9)	42/889 (4.7)
Shivering, Grade 3	5/1768 (0.3)	3/440 (0.7)	0/449 (0)	3/889 (0.3)
Fever, Any	7/1761 (0.4)	3/437 (0.7)	5/448 (1.1)	8/885 (0.9)
Fever, Grade 3	3/1761 (0.2)	1/437 (0.2)	1/448 (0.2)	2/885 (0.2)
All grade 3 solicited reactions	44/1768 (2.5)	5/440 (1.1)	8/449 (1.8)	13/889 (1.5)
Grade 3 injection site reactions	26/1768 (1.5)	2/440 (0.5)	2/449 (0.4)	4/889 (0.4)
Grade 3 systemic reactions	28/1768 (1.6)	3/440 (0.7)	6/449 (1.3)	9/889 (1.0)

Source: Adapted from STN 103914/6290. QHD00013 Clinical Study Report, Tables 9.25, 9.26, 9,28, 9.36

n: number of subjects experiencing the endpoint listed in the first column

M: number of subjects with available data for the relevant endpoint

Reviewer Comment: ***Slightly greater reactogenicity, including slightly higher rates of grade 3 reactions, in the QIV-HD group is likely due to the higher HA content in the quadrivalent formulation. This does not represent a safety concern.***

Unsolicited Adverse Events

Seven subjects experienced immediate adverse events within 30 minutes of vaccination. Five were in the QIV-HD group (0.3%) and 2 were in the pooled TIV-HD group (0.2%). None of these events were reported as serious or grade 3. The AEs in the QIV-HD group included procedural dizziness, vertigo, conversion disorder (diagnosed as "globus hystericus"), blurred vision, emotional disorder, arthralgia and fatigue. In three of the five subjects in the QIV-HD these resolved on the day of vaccination. In all subjects these resolved by day 28.

Unsolicited AEs within 28 days following vaccination were balanced between groups and occurred in 16.4% of subjects in the QIV-HD group and 16.5% of subjects in the pooled TIV-HD group. The greatest number of subjects experienced AEs in the "infections and infestations" MEDRA system organ class (SOC), occurring in 4.3% of subjects in the QIV-HD group and 4.6% of subjects in the pooled TIV-HD group. Cough was the most common unsolicited AE by preferred term and occurred in 1.7% subjects in both QIV-HD and pooled TIV-HD groups. A slightly higher percentage of subjects in QIV-HD group experienced AEs related to the musculoskeletal system than in the pooled TIV-group, 2.7% vs. 1.5%. Unsolicited adverse events are summarized in Tables 12 and 13 below.

Table 12. Subjects experiencing unsolicited AEs within 28 days after vaccination

Subjects who experienced at least one:	**QIV-HD N=1777**	**TIV-HD1 N=443**	**TIV-HD2 N=450**	**Pooled TIV-HD N=893**
Immediate AE (within 30 minutes) – n (%)	5 (0.3)	0 (0.0)	2 (0.4)	2 (0.2)
Unsolicited AE within 28 days	292 (16.4)	79 (17.8)	68 (15.1)	147 (16.5)
Unsolicited AR within 28 days	35 (2.0)	8 (1.8)	9 (2.0)	17 (1.9)
Unsolicited AE within 7 days	149 (8.4)	41 (9.3)	36 (8.0)	77 (8.6)
Unsolicited AR within 7 days	34 (1.9)	7 (1.6)	9 (2.0)	16 (1.8)
Grade 3 unsolicited non-serious AE within 28 days	14 (0.8)	3 (0.7)	7 (1.6)	10 (1.1)

Source: Adapted from STN 103914/6290. QHD00013 Clinical Study Report, Tables 9.24, 9.43, 9.44.
n: number of subjects experiencing the endpoint listed in the first column

Table 13. Subjects experiencing unsolicited AEs within 28 days following vaccination injection, by MEDRA system organ class (SOC) and preferred term (PT)

