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Review Completion Date / Stamped Date	
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Applicant	Seqirus Inc.
Established Name	Influenza Vaccine, Adjuvanted
Trade Name	Fluad aQIV
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Influenza Virus Vaccine, active
Dosage Form(s) and Route(s) of Administration	Suspension for injection, 0.5mL single dose pre-filled syringe; Intramuscular injection.
Dosing Regimen	A single 0.5 mL dose
Indication(s) and Intended Population(s)	For the active immunization against influenza disease caused by seasonal influenza virus subtypes A and B contained in the vaccine for persons 65 years of age and older.

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GLOSSARY

AE – Adverse events
AESI – Adverse events of Special Interest
aQIV – Fluad quadrivalent influenza vaccine
aTIV – Fluad trivalent influenza vaccine
CI – Confidence interval
FAS – Full analysis set
GLM – General Linear Model
GMT – Geometric mean titer
GMR – Geometric mean ratio
HA - hemagglutinin
HI – hemagglutination inhibition
HR– hazard ratio
ILI – influenza-like illness
LL – Lower limit
NOCD – New onset of chronic disease
PPS – Per protocol set
RT-PCR – Reverse transcriptase-polymerase chain reaction
SAE – Serious adverse events
SCR – Seroconversion rate
TEAE – Treatment-emergent adverse event
VE – Vaccine efficacy

1. EXECUTIVE SUMMARY

Seqirus submitted a BLA supplement to request accelerated approval of its MF59-adjuvanted quadrivalent influenza vaccine, hereafter referred to as Fluad aQIV, or in short, aQIV, for persons 65 years and older. To support this indication, the applicant submitted the results of clinical studies V118_18 and V118_20. V118_18 was a phase 3 randomized, observer-blind, controlled, multicenter, clinical study to evaluate efficacy, safety, and immunogenicity of an MF59-adjuvanted quadrivalent influenza vaccine compared to a non-influenza vaccine comparator in adults ≥ 65 years of age. The vaccine efficacy of aQIV in preventing first occurrence Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) confirmed influenza A and/or B due to any strain of influenza (using the protocol-defined influenza-like illness (ILI)) was estimated to be 19.80% (97.45% CI: -5.27%, 38.91%) [Full Analysis Set], which did not meet the pre-specified success criterion of lower limit ≥40%. The applicant stated that most influenza cases were caused by A/H3N2 strains (51 out of 58 culture-confirmed, protocol-defined ILI cases) and were antigenically unmatched (47 out of 51 culture-confirmed, protocol-defined ILI A/H3N2 cases) to the vaccine strain. The applicant has indicated the intention to reassess vaccine efficacy in a future confirmatory study V118_24. With respect to immunogenicity, for all strains, the lower limits of the 95% confidence intervals (CIs) for the percentages of subjects achieving an HI antibody titer ≥1:40 were ≥77.0%, and the lower limits of the 95% CIs for the percentages of subjects achieving seroconversion 21 days post-vaccination were ≥57.8%, which met the CBER immunogenicity criteria as described in the "Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines" guidance (i.e., the lower limits of the 95% CIs for the percentages of subjects achieving an HI antibody titer ≥1:40 must be ≥60% and the lower limits of the 95% CIs for the percentages of subjects achieving seroconversion must be ≥30%). Therefore, the immunogenicity results were considered by the review team to be supportive of accelerated approval.

V118_20 was a phase 3, randomized, double-blind, controlled study to evaluate safety and immunogenicity of aQIV compared to MF59-adjuvanted trivalent subunit influenza vaccine (aTIV-1) and an MF59-adjuvanted trivalent subunit influenza vaccine containing an alternate B strain (aTIV-2) in adults aged 65 and older. For all strains, the success criteria for demonstrating non-inferiority of aQIV to aTIV-1 and aTIV-2 in terms of geometric mean titer (GMT) ratios and differences of seroconversion (SCR) rates were met. However, the CBER immunogenicity criteria were not met for the B/Yamagata and B/Victoria strains.

The applicant hypothesized that the reason that V118_20 failed to meet the CBER immunogenicity criteria for the B strains while V118_18 successfully met the CBER immunogenicity criteria might be due to the difference in assay methods used in the two studies, because V118_18 samples were tested using the HI assays by (b) (4) and V118_20 samples were tested using the HI assays by (b) (4). The applicant conducted a post-hoc exploratory study to assess this hypothesis by re-testing (b) (4) randomly selected aQIV samples from each of the V118_20 and V118_18 studies, using the (b) (4) HI assays. For the V118_20 samples, the reverse cumulative distribution curve and (b) (4) regression plot show a shift in titers between

the post-hoc and primary testing results for each B strain. The difference between the two assay methods appears to be one of the contributing factors for the differences in immune responses observed between the two studies. In the re-tested (post-hoc) V118_20 samples, the percentages of subjects achieving HI titer ≥1:40 were high ((b) (4), with lower limits (b) (4)) and met the CBER criteria for both B/Yamagata and B/Victoria strains. However, the percentages of subjects achieving seroconversion were still low for the B/Yamagata ((b) (4)) and B/Victoria strains ((b) (4)]) and did not meet the CBER criteria.

In V118_18, the percentages of subjects experiencing local and systemic solicited AEs in the aQIV group appear to be slightly higher than those of the comparator group. For non-solicited AEs, the percentages of subjects experiencing each category of SAE in terms of System Organ Classes and Preferred Terms appear to be comparable between the groups. In V118_20, the percentages of subjects experiencing local and systemic solicited AEs in the aQIV group appear to be similar to those of the aTIV-1 and aTIV-2 groups. The percentages of subjects experiencing each category of unsolicited AEs also appear to be comparable across the aQIV, aTIV-1, and aTIV-2 groups.

In summary, the safety profiles of subjects who received aQIV appear to be acceptable in both studies. The results of Fluad aQIV met the CBER immunogenicity criteria in V118_18. In V118_20, the CBER immunogenicity criteria for seroconversion rate were not met for the B/Yamagata and B/Victoria strains. I defer to the clinical review team to interpret the mixed conclusions from the two studies and determine whether the immunogenicity results are acceptable to support accelerated approval.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

V118_20 recruited subjects who were healthy or had co-morbidities which could increase their risk of complications from influenza. Subjects were administered with aQIV/aTIV-1/aTIV-2 for the prevention of seasonal influenza virus subtypes A and B.

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

I defer to the clinical reviewer to assess the current treatment options.

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

In November 2015, FDA approved Seqirus' Fluad trivalent influenza vaccine (aTIV) via accelerated pathway for use in 65 years and older subjects (BLA 125510/0). Fluad aTIV was the first approved seasonal influenza vaccine containing an adjuvant in the US.

On September 20, 2013, in a written response to a Type C Meeting request (IND 014368, CRMTS #9068), FDA agreed to use aQIV rather than aTIV to confirm efficacy in V118_18. In addition, Seqirus proposed to conduct an additional immunogenicity and

safety study V118_20 to demonstrate immunological non-inferiority of aQIV to the licensed aTIV.

The applicant is seeking accelerated approval of Fluad aQIV to support the transition of its influenza vaccine from trivalent to quadrivalent form.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission quality appears to be acceptable.

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

None.

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

5.1 Review Strategy

I reviewed the clinical study reports of V118_18, V118_20, and the results of the exploratory study of retesting samples from V118_18 and V118_20 using the (b) (4) HI assays.

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

- BLA 125510/143.0 dated 1/22/2019
  - Module 2.5 *Clinical Overview*
  - Module 2.7.3 *Summary of Clinical Efficacy*
  - Module 2.7.4 *Summary of Clinical Safety*
  - Module 5.3.5.1 *Study V118-20 – Report Body*
- BLA 125510/143.5 dated 5/1/2019
  - Module 5.3.5.1 *Report Body* (Clinical study report for V118_18)
  - Module 5.3.5.3 *Report Body, Appendix 1, Appendix 3, Tables, Figures*
- BLA 125510/143.9 dated 8/13/2019
  - Module 1.2 *Attachment 1 Response to RFI Reanalysis of HI titers*

5.3 Table of Studies/Clinical Trials

- Study V118_18: a phase 3 randomized, observer-blind, controlled, multicenter, clinical study to evaluate efficacy, safety and immunogenicity of an MF59-adjuvanted quadrivalent influenza vaccine compared to non-influenza vaccine comparator in adults ≥ 65 years of age.
- Study V118_20: a phase 3 randomized, double-blind, controlled, multicenter, clinical study to evaluate safety and immunogenicity of an MF59-adjuvanted quadrivalent subunit influenza vaccine in comparison with an MF59-adjuvanted trivalent subunit influenza vaccine and an MF59-adjuvanted trivalent subunit

influenza vaccine containing the alternate B strain, in adults aged 65 years and above.

5.4 Consultations

Not applicable.

5.5 Literature Reviewed

Not applicable.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Clinical Trial V118_18

Title of Study: A phase 3 randomized, observer-blind, controlled, multicenter, clinical study to evaluate efficacy, safety and immunogenicity of an MF59-adjuvanted quadrivalent influenza vaccine compared to non-influenza vaccine comparator in adults ≥ 65 years of age

6.1.1 Objectives

Efficacy:
Primary:

- To demonstrate absolute Vaccine Efficacy (VE) of aQIV versus non-influenza comparator (Boostrix) when administered as a single dose to prevent first occurrence Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine, in subjects ≥ 65 years of age.

Secondary:

- To demonstrate absolute VE of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to strains antigenically matched to the strains selected for the seasonal vaccine.
- To evaluate absolute VE of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to any strain of influenza regardless of antigenic match to the strains selected for the seasonal vaccine.
- To evaluate absolute VE of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence culture-confirmed influenza, due to strains antigenically unmatched to the strains selected for the seasonal influenza vaccine.
- To evaluate absolute efficacy of aQIV versus non-influenza comparator when administered as a single dose to prevent first occurrence RT-PCR confirmed influenza due to any strain of influenza regardless of antigenic match from 7 days to 180 days after vaccination or at the end of influenza season, whichever was longer (early efficacy).