Subjects who experienced at least one AE by SOC, PT:	QIV-HD N=1777	TIV-HD1 N=443	TIV-HD2 N=450	Pooled TIV-HD N=893
Infections and infestations – n (%)	77 (4.3)	23 (5.2)	18 (4.0)	41 (4.6)
Upper respiratory tract infection	19 (1.1)	9 (2.0)	3 (0.4)	12 (1.3)
Urinary Tract infection	14 (0.8)	2 (0.5)	2 (0.4)	4 (0.4)
Nasopharyngitis	12 (0.7)	3 (0.7)	2 (0.4)	5 (0.6)
Respiratory, thoracic and mediastinal	61 (3.4)	21 (4.7)	13 (2.9)	34 (3.8)
Cough	30 (1.7)	10 (2.3)	5 (1.1)	15 (1.7)
Rhinorrhea	14 (0.8)	4 (0.9)	1 (0.2)	5 (0.6)
Oropharyngeal pain	12 (0.7)	4 (0.9)	4 (0.9)	8 (0.9)
Nasal congestion	8 (0.5)	5 (1.1)	3 (0.7)	8 (0.9)
Musculoskeletal and connective tissue	48 (2.7)	7 (1.6)	6 (1.3)	13 (1.5)
Back pain	10 (0.6)	2 (0.5)	1 (0.2)	3 (0.3)
Gastrointestinal	40 (2.3)	11 (2.5)	6 (1.3)	17 (1.9)
Diarrhea	14 (0.8)	1 (0.2)	4 (0.9)	5 (0.6)
Nausea	12 (0.7)	4 (0.9)	2 (0.4)	6 (0.7)
General and administration site	33 (1.9)	8 (1.8)	10 (2.2)	18 (2.0)
Injury, poisoning and procedural complications	30 (1.7)	7 (1.6)	8 (1.8)	15 (1.7)
Nervous system	20 (1.1)	7 (1.6)	9 (2.0)	16 (1.8)
Headache	6 (0.3)	2 (0.5)	3 (0.7)	5 (0.6)
Skin and subcutaneous tissue	13 (0.7)	5 (1.1)	4 (0.9)	9 (1.0)
Cardiac	9 (0.5)	2 (0.5)	4 (0.9)	6 (0.7)
Ear and labyrinth	8 (0.5)	1 (0.2)	0 (0.0)	1 (0.1)
Eye	6 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular	6 (0.3)	0 (0.0)	1 (0.2)	1 (0.1)
Investigations	5 (0.3)	0 (0.0)	3 (0.7)	3 (0.3)
Renal and Urinary	5 (0.3)	1 (0.2)	1 (0.2)	2 (0.2)
Neoplasms	4 (0.2)	2 (0.5)	3 (0.7)	5 (0.6)
Psychiatric	4 (0.2)	2 (0.5)	2 (0.4)	4 (0.4)
Metabolism	3 (0.2)	1 (0.2)	2 (0.4)	3 (0.3)
Blood and lymphatic	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Immune System	2 (0.1)	0 (0.0)	1 (0.2)	1 (0.1)
Endocrine	1 (<0.1)	0 (0.0)	1 (0.2)	1 (0.1)
Hepatobiliary	1 (<0.1)	0 (0.0)	1 (0.2)	1 (0.1)
Reproductive systems and breast	1 (<0.1)	1 (0.2)	1 (0.2)	2 (0.2)

Source: Adapted from STN 103914/6290. QHD00013 Clinical Study Report, Table 9.47
n: number of subjects experiencing the endpoint listed in the first column

<u>Reviewer Comment:</u> Total unsolicited AEs, including grade 3 AEs, were balanced between the groups. A slightly higher percentage of subjects in the QIV-HD group had AEs related to the musculoskeletal system. However, the overall number of events was low making it difficult to determine the significance of this difference.

6.1.12.3 Deaths

Five deaths were reported during the 180-day trial period. Three occurred in the QIV-HD group and 2 occurred in the TIV-HD1 group. One death in the QIV-HD group occurred within the first 7 days following vaccine injection and 1 death in the TIV-HD1 group occurred within 28 days following vaccine injection. None were assessed to be related to the vaccine by the investigator. The deaths are summarized below:

- Subject (b) (6) in the QIV-HD group was a 75-year-old male who died suddenly of natural causes (b) (6) days after vaccination. His known medical problems included hypertension and coronary artery disease (CAD) and a history of a previous myocardial infarction and angina with exertion. The subject was found unresponsive in his garage by a neighbor five hours after he had been working in his yard with his neighbor. He was suspected of having a myocardial infarction (MI), arrythmia or massive stroke by a cardiologist. No diagnostics, including no laboratory tests or an autopsy, were performed.
- Subject (b) (6) in the TIV-HD1 group was a 75-year-old female who experienced an MI 25 days after vaccination. Her known medical problems included CAD hypercholesterolemia, COPD, depression and hypertension. The subject had an MI leading to hospitalization and death on the (b) (6). An autopsy performed the day after death revealed an MI as the primary cause of death.
- Subject (b) (6) in the TIV-HD1 group was a 92-year-old man who was diagnosed with pneumonia 87 days after vaccination requiring hospitalization. The subject's known medical problems included CAD, hypothyroidism, dementia, sleep apnea, hypertension, peripheral edema, esophageal varices, esophagitis and atrial fibrillation. Thirty-four days following receipt of the control vaccine, the subjected was admitted to the hospital for a syncopal episode and productive cough. Left upper lobe pneumonia was seen on chest x-ray. He received antibiotics and was discharged 2 days later. On day 87 following vaccination he had 2 falls and experienced loss of consciousness. He was taken to the emergency room and developed a fever later that day. Pneumonia was diagnosed. He was admitted to the hospital the following day and developed signs of severe sepsis. He died 19 days later following a cardiac arrest.
- Subject (b) (6) in the QIV-HD group was a 90-year-old man admitted to the hospital with prostate cancer 105 days after vaccination. His known medical problems included diabetes mellitus, enlarged prostate, hematuria and dementia. He was admitted to the hospital 105 days after vaccination for decreased ability to reorient and increased fatigue. Prostate cancer with metastasis was seen on imaging studies. On the day following hospital admission a blood culture grew methicillin sensitive *staphylococcus aureus.* The subject died 6 days later.
- Subject (b) (6) in the QIV-HD group was an 80-year-old female who experienced an acute respiratory infection 168 days after vaccination. Her known medical problems included COPD. She was admitted to the hospital with cough and shortness of breath. She was admitted to the hospital for an exacerbation of COPD. She treated with IV antibiotics and steroids but her condition continued to deteriorate. The subject died 5 days later.

Reviewer Comment: ***One subject in the QIV-HD group died within 7 days of vaccination, and the cause of death is unknown. According to the narrative provided in the CSR appendix 19 as summarized above, the subject was a 75-year-old male with a long-standing history (>20 years) of hypertension, coronary artery disease and had a previous myocardial infarction. He reportedly had a negative thallium stress test 2 days prior to vaccination.*** (b) (6) ***days following vaccination the subject was found unresponsive in his home by a neighbor. No lab tests or autopsy was performed. His death was presumed to be the result of a myocardial infarction, arrythmia or stroke. In the opinion of the reviewer, these suspected causes of death are more likely than a vaccine-related event***

given the subject's age and comorbidities. The overall favorable safety profiles of inactivated influenza vaccines, and Fluzone specifically, favor that the subject's death was unrelated to vaccination with Fluzone QIV-HD.

6.1.12.4 Nonfatal Serious Adverse Events

A total of 128 subjects experienced SAEs during the trial period: 80/1777 (4.5%) in the QIV-HD group and 48/493 (5.4%) in the pooled TIV groups. Of these, 123 subjects had non-fatal SAEs. The greatest percentage of subjects experienced cardiac-related SAEs, occurring in 16 (0.9%) subjects in the QIV-HD group and 10 (1.1%) subjects in the pooled TIV-HD group. SAEs by SOC and PT during the first 28 days are summarized in Table 14 below. Most of the SAEs occurred following the 28-day post vaccination period. None of the SAEs within the 28-day period were considered related to vaccination. One SAE was considered related to vaccination by the investigator: A subject in the QIV-HD group was diagnosed with small fiber inflammatory neuropathy 40 days following vaccination. Her symptoms included, tinnitus, fatigue, shaking, numbness/tingling in hands and feet, and taste of infection in her mouth. She was reported to have a mild upper respiratory tract infection 1 week prior to symptom onset. She was diagnosed with a vitamin B12 deficiency about 1 month after symptoms started for which supplements were started. This adverse event was considered related to vaccination by the investigator, but unrelated by the sponsor.