Immunogenicity:
Secondary:

- To evaluate the immunogenicity of aQIV measured by HI titer 21 days after vaccination, against influenza strains homologous to the seasonal vaccine.

Primary safety objectives:

- To evaluate the safety of aQIV through assessment for local and systemic solicited adverse events (AEs) through Day 7 in a subset of subjects.
- To evaluate the rates in each vaccine group of medically attended AEs within 30 days after the first occurrence RT-PCR confirmed influenza-like illness (ILI).
- To evaluate the rates in each vaccine group of unsolicited AEs for 21 days after vaccination and AEs leading to withdrawal, SAEs, adverse events of special interest (AESI), and new onset of chronic diseases (NOCD) for 365 days after vaccination.

6.1.2 Design Overview

In V118_18, subjects were randomized to receive either aQIV or Boostrix in 1:1 ratio on Day 1. Subjects were followed for 12 months: treatment period (Day 1 to Day 22) and follow-up period (Day 23 to Day 366). The study was conducted in the Northern Hemisphere (NH) 2016/17 and Southern Hemisphere (SH) 2017 seasons.

Randomization:
Subjects were randomized via an Interactive Response Technology System to receive either aQIV or Boostrix in a 1:1 ratio. Randomization was stratified by age (cohorts 65 to 74 years and 75 years and above) and comorbidity status (assessment score < 50 or ≥ 50). The comorbidity assessment score, which incorporates medical comorbidity among other baseline characteristics, is a validated predictor of risk of complications from influenza in subjects ≥65 years of age.

Efficacy assessment:

- During the first active ILI surveillance period (Day 1 – Day 181), all subjects received, at a minimum, weekly phone calls or messages to assess the primary protocol-defined ILI symptoms. During the second active ILI surveillance period (Day 181 / end of the regional seasonal influenza season until the end of study), all subjects received phone ILI surveillance phone calls/message every 2 weeks. Primary protocol-defined ILI would trigger a nasopharyngeal swab collection during the ILI surveillance period. Nasopharyngeal swabs were processed for viral culture and RT-PCR confirmation. Culture positive samples underwent antigenic characterization.
    - Primary protocol-defined ILI: At least one of the following respiratory symptoms: sore throat, cough, sputum production, wheezing, or difficulty breathing; concurrently with at least one of the following systemic symptoms: temperature of > 37.2°C/99°F, chills, tiredness, headache, or myalgia.

Immunogenicity assessment:
Samples from ~2800 subjects participating in the NH2016/17 season were collected at Day 1 and Day 22 for immunogenicity assessment. To maintain the study blind, equal numbers of subjects from both vaccine groups were asked to provide blood specimens. After all the blood specimens had been obtained, a subset of samples from those collected were randomly selected in a 4:1 ratio (1362 aQIV; 340 Boostrix) for immunogenicity assessment. (b) (4) validated HI assays were used to assess immunogenicity. Refer to section 6.2.10.5 for more information about the HI assays used in V118_18.

Safety assessment:

- All subjects were followed for any unsolicited AE and concomitant medication use. Safety data were collected through Day 15 safety phone call and Day 22 clinic visit. During the follow-up period, AEs leading to withdrawal, AESI, NOCD, SAE, and concomitant medication use related to these events were captured via safety phone calls or clinic visits. A safety follow-up call was made 30 days after an ILI onset to determine if subsequent medically attended AEs occurred.
- A subset of approximately 2100 subjects from multiple seasons and countries participating in the study were randomly selected for participation in the solicited safety subset. Equal numbers of subjects from both treatment arms were selected through the Interactive Response Technology System. These subjects were requested to complete their dairy card.

Observer-blind:

- Designated unblinded nurses or physicians were instructed not to reveal the identity of the study vaccines either to the subject or the investigative site staff (i.e., investigator and study nurse) involved in the monitoring of conduct of the study up until completion of the study and final data review, except in a medical emergency.
- The subjects and any of the investigative staff who were involved in the treatments or clinical evaluation of the subject were not aware of the vaccine administered.
- The unblinded personnel were not involved in data collection, such as safety assessments and/or physical assessment, and did not have access to the blinded data entry fields.
    - In case of an emergency, the investigator disclosed the subject's assigned vaccine. Except in the case of medical necessity, a subject's treatment was not unblinded without the approval of the Sponsor.
- All personnel involved in performing laboratory assays and others who were directly involved in the conduct of the study or in the analysis of the final study results remained blinded to the treatment codes until at least the database has been locked for final analysis.

6.1.3 Population

A total of 6790 subjects were enrolled (3394 in aQIV and 3396 in Boostrix).
Males and females ≥ 65 years old who were healthy or had co-morbidities were enrolled into the study. A subject was to be excluded if the subject had received a diphtheria or Tetanus Toxoid or pertussis vaccine within the previous 5 years, received any influenza vaccine within 6 months prior to enrolment in the study or planned to receive influenza vaccine while participating in the study, or had various other clinical conditions defined in the exclusion criteria. The complete list of inclusion and exclusion criteria was documented on page 42 of the Clinical Study Report of V118_18.

6.1.4 Study Treatments or Agents Mandated by the Protocol

- Fluad aQIV: 0.5 mL dose of aQIV (quadrivalent MF59C.1 adjuvanted inactivated egg-derived influenza vaccine) contained 60 µg of HA: 15 µg of HA of each of these strains:
    - NH 2016/17 season: A/California/7/2009pdm (NYMC X-181) (H1N1), A/HongKong/4801/2014 NYMC (X-263B) (H3N2), B/Brisbane/9/2014 (Yamagata lineage), and B/Brisbane/60/2008 (Victoria lineage)
    - SH 2017 season: identical to NH 2016/17 season except that the H1N1 strain was replaced by A/Singapore/GP1908/2015 IVR-180
- Boostrix: 0.5 mL dose of Boostrix, a combined Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed. The active ingredients included Diptheria toxoid, Tetanus toxoid, Bordetella pertussis antigens, Pertussis toxoid, Filamentous Hemagglutinin, Pertactin, adsorbed on aluminum hydroxide (adjuvant)

6.1.5 Sites and Centers

The study was conducted in 89 sites in 12 countries; 11 sites in Bulgaria, 7 sites in Colombia, 5 sites in Czech Republic, 6 sites in Estonia, 4 sites in Latvia, 7 sites in Lithuania, 8 sites in Malaysia, 6 sites in the Philippines, 15 sites in Poland, 8 sites in Romania, 4 sites in Thailand, and 8 sites in Turkey.

6.1.6 Surveillance/Monitoring

Not applicable.

6.1.7 Endpoints and Criteria for Study Success

Efficacy:
Primary:

- Time to first occurrence of RT-PCR confirmed influenza from 21 through 180 days after vaccination or end of the influenza season, whichever was longer
    - An influenza event was defined as RT-PCR confirmed influenza infection in the setting of an ILI. The primary protocol-definition of ILI was used to determine success for the primary and key secondary efficacy endpoints.

- Success Criterion: the lower limit of the two-sided 95% confidence interval (CI) of absolute VE estimate must be > 0.4 using the primary protocol-definition of ILI. In case an interim analysis was conducted, the type 1 error was to be adjusted.

Secondary:

- Time to first occurrence of influenza from Day 21 to Day 180 after vaccination or end of the influenza season, for
  - culture-confirmed influenza antigenically matched to the vaccine strains (key secondary efficacy objective)
    - Success Criterion for the key secondary efficacy objective: the lower limit of the two-sided 95% CI of absolute VE estimate must be > 0.4.
  - culture-confirmed influenza regardless of antigenic match to the vaccine strain
  - culture-confirmed influenza antigenically unmatched to the vaccine strains
- Time to first occurrence of RT-PCR confirmed influenza from Day 7 to Day 180 after vaccination or end of influenza season, whichever was longer (early efficacy)

Both the primary protocol-definition of ILI and modified Center for Disease Control and Prevention (CDC) definition of ILI were used to determine the efficacy endpoints, but the protocol-definition of ILI was used to determine the success of secondary endpoints.

- Modified CDC ILI definition: Fever (temperature of > 37.2°C/99°F) with cough or sore throat.

Immunogenicity:

Secondary:

- HI titers against homologous strains at Day 1 and Day 22. The derived endpoints include
  - Geometric mean titers (GMTs) for HI
  - Geometric mean ratios (GMRs) for HI Day 22/Day 1
  - Percentages of subjects achieving an HI titer ≥ 1:40
  - Percentages of subjects who achieved seroconversion on Day 22
    - HI ≥ 1:40 for subjects sero-negative at baseline [HI titer < 1:10]; or a minimum 4-fold increase in HI titer for subjects sero-positive at baseline [HI titer ≥ 1:10])
  - Reverse cumulative distributions of HI titers at Day 22

For each strain, the CBER immunogenicity criteria were used as the success criteria:

- The lower limit of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should have met or exceeded 30%.
- The lower limit of the two-sided 95% CI for the percent of subjects who achieved an HI antibody titer ≥ 1:40 should have met or exceeded 60%.

Primary safety endpoints

- Solicited local and systemic adverse events (AEs) from Day 1 through Day 7.
- Medically attended AEs within 30 days after the first occurrence RT-PCR confirmed ILI.
- Unsolicited AE and concomitant medications reported from Day 1 to Day 22.
- Serious adverse events (SAEs), AEs leading to withdrawal from the study, new onset of chronic diseases (NOCDs), adverse events of special interest (AESIs) reported from Day 1 to Day 366 and all concomitant medications associated with these events.

6.1.8 Statistical Considerations & Statistical Analysis Plan

Efficacy

Primary vaccine efficacy analyses were performed using the Full Analysis Set (FAS) Efficacy and repeated on the Per Protocol Set (PPS) Efficacy.