***Reviewer Comment:* SAEs in this trial were balanced between treatment arms and largely consistent with medical conditions observed in the age group studied. According to the Centers for Disease Control, heart disease is the leading cause of mortality and morbidity in adults 65 years and older. Approximately 25% of this population has a diagnosed heart disease. There were no concerning signals of imbalance between study groups. Regarding the single SAE deemed related to vaccination by the investigator, this reviewer is of the opinion that the vitamin B12 deficiency is a plausible etiology for the subject's symptoms and it is unlikely that this SAE was vaccine related. The occurrence in a single subject does not represent a significant safety concern.**

Table 14. Subjects experiencing SAEs with 28 days following vaccination by system organ class (SOC) and preferred term (PT)

Subjects who experienced SAE by SOC, PT:	QIV-HD N=1777	TIV-HD1 N=443	TIV-HD2 N=450	Pooled TIV-HD N=893
All SAEs – n (%)	19 (1.1)	7 (1.6)	5 (1.1)	12 (1.3)
Cardiac disorders	7 (0.4)	2 (0.5)	1 (0.2)	3 (0.3)
Acute myocardial infarction	2 (0.1)	0 (0)	0 (0)	0 (0)
Myocardial infarction	2 (0.1)	1 (0.2)	0 (0)	1 (0.1)
Atrial fibrillation	1 (<0.1)	0 (0)	0 (0)	0 (0)
Coronary artery disease	1 (<0.1)	1 (0.2)	0 (0)	1 (0.1)
Sinus bradycardia	1 (<0.1)	0 (0)	0 (0)	0 (0)
Ventricular tachycardia	1 (<0.1)	0 (0)	0 (0)	0 (0)
Cardiac failure congestive	0 (0)	0 (0)	1 (0.2)	1 (0.1)
Gastrointestinal disorders	3 (0.2)	2 (0.5)	0 (0)	2 (0.2)
Pancreatitis	2 (0.1)	0 (0)	0 (0)	0 (0)
Small intestinal obstruction	1 (<0.1)	0 (0)	0 (0)	0 (0)
Diverticulum intestinal hemorrhagic	0 (0)	1 (0.2)	0 (0)	1 (0.1)
Gastrointestinal hemorrhage	0 (0)	1 (0.2)	0 (0)	1 (0.1)
General disorders and administration site conditions	2 (0.1)	0 (0)	1 (0.2)	1 (0.1)
Non-cardiac chest pain	1 (<0.1)	0 (0)	0 (0)	0
Pyrexia	0 (0)	0 (0)	1 (0.2)	1 (0.1)
Sudden death	1 (<0.1)	0 (0)	0 (0)	0 (0)
Infections and infestations	2 (0.1)	0 (0)	0 (0)	0 (0)
Diverticulitis	1 (<0.1)	0 (0)	0 (0)	0 (0)
Bacteremia	1 (<0.1)	0 (0)	0 (0)	0 (0)
Nervous system disorders	2 (0.1)	0 (0)	2 (0.4)	2 (0.2)
Syncope	0 (0)	0 (0)	1 (0.2)	1 (0.1)
Transient ischemic attack	1 (<0.1)	0 (0)	0 (0)	0 (0)
Cerebrospinal fluid leakage	1 (<0.1)	0 (0)	0 (0)	0 (0)
Seizure	0 (0)	0 (0)	1 (0.2)	1 (0.1)
Musculoskeletal and connective tissue disorders	1 (<0.1)	0 (0)	0 (0)	0 (0)
Back pain	1 (<0.1)	0 (0)	0 (0)	0 (0)
Neoplasms benign, malignant and unspecified	1 (<0.1)	1 (0.2)	0 (0)	1 (0.1)
Cholangiocarcinoma	1 (<0.1)	0 (0)	0 (0)	0 (0)
Uterine leiomyoma	0 (0)	1 (0.2)	0 (0)	1 (0.1)
Psychiatric disorders	1 (<0.1)	0 (0)	0 (0)	0 (0)
Mental status changes	1 (<0.1)	0 (0)	0 (0)	0 (0)
Renal and urinary disorders	1 (<0.1)	0 (0)	0 (0)	0 (0)
Nephropathy	1 (<0.1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorder	1 (<0.1)	1 (0.2)	0 (0)	1 (0.1)
Pulmonary embolism	1 (<0.1)	0 (0)	0 (0)	0 (0)
Chronic obstructive pulmonary disease	0 (0)	1 (0.2)	0 (0)	1 (0.1)
Vascular disorders	1 (<0.1)	0 (0)	0 (0)	0 (0)
Peripheral vascular disorders	1 (<0.1)	0 (0)	0 (0)	0 (0)
Hepatobiliary disorders	0 (0)	0 (0)	1 (0.2)	1 (0.1)
Cholangitis	0 (0)	0 (0)	1 (0.2)	1 (0.1)
Injury, poisoning and procedural complications	0 (0)	1 (0.2)	0 (0)	1 (0.1)
Bone contusion	0 (0)	1 (0.2)	0 (0)	1 (0.1)
Rib fracture	0 (0)	1 (0.2)	0 (0)	1 (0.1)
Metabolism and nutrition disorders	0 (0)	0 (0)	1 (0.2)	1 (0.1)
Type 2 diabetes mellitus	0 (0)	0 (0)	1 (0.2)	1 (0.1)

Source: Adapted from STN 103914/6290. QHD00013 Clinical Study Report, Table 9.57
n: number of subjects experiencing the endpoint listed in the first column

6.1.12.5 Adverse Events of Special Interest (AESI)

AESIs were captured as SAEs throughout the 180-day trial period. AESIs included: new onset of GBS, encephalitis/myelitis (including transverse myelitis), Bell's palsy, optic neuritis and brachial neuritis. Three AESIs occurred during the trial, 1 in QIV-HD group and 2 in TIV-HD2 group. All 3 occurred following 28 days post-vaccination. They are summarized below:

- Subject (b) (6) in the QIV-HD group was a 78 year-old male who experienced facial paralysis and was diagnosed with Bell's palsy 60 days after vaccination. The subject experienced diverticulitis at the same time and was hospitalized. The subject recovered from Bell's palsy 2 days later.
- Subject (b) (6) in the TIV-HD2 group was a 66 year year-old woman who experienced facial paralysis 31 days after vaccination and was diagnosed with bilateral Bell's palsy. The subject was recovering from the condition by the end of the 6-month follow-up period.
- Subject (b) (6) in the TIV-HD2 group was a 75 year-old male who experienced facial paralysis 171 days after vaccination and was diagnosed with Bell's palsy on the right side of the face. By the end of the 6-month follow-up period, the event was ongoing and the subject had not reported recovering from the condition.

Reviewer Comment: ***Few AESIs were reported in this trial and they were distributed among groups. These do not represent a safety concern for QIV-HD.***

6.1.12.7 Dropouts and/or Discontinuations

A total of 16 subjects (0.6%) were discontinued from the trial prior to 28 days. Four of these were due to an AE; two subjects each in the QIV-HD and TIV-HD1 groups. The other subjects were discontinued due to loss to follow-up, protocol deviations and voluntary withdrawal. See Table 5 above titled "Subject Disposition" for discontinuations by study group.

Review Comment: ***As very few subjects were discontinued from the trial this does not present a concern for the integrity of the safety data. Of note, subject*** (b) (6) ***is listed as discontinued due to a protocol deviation. This subject missed visit 2 due to a myocardial infarction. This event was recorded as an SAE.***

6.1.12.8 Subpopulation Analyses

A post-hoc analysis of safety, including ARs within 7 days, AEs within 28 days, SAEs, deaths and AESIs during the entire trial period, by age (65 through <75 years and ≥ 75 years), gender and race did not reveal any imbalance between QIV-HD and the pooled TIV-HD group.

6.1.13 Study Summary and Conclusions

In summary, study QHD00013 was a Phase III, randomized, modified double-blind, active-controlled, multi-center study in healthy adults 65 years of age and older to evaluate the safety and immunogenicity of Fluzone High-Dose Quadrivalent Influenza Vaccine (QIV-HD) compared to the licensed Fluzone High-Dose (Trivalent; TIV-HD1) or an investigational TIV-HD2 containing the alternate B strain. A total of 2,670 subjects were randomly assigned in 4:1:1 ratio to one the three treatment arms.