The primary measurement of absolute efficacy was tested in subjects ≥ 65 years of age according to the following null (H0) and alternative (H1) hypotheses:

- H0: 1- HR = VE ≤ 0.4 versus H1: VE > 0.4,
    - where HR is the hazard ratio of the incidence of protocol-defined ILI in aQIV versus a non-influenza comparator estimated by the Cox proportional hazards model, and VE is vaccine efficacy.
    - A Cox proportion hazard model was fit with treatment effect as a fixed effect and stratifying covariates as a random effect. Estimate for hazard ratio was calculated by maximizing the partial likelihood function.
        - $h(t|X) = h_0(t) \exp(\beta^T X + b^T Z)$, with t denoting time to influenza infections, β is the effect of treatment group indicated by X, b is random effect (assumed as a multivariate random gaussian variable with zero mean and diagonal covariance matrix), Z is random effect covariate (reflecting randomization strata).
        - A penalized Maximum Likelihood approach would be used in case of problems with convergence.
- A protocol specified unblinded interim analysis was conducted by the Data Monitoring Committee on Aug 3, 2017 for evaluation of the primary efficacy objective (VE against any influenza) using 167 RT-PCR confirmed influenza cases exclusively from the NH 2016/17 season.
    - To control the overall type 1 error alpha ≤ 0.05, the CIs for the final analysis of primary efficacy objective were adjusted via an error-spending function at the interim analysis.

Immunogenicity:

Immunogenicity data were analyzed using FAS Immunogenicity and repeated using PPS Immunogenicity.

For the CBER's immunogenicity criteria, for each strain k:

- H_{0k}: $\pi_k \leq 0.3$ vs. H_{1k}: $\pi_k > 0.3$
- H_{0k}: $\tau_k \leq 0.6$ vs. H_{1k}: $\tau_k > 0.6$

  - where π_k is the proportion of subjects achieving seroconversion and τ_k is the proportion of subjects achieving an HI antibody titer ≥1:40
- The binary endpoints were summarized using unadjusted estimates and were reported together with 2-sided 95% Clopper Pearson CIs. Differences of proportions were reported with 95% CIs calculated using the Miettinen and Nurminen's method.
- Crude estimates for GMTs, GMRs and pertaining two-sided 95% CIs were calculated assuming lognormal distribution of the titers. Additional summary statistics, such as minimum, maximum and median titers for each vaccine group, were also provided.
- Reverse Cumulative Distribution Curves were generated to display the distribution of the antibody responses at Day 22.
- Missing immunogenicity values were assumed to be missing completely at random.
- Individual HI titers below detection limit (<10) were set to half of that limit (5).

Safety:

- For all safety endpoints, frequencies were analyzed descriptively by vaccine group for the All Enrolled Set.

Power Calculations

The study used a group sequential design for demonstrating efficacy in the placebo-controlled study, using a 1-sided alpha of 2.5% and a success criterion that requires the lower limit of the 2-sided 95% CI of VE > 0.40. A first interim analysis was planned to be performed after observing approximately 50% of planned RT-PCR confirmed influenza cases. At the interim, the decision boundaries for declaring efficacy and futility were calculated, based on the actual number of events obtained at the interim. In addition, the decision boundaries for the final analysis were calculated with appropriate adjustment to maintain the overall type I error. Attack rates of influenza of 3.5% in the non-influenza comparator group and 1.4% in the aQIV group were assumed. A total of 238 events (4860 subjects under an assumed accrual rate) were needed to achieve 86.5% power to show absolute efficacy of aQIV vs. non-influenza comparator. Accounting for a drop-out rate of 10%, approximately 5346 subjects per vaccine group were needed.

For the immunogenicity objective, a significance level of 5% (2-sided) [2.5% (one-sided)] was used. Approximately 1702 samples were planned to be included in the analysis (1362 aQIV; 340 Boostrix), assuming a 10% drop-out rate, to achieve 99% power to demonstrate fulfillment of the CBER criteria for seroconversion for each of the strains, and 99% and 82% power for HI titer ≥1:40 for each of the A and B strains, respectively. In the power calculation, the assumed seroconversion rates (H1N1: 77%, H3N2: 74%, and B: 47%) and percentages of subjects with a HI titer ≥ 1:40 (H1N1: 91%, H3N2: 99%, and B: 64.6%) were based on the V70_27 study in elderly adult subjects who received aTIV.

For safety, with 4860 evaluable subjects in each vaccine group, the probability of detecting a rare safety event which occurred at 0.001 rate was 99%. With 1000 evaluable

subjects in each vaccine group of the Solicited Safety Set, the probability of detecting an event which occurred at a rate of 0.002 was ≥ 86%, assuming a drop-out/missing data rate of up to 5%.

Reviewer's comments:

- *I verified the applicant's power calculation of the efficacy objective using the PROC SEQDESIGN in SAS 9.4.*

6.1.9 Study Population and Disposition

6.1.9.1 Populations Enrolled/Analyzed

The following analysis sets were used:

- All Enrolled Set included all screened subjects who provided informed consent and provided demographic and/or other baseline screening measurements, received a Subject ID, regardless of the subject's randomization and vaccination status in the study.
- Full Analysis Set (FAS) Efficacy included subjects in the All Enrolled Set who were randomized and received a study treatment, were under observation for at least 21 days post-vaccination and provided efficacy data.
- Full Analysis Set Immunogenicity included randomly selected sample of 1702 subjects, including subjects from both treatment arms (1362 aQIV; 340 Boostrix), in the All Enrolled Set who were randomized, received a study treatment, and provided immunogenicity data at Days 1 and 22.
- Per Protocol Set (PPS) for Efficacy/Immunogenicity analysis included subjects who correctly received the vaccine (i.e., received the vaccine to which the subjects were randomized to receive), had no Clinical Study Report (CSR)-reportable protocol deviation leading to exclusion as defined prior to unblinding, and were not excluded due to other reasons defined prior to unblinding.
- Exposed Set included all subjects in the All Enrolled Set who received a study treatment.
- Solicited Safety Set included designated subjects (reactogenicity subset) in the Exposed Set, with solicited safety assessments beyond 30 minutes.
- Unsolicited Safety Set includes subjects in the Exposed Set with unsolicited AE data.
- Overall Safety Set includes subjects who were in the Solicited Safety Set and/or in the Unsolicited Safety Set.

6.1.9.1.1 Demographics

The baseline characteristics of the subjects in V118_18 are summarized in Table 1. In the All-enrolled sets, most subjects were between 65-74 years old, non-Hispanic, either White or Asian, and did not receive an influenza vaccine in the past 5 years.

Table 1. Baseline Characteristics - All Enrolled Set and Per Protocol Immunogenicity

-	All Enrolled Set	All Enrolled Set	All Enrolled Set	Per Protocol Immunogenicity	Per Protocol Immunogenicity	Per Protocol Immunogenicity
Baseline characteristic	**aQIV (N =3394)**	**Boostrix (N = 3396)**	**Total (N =6790)**	**aQIV (N = 1256)**	**Boostrix (N = 324)**	**Total (N = 1580)**
Age (years) - Mean (SD)	71 9 (5 53)	71 8 (5 36)	71 9 (5 44)	72 2 (5 63)	72 1 (5 23)	72 2 (5 55)
Age Group - 65 to 74 years	2416 (71 2%)	2406 (70 8%)	4822 (71 0%)	869 (69 2%)	224 (69 1%)	1093 (69 2%)
-75 to 84 years	893 (26 3%)	928 (27 3%)	1821 (26 8%)	353 (28 1%)	93 (28 7%)	446 (28 2%)
-≥ 85 years	85 (2 5%)	62 (1 8%)	147 (2 2%)	34 (2 7%)	7 (2 2%)	41 (2 6%)
Sex - Male	1289 (38 0%)	1307 (38 5%)	2596 (38 2%)	518 (41 2%)	133 (41 0%)	651 (41 2%)
Ethnicity - Hispanic or Latino	615 (18 1%)	607 (17 9%)	1222 (18 0%)	5 (0 4%)	0	5 (0 3%)
Race	-	-	-	-	-	-
-American Indian or Alaska Native	62 (1 8%)	59 (1 7%)	121 (1 8%)	1 (0 1%)	0	1 (0 1%)
-Asian	1139 (33 6%)	1159 (34 1%)	2298 (33 8%)	134 (10 7%)	32 (9 9%)	166 (10 5%)
-Black or African American	1 (0 0%)	0	1 (0 0%)	0	0	0
-White	1642 (48 4%)	1629 (48 0%)	3271 (48 2%)	1120 (89 2%)	292 (90 1%)	1412 (89 4%)
-Other	550 (16 2%)	549 (16 2%)	1099 (16 2%)	1 (0 1%)	0	1 (0 1%)
Body Mass Index (kg/m2) - Mean (SD)	27 05 (4 99)	26 96 (5 00)	27 00 (4 99)	28 36 (4 88)	28 32 (4 75)	28 35 (4 85)
Previous Seasonal Influenza Vaccine in the Past 5 Years	991 (29 2%)	1021 (30 1%)	2012 (29 6%)	376 (29 9%)	107 (33 0%)	483 (30 6%)
Comorbidity Score < 50	2472 (72 8%)	2474 (72 9%)	4946 (72 8%)	826 (65 8%)	214 (66 0%)	1040 (65 8%)
Smoking	325 (9 6%)	335 (9 9%)	660 (9 7%)	123 (9 8%)	32 (9 9%)	155 (9 8%)

Source: Tables 15 and Table 14.1.1.3.4 of the Clinical Study Report submitted to BLA 125510/143.5.

Reviewer's comments:

- *In the All Enrolled Set, the baseline characteristics of the subjects were similar between the aQIV and Boostrix groups. In the Per Protocol Set Immunogenicity, the baseline characteristics of the subjects were also similar between the groups.*
- *The Per Protocol Set Immunogenicity, which were sampled from subjects who participated in the NH2016/17 season only, appears to have similar distributions as the All Enrolled Set in terms of age, sex, body mass index, previous influenza vaccination status in the past 5 years, and smoking status. However, the distributions of race and ethnicity were somewhat different between the two sets. The percentages of subjects who were White were 89.4% in the Per Protocol Set Immunogenicity and only 48.2% in the All Enrolled Set.*

6.1.9.1.2 Medical/Behavioral Characterization of the Enrolled Population
Not applicable.

6.1.9.1.3 Subject Disposition
The study disposition of V118_18 was summarized in Table 2. A total of 3.7% of subjects discontinued from the study. The most frequent reason for discontinuation from study was withdrawal by subject (1.9%).

Table 2. Study disposition of V118 18 (As treated, all enrolled set)

Disposition	**aQIV (N = 3394)**	**Boostrix (N = 3396)**	**Total (N = 6790)**
Total Number of Subjects Enrolled	3394 (100.0%)	3396 (100.0%)	6790 (100.0%)
Primary Reason for Discontinuation from Study	131 (3.9%)	123 (3.6%)	254 (3.7%)
-Adverse Event	3 (0.1%)	3 (0.1%)	6 (0.1%)
-Death	33 (1.0%)	34 (1.0%)	67 (1.0%)
-Withdrawal by Subject	66 (1.9%)	61 (1.8%)	127 (1.9%)
-Lost to Follow-up	21 (0.6%)	19 (0.6%)	40 (0.6%)
-Protocol Deviation/Violation	6 (0.2%)	5 (0.1%)	11 (0.2%)
-Other	2 (0.1%)	1 (0.0%)	3 (0.0%)

Source: Table 10 of the clinical study report of V118_18 submitted to BLA 125510/143.5

Reviewer's comment:

- *For each reason, the percentage of subjects discontinued from the study appear to be comparable between the aQIV and Boostrix groups.*

6.1.10 Efficacy Analyses

Interim Analysis:

In the unblinded interim analysis, using the FAS Efficacy, VE was 26.20% (97.55% CI: -9.23%, 50.14%) and p-value was 0.8139, which was greater than the p-value futility boundary of 0.12829. Using the PPS Efficacy, the VE was 30.64% (97.55% CI: -3.44%, 53.49%) and p-value was 0.6364. The DMC informed Seqirus that "based solely on the charter's statistical rule for stopping, the study reached the pre-specified stopping p-value for futility for the primary efficacy objective, however, Seqirus may choose to continue the study to completion for clinical or epidemiological reasons given that there is no safety reason to stop the study." Seqirus continued the study while remained blinded. As a consequence of the interim analysis, the CIs of the final primary efficacy analysis were updated from 95% to 97.45% to control the overall type I error under 5%.

Primary Efficacy Objective:

At the end of the study, a total of 273 cases of RT-PCR confirmed influenza due to any strain were reported in the study (122 in the aQIV group and 151 in the Boostrix group).

The VE of aQIV in preventing first occurrence of any RT-PCR confirmed influenza A and/or B due to any influenza strain was estimated to be 19.80% (97.45% CI: -5.27%, 38.91%) [FAS Efficacy Set] and (b) (4)) [PPS Efficacy], using the protocol-defined ILI definition.

Reviewer's comments:

- *In the interim analysis, 167 out of the planned 238 cases were collected. Because the information fraction at the interim analysis was 0.7, the stopping rule based on the pre-specified type I error spending function was determined as to stop*

*early for efficacy if the one-sided p-value was lower than 0.01225. With an overall one-sided alpha level of 0.025 (i.e., a two-sided alpha level of 0.05), it appears that the applicant calculated the remaining one-sided alpha level for the final analysis as 0.025 – 0.01225 = 0.01275, for which the applicant reported the two-sided 97.45% CI (1 – 0.01275*2 = 97.45%).*

- *It appears that the applicant could have calculated the nominal one-sided alpha level for the final analysis following the group sequential design based on the pre-specified type I error spending function, which would yield a one-sided alpha level greater than 0.01275 for the final analysis, because of the positive correlation between the test statistics for the interim and final analyses. The corresponding one-sided alpha level should be between 1.275% and 2.5%, which would be less conservative than the one-sided alpha level (1.275%) that the applicant used. Nonetheless, the main conclusion would not change, based on my sensitivity analysis, since the efficacy results missed the success criterion by a large margin.*
- *The pre-specified success criterion for the primary efficacy objective (VE: 19.80% (97.45%: -5.27%, 38.91%) in the FAS Efficacy) was not met, because the lower limit of the confidence interval of the VE estimate was below 40%.*
- *I verified the applicant's analysis of the primary efficacy endpoint.*

Secondary efficacy objectives:
In total, only 21 influenza cases were defined as matched to the strains contained in the aQIV vaccine (as defined by strains with <8-fold difference in titer as compared to the vaccine strain). Among those cases, 7 cases were in the aQIV group with 3368 subjects, and 14 cases were in the Boostrix group with 3372 subjects. The VE of aQIV for antigenically matched culture-confirmed influenza was estimated to be 49.95% (95% CI: -24.0%, 79.8%) [FAS Efficacy set].

The applicant evaluated the VE of aQIV in preventing first occurrence RT-PCR confirmed influenza A and/or B due to any influenza strain, using the modified CDC definition of ILI instead. Using this definition on the FAS Efficacy set, the VE of aQIV was estimated to be 32.12% [95% CI: 10.23%, 48.67%], and the lower limit was still below 40%.

6.1.11 Immunogenicity Analyses

6.1.11.1 Analyses of Endpoints

Immunogenicity results of the aQIV and Boostrix groups at Day 22 are summarized in Table 3.

Table 3. Immunogenicity as measured by percentages of subjects with HI titer ≥1:40 and seroconversion rates at Day 22 (Per Protocol Set Immunogenicity)

-	**aQIV (N=1256)**	**Boostrix (N=324)**
A/H1N1	-	-
Day 22 Post-Vaccination % HI titer ≥1:40 (95% CI)	96.1 (94.9, 97.1)	46.9 (41.3, 52.5)
SCR (%) (95% CI)	77.6 (75.2, 79.9)	2.2 (0.9, 4.4)
A/H3N2	-	-
Day 22 Post-Vaccination % HI titer ≥1:40 (95% CI)	96.0 (94.8, 97.0)	40.9 (35.5, 46.5)
SCR (%) (95% CI)	84.7 (82.6, 86.7)	4.0 (2.2, 6.8)
B/Yamagata	-	-
Day 22 Post-Vaccination % HI titer ≥1:40 (95% CI)	79.3 (77.0, 81.5)	21.4 (17.1, 26.3)
SCR (%) (95% CI)	60.6 (57.8, 63.3)	3.7 (1.9, 6.4)
B/Victoria	-	-
Day 22 Post-Vaccination % HI titer ≥1:40 (95% CI)	81.4 (79.1, 83.5)	18.6 (14.5, 23.3)
SCR (%) (95% CI)	65.0 (62.2, 67.6)	2.2 (0.9, 4.4)

The actual numbers of subjects in which the % HI titer ≥1:40 endpoints were calculated were 1256, 1256, 1252, and 1252 in the aQIV group and 322, 323, 322, 323 in the Boostrix group, for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria, respectively. The actual numbers of samples in which the SCR endpoints were calculated were 1252, 1256, 1249, and 1247 in the aQIV group and 323, 323, 322, 323 in the Boostrix group, for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria, respectively.
Source: Tables 14.2.1.2.6 and 14.2.1.3.6 of the Clinical Study Report of V118_18 submitted to BLA 125510/143.5.

Reviewer's comments:

- *In the aQIV group, the percentages of subjects achieving HI titer ≥1:40 and percentages of subjects achieving seroconversion met the CBER criteria for all strains.*
- *I verified the statistical analyses presented in Table 3.*

6.1.11.2 Subpopulation Analyses:

The applicant performed subgroup analyses by age, comorbidity score, previous vaccination status, sex, and race.

Reviewer's comments:

- *Overall, the percentages of subjects achieving HI titer ≥1:40 and percentages of subjects achieving seroconversion 21 days post-vaccination were similar across different age, comorbidity score, and sex subgroups.*
- *For each strain, pre-vaccination GMT and percentage of subjects achieving HI titer ≥1:40 pre-vaccination were higher in subjects who received previous influenza vaccination (in the past 5 years) than in subjects who did not receive previous influenza vaccination. For each strain, the post-vaccination GMT was numerically similar or lower in subjects who received previous influenza vaccination than in subjects who did not receive previous influenza vaccination. For each strain, the percentage of subjects achieving seroconversion was*

numerically lower in subjects who received previous influenza vaccination than in subjects who did not receive previous influenza vaccination.

- *Asian subjects had relatively higher estimated percentages of subjects achieving HI titer ≥1:40 pre-vaccination than White subjects for the A/H1N1 and A/H3N2 strains. However, the two groups had similar percentages of subjects achieving HI titer ≥1:40 post-vaccination for all strains.*

6.1.11.3 Dropouts and Discontinuations:

Low percentages of subjects in the aQIV group (3.9%) and Boostrix group (3.6%) were discontinued from the study.

In the aQIV group, a total of 1256 out of 1324 subjects in the FAS Immunogenicity were included in the PPS Immunogenicity. The most common reasons for exclusion from the PPS Immunogenicity were due to serum sample obtained outside window (40), influenza positive swab prior to Visit 3 (12), and subjects did not meet the inclusion/exclusion criteria (12) but the study vaccines were given.

6.1.12 Safety Analyses

Solicited AEs:

- Slightly higher percentage of subjects experienced local and systemic AEs in the aQIV group than in the Boostrix group (24.4% vs. 19.6% for local reactions, and 19.2% vs. 16.3% for systemic reactions, respectively).
- In the aQIV group, the most frequent solicited local AEs was pain (16.3%). The most frequent solicited systemic AEs were headache (10.8%) and fatigue (10.5%) (Tables 4 and 5).