The primary immunogenicity objective was met with demonstration of non-inferiority of QIV-HD to TIV-HD1 and TIV-HD2 as assessed by HAI GMTs and seroconversion rates for all 4 influenza strains 28 days post-vaccination. The secondary immunogenicity objective of the study was met with

demonstration that each B strain in QIV-HD induces an immune response (as assessed by HAI GMTs and seroconversion rates) that is superior to the response induced by the TIV-HD that does not contain the corresponding B strain.

Safety data showed that local and systemic reactogenicity were balanced between treatment arms. No imbalances in the frequency or severity of unsolicited adverse events were observed between the treatment arms, and serious or uncommon conditions were not observed at unexpectedly high frequencies in any group. SAEs in the first 28 days and throughout the trial period occurred at similar rates in all groups. Five deaths occurred during the trial and were all considered unrelated to vaccination.

In conclusion, the efficacy and safety data from QHD00013 supports the use of Fluzone High-Dose Quadrivalent in adults 65 years of age and older.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No pregnancies were reported in this study as it was conducted in an older adult population. There are insufficient data to establish the safety of Fluzone HD Quadrivalent in pregnant women.

9.1.2 Use During Lactation

No data were reported regarding use during lactation in this study which was conducted in an older adult population.

9.1.3 Pediatric Use and PREA Considerations

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), an assessment of the safety and effectiveness of the product for the claimed indication in all pediatric age groups must be submitted at the time an application for a new active ingredient is submitted, unless the requirement for assessment has been deferred or waived. A partial waiver for conducting studies with QIV-HD in children from birth to <6 months of age was granted because the necessary studies are impossible or highly impracticable to conduct in this age group [Section 505B(a)(4)(i)]. In children <6 months of age, a clinical endpoints study would be necessary to support licensure, because the association between hemagglutination inhibition (HI) titer and protection from influenza is not well-established in this age group and the presence of maternal antibodies would confound the interpretation of immunogenicity data without relying on clinical endpoints to assess efficacy. An efficacy study would be impracticable due to considerations such as need for large sample size, timely recruitment of infants in this age cohort, and the logistics of administering 2 doses of vaccine early in the influenza season in order to assess for efficacy during the remainder of season. A deferral was granted for children 6 months through 18 years of age [Section 505B(a)(3)]. The pediatric development plan was presented to the Pediatric Review Committee on August 21, 2019, and the Committee concurred with CBER's assessment.

9.1.4 Immunocompromised Patients

Fluzone QIV-HD has not been studied in immunocompromised patients.