Table 4. Number (%) of subjects with local solicited adverse events from Day 1 (excluding reactions occurring within 30 minutes after vaccination) through Day 7 after vaccination - Solicited Safety Set

Adverse Event	**aQIV [N=665]**	**aQIV [N=665]**	**Boostrix [N=667]**	**Boostrix [N=667]**
-	**Any**	**Severe***	**Any**	**Severe***
Pain	102 (16.3%)	2 (0.3%)	71 (11.2%)	2 (0.3%)
-	**≥25mm**	**>100mm**	**≥25mm**	**>100mm**
Erythema	23 (4.0%)	0	11 (1.8%)	3 (0.5%)
Induration	24 (4.0%)	1 (0.2%)	16 (2.6%)	2 (0.3%)
Ecchymosis	3 (0.5%)	0	4 (0.7%)	0

The actual numbers of subjects with data available were ≥595 in the aQIV group and ≥607 in the Boostrix group.
*Severe = prevents daily activity.
Source: Table 39 of the Clinical Study Report of V118_18 submitted to BLA 125510/143.5.

Table 5. Number (%) of subjects with systematic solicited adverse events and other indicators of reactogenicity from Day 1 (excluding reactions occurring within 30 minutes after vaccination) through Day 7 after vaccination – Solicited Safety Set

Adverse Event	**aQIV-Any**	**aQIV-Severe**	**Boostrix-Any**	**Boostrix-Severe**
-	**N=665**	**N=665**	**N=667**	**N=667**
Headache	69 (10.8%)	5 (0.8%)	53 (8.3%)	3 (0.5%)
Fatigue	67 (10.5%)	7 (1.1%)	56 (8.8%)	3 (0.5%)
Myalgia	49 (7.7%)	5 (0.8%)	39 (6.1%)	3 (0.5%)
Arthralgia	47 (7.3%)	4 (0.6%)	42 (6.6%)	4 (0.6%)
Loss of Appetite	23 (3.6%)	0	23 (3.6%)	2 (0.3%)
Nausea	24 (3.8%)	1 (0.2%)	15 (2.3%)	1 (0.2%)
Vomiting	5 (0.8%)	1 (0.2%)	7 (1.1%)	1 (0.2%)
Diarrhea	26 (4.1%)	3 (0.5%)	19 (3.0%)	2 (0.3%)
Chills	32 (5.0%)	3 (0.5%)	25 (3.9%)	2 (0.3%)
Fever - Moderate (38.5°C-38.9°C)	4 (0.6%)	-	1 (0.2%)	-
Fever - Severe (39.0°C-40°C)	3 (0.5%)	-	2 (0.3%)	-
Fever - Potentially life threatening (≥ 40.0°C)	0	-	0	-

The actual number of subjects with data available was ≥638 in each group.
Source: Table 40 of the Clinical Study Report of V118_18 submitted to BLA 125510/143.5.

Unsolicited AEs:

- Similar percentages of subjects experienced unsolicited AEs during the treatment period (21.5% in aQIV group and 21.2% in Boostrix group).
- The most frequent unsolicited AEs during treatment period (Day 1 to Day 22) was Influenza-like-illness (4.6% in aQIV and 4.6% in Boostrix).

Reviewer's comment:

- *For each System Organ Class and Preferred Term, the percentage of subjects experiencing the unsolicited AE appear to be similar between the aQIV and Boostrix groups.*

6.1.13.1 Deaths

A total of 67 deaths (33 (1.0%) in the aQIV group and 34 (1.0%) in the Boostrix group) were reported during the study. Table 44 of the study report listed the deaths by System Organ Class and Preferred Term. None of the deaths were considered by the investigator to be related to the study vaccines.

Reviewer's comment:

- *The percentage of deaths for each specific System Organ Class and Preferred Term appears to be comparable between the aQIV and Boostrix groups. I defer to the clinical reviewer to further evaluate each specific death event.*

6.1.13.2 Nonfatal Serious Adverse Events

- A total of 238 (7.0%) subjects in the aQIV group and 234 (6.9%) subjects in the Boostrix group reported at least one SAE during the study period.
- The most frequent unsolicited SAEs were pneumonia (0.6% in aQIV and 0.5% in Boostrix), acute myocardial infarction (0.4% in aQIV and 0.6% in Boostrix), chronic obstructive pulmonary disease (0.4% in aQIV and 0.4% in Boostrix), and atrial fibrillation (0.3% in aQIV and 0.3% in Boostrix).
- Among the SAEs, one subject in the aQIV group (rheumatoid arthritis) and one subject in the Boostrix group (acute myocardial infarction and ILI) experienced SAEs that were considered to be related to the study vaccines.

Reviewer's comment:

- *For each type of SAE in terms of System Organ Class, Preferred Term, the percentage of subjects experiencing such SAE appears to be similar between the aQIV and Boostrix groups.*

6.1.13.3 Adverse Events of Special Interest (AESI)

A total of 4 subjects in the aQIV group and 6 subjects in the Boostrix group experienced AESIs.

- aQIV: 2 subjects with Rheumatoid arthritis, 1 subject with Polymyalgia rheumatica, and 1 subject with Pemphigus
    - 1 case of Rheumatoid arthritis was considered by the investigator to be related to the study treatment.
- Boostrix: 2 subjects with Autoimmune thyroiditis, 1 subject with Rheumatoid arthritis, 1 subject with facial paralysis, 1 subject with VIth nerve disorder, and 1 subject with Psoriasis.

6.1.13.4 Clinical Test Results

No laboratory assessments of hematology, blood chemistry, or urine chemistry were specified in the protocol.

6.1.13.5 Dropouts and/or Discontinuations

In each group, 1.1% of subjects experienced unsolicited AE that led to premature withdrawal.

6.2 Clinical Trial V118_20

Title of Study: A phase 3 randomized, double-blind, controlled, multicenter, clinical study to evaluate safety and immunogenicity of an MF59-adjuvanted quadrivalent subunit influenza vaccine in comparison with an MF59-adjuvanted trivalent subunit influenza vaccine and an MF59-adjuvanted trivalent subunit influenza vaccine containing the alternate B strain, in adults aged 65 years and above

6.2.1 Objectives

Immunogenicity:
Co-Primary:

- To demonstrate that vaccination with aQIV elicits an immune response that is not inferior to that of an aTIV containing the same virus strains as the licensed adjuvanted influenza vaccine (FLUAD, aTIV-1), and an aTIV containing the alternate B strain (aTIV-2) among adults ≥65 years of age.
- To assess the immunogenicity of aQIV in adults ≥65 years of age based on the CBER recommendations.

Secondary:

- To characterize the immunogenicity of aQIV, the aTIV-1 containing the same virus strains as the licensed adjuvanted trivalent influenza vaccine, and the aTIV-2 containing the alternate B strain, by HI assays.
- To demonstrate the immunological superiority of aQIV compared to aTIV-1 and aTIV-2 for the B strain that is not included in each TIV vaccine separately.

Safety:

- To assess safety and tolerability of aQIV, aTIV-1, and aTIV-2 among adults ≥65 years of age.

6.2.2 Design Overview

In V118_20, subjects were randomized to 1 of 3 treatment groups in a 2:1:1 ratio to receive study vaccination. Each subject was followed for 181 days.

Randomization:

- Subjects were randomized to receive either the aQIV, aTIV-1, or aTIV-2, using the Interactive Response Technology system.

Double-Blind:

- Vaccines were selected and administered according to the Pack ID assigned to the subjects by the Interactive Response Technology system. The subjects, investigative staff involved in administering the vaccines or clinical evaluation of

the subject, personnel involved in performing laboratory assays, and others directly involved in the conduct of the study were blinded.

Immunogenicity assessments were conducted on blood samples collected on Days 1 and 22.

Safety evaluation was as follows:

- Solicited local and systemic AEs for 7 days after vaccination (Day 1 to Day 7)
- All unsolicited AEs for 21 days after vaccination (Day 1 to Day 22)
- SAEs, AEs leading to withdrawal from the study, NOCDs, AESIs, and concomitant medications associated with these events as collected from Day 1 to Day 181.

6.2.3 Population

Males and females ≥ 65 years old who were healthy, or had comorbidities but were able to attend all scheduled visits and comply with study procedures were enrolled. The details of entry criteria were listed on page 26 of the clinical study report of V118_20.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Both the investigational and licensed vaccines used strains recommended by the World Health Organization.

- aQIV group: A 0.5 mL dose of aQIV contains nominally 15 mcg of hemagglutinin (HA) of each of the 2 influenza type A strains and each of the 2 influenza type B strains for a total of 60 mcg of HA. The strains were:
    - A/Michigan/45/2015 (H1N1)-like virus; A/Hong Kong/4801/2014 (H3N2)-like virus; B/Phuket/3073/2013-like virus (Yamagata lineage); B/Brisbane/60/2008-like virus (Victoria lineage).
- aTIV-1 group: A 0.5 mL dose of aTIV-1 contains nominally 15 mcg of HA of each of the 2 influenza type A strains and the recommended influenza type B strain for a total of 45 mcg of HA. The strains were:
    - A/Michigan/45/2015 (H1N1)-like virus; A/Hong Kong/4801/2014 (H3N2)-like virus; B/Brisbane/60/2008-like virus (Victoria lineage).
- aTIV-2 group: A 0.5 mL dose of aTIV-1 contains nominally 15 mcg of HA of each of the 2 influenza type A strains and the recommended influenza type B strain for a total of 45 mcg of HA. The strains were:
    - A/Michigan/45/2015 (H1N1)-like virus; A/Hong Kong/4801/2014 (H3N2)-like virus; B/Phuket/3073/2013-like virus (Yamagata lineage).

Reviewer's comments:

- *The investigational aQIV vaccine was compared to the aTIV-1 and aTIV-2 vaccines. Of note, the aTIV-1 vaccine was licensed under accelerated approval instead of traditional approval.*
- *For the Yamagata virus strain, study V118_20's aQIV vaccine used B/Phuket/3073/2013-like, while study V118_18's aQIV vaccine used B/Brisbane/9/2014.*

6.2.5 Sites and Centers

The studies were conducted in 20 centers in US.

6.2.6 Surveillance/Monitoring

Not applicable.

6.2.7 Endpoints and Criteria for Study Success

Immunogenicity endpoints:

- HI titers at Day 1 and Day 22

Derived co-primary endpoints:

- GMT ratios for the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains at Day 22
    - GMT ratio: geometric mean of the post-vaccination (Day 22) HI titer for aTIV-1 (or aTIV-2) over the geometric mean of post-vaccination (Day 22) HI titer for aQIV
- Difference between the SCRs for the A/H1N1, A/H3N2, B/ Yamagata, and B/Victoria strains at Day 22
    - SCR: percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination HI titer ≥1:40 or a ≥4-fold increase in post-vaccination HI titer.
    - Success criteria: if, for each of the 4 strains:
        - The upper bound of the two-sided 95% confidence interval (CI) for the ratio of the GMTs did not exceed 1.5. The GMT ratio was calculated as GMT_{aTIV}/GMT_{aQIV}.
        - The upper bound of the two-sided 95% CI for the difference between the SCRs did not exceed 10%. The difference in SCRs was calculated as $SCR_{aTIV}–SCR_{aQIV}$.

- Percentage of subjects achieving seroconversion for HI antibody (Day 22)
- Percentage of subjects achieving an HI antibody titer ≥1:40 (Day 22)

  Success criteria (the CBER immunogenicity criteria): if, for each of the 4 strains:
    - The lower bound of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody should have met or exceeded 30%.
    - The lower bound of the two-sided 95% CI for the percentage of subjects achieving a post-vaccination HI antibody titer ≥1:40 should have met or exceeded 60%.

Derived secondary endpoints:

- GMT: Geometric mean of HI titers on Day 1 (pre-vaccination) and Day 22 (post-vaccination)

- GMR: the geometric mean of the fold increase of post-vaccination HI titer over the pre-vaccination HI titer (Day 22/Day 1)
- The percentage of subjects achieving HI titer ≥1:40 at Day 1 and Day 22.
- SCR.

Superiority of aQIV vs. aTIV-1 and aTIV-2 for the alternate B strain was assessed using the GMT ratio (GMT_{aTIV}/GMT_{aQIV}) and difference in SCR ($SCR_{aTIV}–SCR_{aQIV}$) at Day 22. Superiority was declared if the upper limit of the two-sided 95% CI for the GMT ratio (aTIV/aQIV) was <1, and the upper limit of the two-sided 95% CI for the difference in SCRs (aTIV–aQIV) was <0, for both B strains.

Safety endpoints:
Secondary:

- Solicited local and systemic AEs for 7 days after vaccination (Day 1 through Day 7)
- All unsolicited AEs for 21 days after vaccination (Day 1 through Day 22)
- SAEs, AEs leading to withdrawal from the study, NOCDs, and AESIs from Day 1 through Day 181

6.2.8 Statistical Considerations & Statistical Analysis Plan

Immunogenicity:
Statistical hypotheses for the primary objectives were, for each strain i:

- H0: $GMRr_i > 1.5$ vs. Ha: $GMRr_i \leq 1.5$
- H0: $D_i > 10\%$ vs. Ha: $D_i \leq 10\%$
    - $GMRr_i$ is a strain-specific post dose GMT ratio:
        - $GMT_{aTIV\text{-}1}/ GMT_{aQIV}$ for B/Victoria strain
        - $GMT_{aTIV\text{-}2}/ GMT_{aQIV}$ for B/Yamagata strain
        - Pooled $GMT_{(aTIV\text{-}1 \text{ and } aTIV\text{-}2)} /GMT_{aQIV}$ for A/H1N1 strain
        - Pooled $GMT_{(aTIV\text{-}1 \text{ and } aTIV\text{-}2)} /GMT_{aQIV}$ for A/H3N2 strain
    - D_i is the strain-specific post dose SCRs ($\pi_{aTIV\text{-}1}$, $\pi_{aTIV\text{-}2}$, π_{aQIV}) difference
        - $\pi_{aTIV\text{-}1} – \pi_{aQIV}$ for B/Victoria strain
        - $\pi_{aTIV\text{-}2} – \pi_{aQIV}$ for B/Yamagata strain
        - Pooled $\pi_{(aTIV\text{-}1 \text{ and } aTIV\text{-}2)} – \pi_{aQIV}$ for A/H1N1 strain
        - Pooled $\pi_{(aTIV\text{-}1 \text{ and } aTIV\text{-}2)} – \pi_{aQIV}$ for A/H3N2 strain

In addition, for each strain k (i.e., CBER immunogenicity criteria):

- H_{0k}: $\pi_k \leq 0.3$ vs. H_{1k}: $\pi_k > 0.3$
- H_{0k}: $\tau_k \leq 0.6$ vs. H_{1k}: $\tau_k > 0.6$
    - where π_k is the proportion of subjects achieving seroconversion and τ_k is the proportion of subjects achieving an HI antibody titer ≥1:40 at Day 22

The PPS Immunogenicity was used for assessing the primary/secondary immunogenicity endpoints. The FAS was used for assessing the secondary immunogenicity endpoints. For analyses of the A/H1N1 and A/H3N2 strains, the aTIV-1 and aTIV-2 were pooled.

Statistical Analyses

Immunogenicity endpoints:

- In the primary analysis, the adjusted GMT ratio was calculated by fitting a general linear model (GLM) on log-transformed (base 10) post-vaccination HI titer as the dependent variable. The GLM specification was
    - Log10-transformed Post-vaccination HI Titer = Vaccine + Age Strata + Gender + Vaccination History [y/n] + Log10-transformed Pre-vaccination HI Titer + Site + Age Strata*Vaccine.
        - The interaction term Age Strata*Vaccine was to be removed from the model if it is assessed to be not significant at 0.05 level, which was the case in each actual analysis.
        - Age strata was defined as ≥65-74, ≥75-84, and ≥85years
    - Adjusted difference in least square means (on the log scale) and the confidence limits were back-transformed to obtain an adjusted GMT ratio with 95% confidence limits.
- In the secondary analyses, unadjusted GMTs, GMRs and associated two-sided 95% CIs were calculated assuming lognormal distribution of the titers.

- Derived endpoints related to binary data (i.e., percentages of subjects achieving seroconversion, percentages of subjects with titer ≥1:40): Proportion was reported together with two-sided exact 95% CI. The difference in proportions was calculated with 95% CIs. The Statistical Analysis Plan noted that the "difference in SCRs will be presented with exact 95% (CIs). Miettinen and Nurminen method may be used if convergence issues".
    - Missing immunogenicity values were considered to be missing completely at random.
    - Individual HI titers below detection limit (<10) were set to half of that limit (5).
    - Subgroup analyses were based on age at enrollment (≥65 to 74, ≥75 to 84, and ≥85 years), gender, race, previous influenza vaccination in the past 5 years (yes/no), and comorbidity/risk (yes/no, defined as assessment score <50 or ≥50).

Reviewer's comment:

- *In the applicant's actual analysis (i.e., file t-14-02-02-01-01.txt), it appears that the applicant used the command "tables TRTA*CRIT3FL/riskdiff (column=1);" of PROC FREQ in SAS to calculate the confidence interval for the difference in SCRs for each strain. By default, this command provides the Wald asymptotic confidence limits for the risk difference, which is not identical to the pre-specified "exact 95% CIs" or the "Miettinen and Nurminen" method. Nevertheless, this does not change the conclusion since the SCRs of the B strains missed the success criterion by a large margin.*

Safety:

- Frequencies and percentages of subjects experiencing the solicited AEs were presented by severity.
- Unsolicited Adverse Events: AEs occurring during the study were determined either as probably related, possibly related, or not related to vaccination by the Investigator. All reported AEs, as well as AEs determined by the investigator as at least possibly related to study vaccine, were summarized according to System Organ Class and Preferred Term within System Organ Class. These summaries were presented by vaccination group and by interval of study observation. When an AE occurred more than once for a subject, the maximal severity and strongest relationship to the vaccine group was counted.
- Subgroup analysis: Safety analysis of any unsolicited adverse events and any local, any systemic, or any other solicited adverse events (all adverse events combined for each such category) was performed on the following subgroups: age at enrollment (≥65-74, ≥75 to 84, and ≥85years), gender, and race.

Power calculation:
The study planned to recruit 800 subjects in the aQIV group and 400 subjects in each aTIV group. After assuming a 10% drop-out rate, a total of N=1778 subjects were planned to be recruited.

The study was powered to achieve 80% power to demonstrate non-inferiority over 8 co-primary endpoints: SCRs for 4 strains and GMRs for 4 strains. A 1-sided alpha of 0.025 was used for each comparison.

- For the comparison of SCR, a non-inferiority margin of 10% (aTIV – aQIV) was used. Based on the historical data of V70_27, it was assumed that the SCRs for A/H1N1, A/H3N2, and B strains for aTIV were 73%, 73%, and 40%, respectively. The overall power for assessing the 4 endpoints was 82.42%.
- For the comparison of GMTs (aTIV/aQIV), a non-inferiority margin of 1.5 was used. A GMT ratio of 1 and standard deviation of $\log_e$(titer) of 1.2 were assumed. The overall power for assessing the 4 endpoints was 99.96%.

Power for assessing the CBER criteria:

- For the assessment of the percentages of subjects achieving seroconversion, a success criterion of 30% was used. The percentages for A/H1N1, A/H3N2, and B strains were assumed to be 73%, 73%, and 40%, respectively. The overall power for assessing the 4 endpoints was ~100%.
- For the assessment of the percentage of subjects achieving HI antibody titer ≥1:40, a success criterion of 60% was used. Based on the observed percentages in V70_27, the percentages for A/H1N1, A/H3N2, and B strains were assumed to be 91%, 99%, and 64.6%, respectively. The applicant calculated that the power for assessing the A/H1N1, A/H3N2, and each B strain was 100%, 100%, and 76.47%. The applicant stated that the overall power for all 4 tests was 76.47%.