10. CONCLUSIONS

The clinical data submitted in this supplement support the safety and effectiveness of Fluzone Quadrivalent High-Dose in persons 65 years of age and older. The clinical recommendation is for traditional approval, based on the demonstration of non-inferior immunogenicity for the three influenza strains included in the currently licensed Fluzone High-Dose vaccine and superiority for the B strains not included in the trivalent vaccine comparators, as well as a similar safety profile compared to the licensed Fluzone High-Dose trivalent vaccine.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 15. Risk Benefit Considerations for Fluzone High Dose Quadrivalent in Adults >65 years of age.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• During the past influenza season (2018-2019), an estimated 531,000 to 647,000 hospitalizations and 36,000 to 61,200 deaths were related to influenza disease. • An estimated 50 to 70 percent of influenza hospitalizations occur in adults 65 years of age and older • An estimated 70 to 90 percent of influenza deaths occur in adults 65 years of age and older.	• Influenza is a major cause of morbidity and mortality in the US. • A substantial proportion of infections result in serious or life-threatening disease, particularly among high-risk groups such as the elderly
Unmet Medical Need	• Currently, 5 licensed, standard dose, quadrivalent, inactivated influenza vaccines are available to adults 65 years of age and older. However, immune responses to standard dose seasonal influenza vaccination is lower in this population. • One licensed high dose inactivated influenza vaccine, Fluzone HD, is available but only in a trivalent formulation. The high-dose trivalent formulation has been shown to have greater efficacy in prevention of influenza disease than the standard dose trivalent formulation in an elderly population.	• In adults 65 years of age and older, there is an unmet medical need for effective prevention of influenza infection caused by the 4 strains of influenza recommended for inclusion in quadrivalent formulations of the vaccine.
Clinical Benefit	• Clinical trial QHD00013 in adults ≥65 years of age demonstrated immunologic non-inferiority between Fluzone HD Quadrivalent and two alternative Fluzone HD trivalent formulations with respect to the strains matched between vaccines. Immunologic superiority was demonstrated for the B strains contained in the quadrivalent formulation compared with each of the trivalent formulations not containing those strains.	• The submitted study supports clinical effectiveness of Fluzone HD Quadrivalent based on the established non-inferiority criteria for immunogenicity used.
Risk	• Clinical trial QHD00013 did not reveal a significant safety concern associated with the use of Fluzone High-Dose Quadrivalent in adults 65 years of age and older. Data from 2.670 adults 65 years of age and older, did not demonstrated a significant increase in solicited local and systemic adverse reactions within one-week post-vaccination with Fluzone HD Quadrivalent compared to the trivalent formulation (Fluzone HD). No difference in rates of death and SAEs up to 6 months post-vaccination was observed. No other safety signals were apparent.	• The risks of vaccination with Fluzone HD Quadrivalent in adults ≥65 years of age appear to minor and similar to those associated with the trivalent formulation of Fluzone HD.
Risk Management	• The package insert lists the most common risks of vaccination with Fluzone High-Dose Quadrivalent (occurring in > 10% of subjects). These are: injection site pain, myalgia, headache and malaise. However, the majority of these local and systemic injection site reactions are mild in severity and resolved without sequelae.	• The package insert and existing pharmacovigilance plan adequately manage these risks.

11.2 Risk-Benefit Summary and Assessment

Based on the demonstration of non-inferiority in antibody responses (HAI) in comparison to responses to licensed trivalent high dose influenza vaccine, and superiority of HAI responses to influenza B strains in comparison to those elicited by trivalent vaccines that did not include those lineages, the data submitted to this BLA supplement establish clinical benefit in persons 65 years of age and older receiving Fluzone High-Dose Quadrivalent (HD-QIV) for the prevention of influenza disease caused by influenza subtype A viruses and type B virus contained in the vaccine. No safety signals were identified, and the safety profile of HD-QIV is similar to what is already described for Fluzone HD (trivalent). The

observed adverse reactions following vaccination of Fluzone HD-QIV were minimal and are described adequately in the package insert. In the opinion of this reviewer, Fluzone High-Dose Quadrivalent presents a favorable overall risk-benefit profile.

11.3 Discussion of Regulatory Options

This supplement contains data from an adequate and well-controlled clinical trial demonstrating non-inferiority of antibody responses to the shared components of Fluzone High Dose Quadrivalent compared to Fluzone High Dose Trivalent (a U.S. licensed product), as well as the added benefit of the second B strain. The strategy for demonstration of non-inferiority between the trivalent and quadrivalent formulations of this product to support traditional approval is consistent with the approach to licensure for numerous U.S. licensed seasonal inactivated influenza vaccines. Non-inferiority was demonstrated based on demonstration of induction of hemagglutination inhibiting antibody titers (GMT ratios and seroconversion rate)s that met pre-specified criteria to support traditional approval (Refer to: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-data-needed-support-licensure-seasonal-inactivated-influenza-vaccines). Data from a clinical endpoint trial demonstrating the effectiveness of Fluzone High-Dose are relevant to Fluzone High-Dose Quadrivalent because of the similarity of the manufacturing processes between these 2 vaccines.

11.4 Recommendations on Regulatory Actions

This reviewer recommends approval of Sanofi Pasteur's supplement to the biologics license application for Fluzone High-Dose Quadrivalent, which is indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza subtype A viruses and type B virus contained in the vaccine.

11.5 Labeling Review and Recommendations

Revisions to the package insert and carton and container labels were negotiated with the applicant. The main changes to the package insert were the descriptions of the clinical studies and the presentation of data on solicited adverse reactions in the package insert.

11.6 Recommendations on Postmarketing Actions

No changes to the existing routine pharmacovigilance plan for Fluzone High-Dose are recommended based on the information contained in this supplement.