Reviewer's comments:

- *If we assume that all tests were independent, the overall power for assessing the 4 endpoints related to the percentage of subjects achieving HI antibody titer ≥1:40 would be 58.4%, not 76.47%, because there were 2 B strains. The overall power for meeting all 16 success criteria would be ~48%.*

A safety database of N = 800 has a 95% chance of detecting AEs that occur at a rate of 1 in 267. With a single stratum of 800 participants, the probability of observing at least one event for events with population rates of 1 in 300, 1 in 200, and 1 in 100 are 93.1%, 98.2% and 100%, respectively.

6.2.9 Study Population and Disposition

6.2.9.1 Populations Enrolled/Analyzed

A total of 1778 subjects were enrolled: 1220 subjects between ≥65 and 74 years, 499 subjects between ≥75 and 84 years, and 59 subjects ≥85 years.

- The All Enrolled Set, Exposed set, PPS Immunogenicity, Unsolicited Safety Set, and Overall Safety Set were defined in Section 6.1.9.1.
- FAS Immunogenicity includes all subjects in the All Enrolled Set who were randomized, received at least 1 study vaccination, and provided immunogenicity data at Day 1 and Day 22.
- Solicited Safety Set includes all subjects in the Exposed Set with any solicited AE data.

6.2.9.1.1 Demographics

Table 6 summarizes the demographic and baseline characteristics of the subjects in V118_20. Study V118_20 enrolled 889, 445, and 444 subjects into the aQIV, aTIV-1, and aTIV-2 groups. V118_20 enrolled predominantly White (91.6%) subjects. The study enrolled slightly more females (56.6%) than males (43.4%).

Table 6. Demographic and baseline characteristics of subjects in V118_20.

Baseline characteristics	**aQIV N=889**	**aTIV-1 N=445**	**aTIV-2 N=444**	**Total N=1778**
Age in years - Mean (SD)	72.4 (5.5)	72.4 (5.6)	72.6 (5.5)	72.5 (5.5)
Sex, n (%) - Male	372 (41.8)	196 (44.0)	203 (45.7)	771 (43.4)
Race, n (%) -White	814 (91.6)	403 (90.6)	411 (92.6)	1628 (91.6)
-Black or African American	59 (6.6)	37 (8.3)	29 (6.5)	125 (7.0)
-Asian	9 (1.0)	2 (0.4)	1 (0.2)	12 (0.7)
- Native Hawaiian or Pacific Islander	1 (0.1)	1 (0.2)	0	2 (0.1)
- American Indian or Alaska Native	5 (0.6)	0	2 (0.5)	7 (0.4)
- Other	1 (0.1)	2 (0.4)	1 (0.2)	4 (0.2)
- Hispanic or Latino	59 (6.6)	37 (8.3)	31 (7.0)	127 (7.1)
- Not Hispanic or Latino	827 (93.0)	408 (91.7)	410 (92.3)	1645 (92.5)
- Not Reported	2 (0.2)	0	2 (0.5)	4 (0.2)
- Unknown	1 (0.1)	0	1 (0.2)	2 (0.1)
Height (cm) - Mean (SD)	167.5 (9.4)	167.92 (10.5)	168.38 (10.7)	167.84 (10.0)
Weight in kg - Mean (SD)	83.2(19.1)	84.18 (19.0)	84.24 (17.8)	83.73 (18.7)
BMI (kg/m^2) (SD)	29.6 (6.2)	29.79 (5.9)	29.69 (5.6)	29.67 (6.0)
Influenza Vaccination History, n (%)	760 (85.5)	380 (85.4)	401 (90.3)	1541 (86.7)
Total Risk Score (Comorbidity) - Mean (SD)	46.0 (33.5)	44.6 (30.3)	46.5 (34.2)	45.8 (32.9)

Source: Table 8 of the Clinical Study Report of V118_20 submitted to BLA 125510/143.0.

Reviewer's comment:

- *The baseline characteristics appear to be comparable across groups.*

6.2.9.1.2 Medical/Behavioral Characterization of the Enrolled Population
Not applicable.

6.2.9.1.3 Subject Disposition
Table 7 summarizes the subject disposition. The most frequent reason for discontinuation from the study was lost to follow-up (0.7%).

Table 7. Study disposition in subjects ≥65 years of age.

Cohort: Overall	**aQIV(N=889)**	**aTIV-1 (N=445)**	**aTIV-2 (N=444)**	**Overall (N=1778)**
Overall Safety Set	888 (99.9)	444 (99.8)	444 (100)	1776 (99.9)
Full Analysis Set Immunogenicity	886 (99.7)	443 (99.6)	441 (99.3)	1770 (99.6)
Per Protocol Set Immunogenicity	872 (98.1)	436 (98.0)	433 (97.5)	1741 (97.9)
Discontinued Early from the Study	8 (0.9)	5 (1.1)	5 (1.1)	18 (1.0)
*Adverse Event	0	0	0	0
*Withdrawal of Consent	1 (0.1)	1 (0.2)	1 (0.2)	3 (0.2)
*Lost to Follow-up	5 (0.6)	4 (0.9)	4 (0.9)	13 (0.7)
*Protocol Deviation	0	0	0	0
*Administrative Reason	0	0	0	0
*Study Terminated by Sponsor	0	0	0	0
*Death	2 (0.2)	0	0	2 (0.1)
*Other	0	0	0	0

Source: Table 4 of the Clinical Study Report of V118_20 submitted to BLA 125510/143.0.

Reviewer's comment:

- *The percentages of subjects lost-to-follow-up were low and were similar across treatment groups.*

6.2.10 Immunogenicity Analyses

6.2.10.1 Analyses of Primary Endpoints

The analyses of the primary endpoints were summarized in Tables 8 - 10.

Table 8. Analysis of non-inferiority of aQIV relative to aTIVs as measured by HI GMT ratios for each strain on Day 22 in adults aged ≥65 years (Per Protocol Set)

Strain	**aQIV (N=872)**	**aTIV-1 (N=436)**	**aTIV-2 (N=433)**	**aTIV pooled (N=869)**	**GMT ratio (aTIV/aQIV) and 95% CI**	**Met criteria**
A/H1N1	65.01	--	--	75.16	1.16 (1.05, 1.27)	Yes
A/H3N2	294.91	--	--	293.31	0.99 (0.90, 1.09)	Yes
B/Yamagata	24.67	--	24.30	-	0.99 (0.90, 1.08)	Yes
B/Victoria	30.78	30.13	--	-	0.98 (0.89, 1.08)	Yes

Source: Table 9 of the Clinical Study Report of V118_20 submitted to BLA 125510/143.0.

Table 9. Non-inferiority of aQIV relative to aTIVs as measured by HI seroconversion rates for each strain on Day 22 in adults aged ≥65 years (Per Protocol Set)

Subtype	aQIV (N=872) % (95% CI)	aTIV-1 (N=436) % (95% CI)	aTIV-2 (N=433) % (95% CI)	aTIV minus aQIV %	Lower 95%	Upper 95%	Met criteria
A/H1N1	35.2 (32.0, 38.5)	39.5 (34.8, 44.2)	37.4 (32.8, 44.2)	3.2	-1.3	7.8	Yes
A/H3N2	39.3 (36.1, 42.7)	39.7 (36.4, 43.0)	37.2 (32.6, 41.9)	0.4	-4.2	5.0	Yes
B/Yamagata	16.4 (14.0, 19.0)	-	15.5 (12.2, 19.2)	-0.9	-5.1	3.3	Yes
B/Victoria	13.4 (11.2, 15.9)	12.2 (9.2, 15.6)	-	-1.3	-5.1	2.6	Yes

Source: Table 10 of the Clinical Study Report of V118_20 submitted to BLA 125510/143.0.

Table 10. Immunogenicity as measured by percentages of subjects with HI titer ≥1:40 and seroconversion rate to each homologous strain on Day 22 (Per Protocol Set)

Endpoint	**aQIV (N=872) % (95% CI)**	**aTIV-1/aTIV-2[1] (N=869) % (95% CI)**	**Met criteria**
A/H1N1	-	-	-
Day 22 Post-Vaccination % HI titer ≥1:40 (95% CI)	69.4 (66.2, 72.4)	70.3 (67.2, 73.3)	Yes
SCR (%) (95% CI)	35.2 (32.0, 38.5)	38.4 (35.2, 41.8)	Yes
A/H3N2	-	-	-
Day 22 Post-Vaccination % HI titer ≥1:40 (95% CI)	93.9 (92.1, 95.4)	94.8 (93.1, 96.2)	Yes
SCR (%) (95% CI)	39.3 (36.1, 42.7)	39.7 (36.4, 43.0)	Yes
B/Yamagata	-	-	-
Day 22 Post-Vaccination % HI titer ≥1:40 (95% CI)	32.8 (29.7, 36.0)	37.0 (32.4, 41.7)	No
SCR (%) (95% CI)	16.4 (14.0, 19.0)	15.5 (12.2, 19.2)	No
B/Victoria	-	-	-
Day 22 Post-Vaccination % HI titer ≥1:40 (95% CI)	38.2 (35.0, 41.5)	36.9 (32.4, 41.7)	No
SCR (%) (95% CI)	13.4 (11.2, 15.9)	12.2 (9.2, 15.6)	No

1: aTIV-1 and aTIV-2 vaccine groups were pooled for the analysis of A/H1N1 and A/H3N2 strains. For B/Victoria, TIV=aTIV-1 (N=436), for B/Yamagata TIV=aTIV-2 (N=433).
Source: Table 11 of the Clinical Study Report of V118_20 submitted to BLA 125510/143.0.

Reviewer's comments:

- *For all strains, the success criteria for demonstrating non-inferiority of aQIV to aTIV-1 and aTIV-2 in terms of GMT ratios and differences between seroconversion rates were met. However, the CBER criteria (i.e., success criteria for percentages of subjects achieving seroconversion for HI antibody and percentages of subjects achieving an HI antibody titer ≥1:40 21 days post-vaccination) were not met for the B/Yamagata and B/Victoria strains.*
- *For each strain, the immunogenicity results of aQIV and aTIV-1/aTIV-2 that contain the identical vaccine strain appear to be comparable.*
- *I verified the statistical analyses of the primary objectives.*

6.2.10.2 Analyses of Secondary Endpoints

The GMTs on Days 1 and 22 are summarized in Table 11.

Table 11. Geometric mean titers (95% CIs) on Day 1 and Day 22 and Geometric mean ratios (95% CIs) of HI (Day 22/Day 1) by vaccine group (Per Protocol Set).

Strain	Visit	aQIV (N=872)	aTIV-1 (N=436)	aTIV-2 (N=433)	aTIV-pooled (N=869)
A/H1N1	Day 1	19.07 (17.66, 20.60)	--	--	18.77 (17.47, 20.17)
A/H1N1	Day 22	57.07 (52.67, 61.84)	--	--	63.73 (58.60, 69.32)
A/H1N1	Day 22/Day 1	2.99 (2.78, 3.22)	--	--	3.40 (3.14, 3.67)
A/H3N2	Day 1	73.27 (66.36, 80.90)	--	--	71.83 (65.39, 78.90)
A/H3N2	Day 22	245.85 (225.57, 267.95)	--	--	236.27 (217.53, 256.63)
A/H3N2	Day 22/Day 1	3.36 (3.07, 3.66)	--	--	3.29 (3.02, 3.59)
B/Yamagata	Day 1	10.41 (9.86, 10.98)	11.26 (10.35, 12.24)	10.76 (9.97, 11.61)	--
B/Yamagata	Day 22	21.15 (19.75, 22.66)	14.53 (13.24, 15.94)	20.74 (18.86, 22.80)	--
B/Yamagata	Day 22/Day 1	2.03 (1.92, 2.15)	1.29 (1.22, 1.36)	1.93 (1.79, 2.08)	--
B/Victoria	Day 1	14.15 (13.30, 15.05)	15.18 (13.85, 16.64)	14.18 (12.95, 15.51)	--
B/Victoria	Day 22	24.91 (23.21, 26.74)	25.54 (23.03, 28.33)	17.08 (15.62, 18.68)	--
B/Victoria	Day 22/Day 1	1.76 (1.66, 1.86)	1.68 (1.55, 1.82)	1.20 (1.15, 1.26)	--

Source: Tables 13 and 14.2.3.1 of the Clinical Study Report of V118_20 submitted to BLA 125510/143.0.

Reviewer's comment:

- *The geometric mean ratios between Day 22 and Day 1 appear to show that the aQIV vaccine elicited immune responses to all 4 strains. In addition, the HI titers between aQIV and aTIV-1/aTIV-2 appear to be similar for each strain, when the aQIV group is compared to the comparator group that contained the same vaccine strain.*

The pre-specified success criteria for immunogenicity superiority in terms of GMT ratio (GMT_{aTIV}/GMT_{aQIV}) and difference in SCR ($SCR_{aTIV}–SCR_{aQIV}$) at Day 22, comparing aQIV vs. aTIV-1 (without the B/Yamagata strain in the vaccine) for B/Yamagata and aQIV vs. aTIV-2 (without the B/Victoria strain in the vaccine) for B/Victoria, were met (Results not presented here; please refer to Table 12 of the CSR).

6.2.10.3 Subpopulation Analyses

Subgroup analyses by previous vaccination history, age, gender, race, and comorbidity risk score were performed (Results not presented here). The applicant concluded that the similar immunogenicity was observed in the aQIV and aTIV groups, across different age groups (≥65 to 74, ≥75 to 84, and ≥85 years), genders, races, comorbidity statuses, and previous influenza vaccination history statuses.

Reviewer's comments:

- *I made some observations for the subgroup analyses:*
  - *Age: For all strains, the estimated seroconversion rates appear to be higher in the younger (≥65-74 years) group than the older group (≥85 years).*
  - *Gender: For all strains, no meaningful differences in terms of the percentage of subjects achieving HI titer ≥1:40 and seroconversion rate were observed between males and females who received aQIV.*
  - *Race: Most of the subjects were White (N=798 for aQIV) and only a small sample size was available for Black/African American (N=59 for aQIV). The minor differences in terms of the estimated percentage of subjects achieving HI titer ≥1:40 and seroconversion rates may be due to sampling variability.*
  - *Comorbidity risk score: For all strains, aQIV subjects with risk score <50 had higher estimated seroconversion rates than aQIV subjects with risk score ≥50.*
- *For all strains, the estimated percentage of subjects achieving seroconversion was higher in the aQIV group without previous vaccination than in the aQIV group with previous vaccination. In the aQIV group without previous vaccination, the point estimates of seroconversion rates were slightly greater than 30% for the B strains. For the group with previous vaccination [N=748] vs. the group without previous vaccination [N=124], the estimated percentages of aQIV subjects achieving seroconversion were:*
  - *A/H1N1: 31.8% vs. 55.7%*
  - *A/H3N2: 35.2% vs. 64.5%*
  - *B/Yamagata: 13.9% vs. 31.5%*
  - *B/Victoria: 9.6% vs. 36.3%*
- *The estimates of the percentages of aQIV subjects achieving HI titer ≥1:40 were as follows, for the group with previous vaccination [N=748] vs. the group without previous vaccination [N=124]:*
  - *A/H1N1: 69.3% vs. 70.2%*
  - *A/H3N2: 94.0% vs. 93.6%*
  - *B/Yamagata 31.4% vs. 41.1%*
  - *B/Victoria: 36.0% vs. 51.6%*

6.2.10.4 Dropouts and/or Discontinuations

The percentage of subjects discontinued from the study was low (1.0%) and similar across treatment groups.

6.2.10.5 Exploratory and Post Hoc Analyses

In V118_18, the lower limits of the 95% CIs for the percentages of subjects achieving HI titer ≥1:40 and for the percentages of subjects achieving seroconversion met the CBER criteria for the B/Yamagata and B/Victoria strains. These endpoints were also evaluated in V118_20, using an aQIV vaccine from a different influenza season, but the results did not meet the CBER criteria for these strains.

CBER sent the following Information Request to the applicant on March 8, 2019.

- "As just discussed today, we are in need of some information regarding V118_20. If possible, please provide an explanation for not meeting CBER criteria for the B strains in Fluad. Is a possible explanation, assay difference, potency difference and/or population difference? Please provide information to support your explanation."

On March 18, 2019, the applicant submitted a clinical information amendment to respond to this question.

- Potency of study vaccines: The applicant presented stability data over time for the 2 vaccines. The applicant concluded that both study vaccines remained stable over time, well above the HA stability specification of (b) (4) µg/ml, for up to 12 (b) (4) months.
- Study population differences: The applicant noted that the majority (86.8%) of subjects had been vaccinated in the previous 5 years in V118_20, whereas in V118_18 only 30.4% received influenza within the same period. However, the applicant concluded that the difference in the proportion of subjects with history of influenza vaccine between these clinical studies alone cannot explain different immunogenicity results obtained in the V118_18 and V118_20 studies.
- Assay variability: Both assays used for testing the clinical samples in V118_18 and V118_20 were validated. The applicant stated that variability in the results may be related to the differences in biological reagents, protocols, and personnel training. The applicant hypothesized that the differences in (b) (4) used in the 2 clinical studies were likely responsible for the observed inter-laboratory variability and contributed to the differences in post-vaccination B strain immune responses seen in the two trials.
    - (b) (4)
    - (b) (4)

On April 5, CBER sent a "Deficiencies Identified" letter to the applicant. Point #4 is repeated below:

- "We agree with your investigative conclusion (summarized in your response submitted on March 14, 2019, received on March 18, 2019) that the differences in B-specific immunogenicity observed between V118_20 and V118_18 may be due to inter-assay variability rather than vaccine stability, and cannot be completely attributed to differences between the studies in subject's pre-existing influenza immunity. However, it is not clear how the two assays and protocols could have contributed to such different results in B-specific immunogenicity. Please propose a study that re-examines the available sera from the two clinical trials using a

single assay protocol and submit a report of the study results to this sBLA no later than July 1, 2019. Please provide a detailed protocol for the proposed study for our review and concurrence prior to initiating the study no later than April 12, 2019."

On June 28, 2019, the applicant submitted to STN 125510/143.6 a report describing the exploratory study.

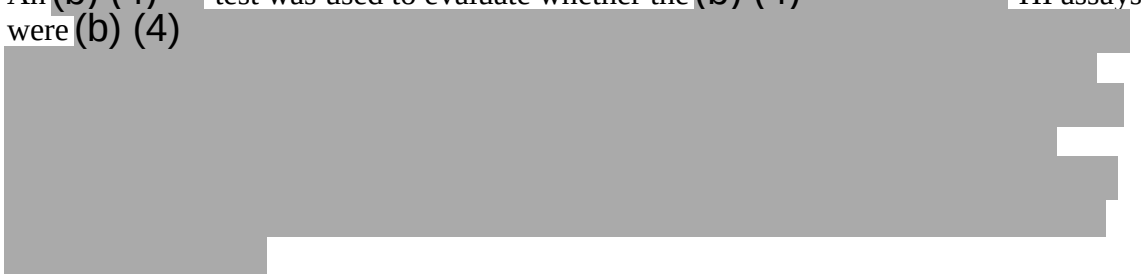
Exploratory study

An exploratory study was conducted to assess the immunogenicity of serum samples from V118_20 and V118_18 using the validated (b) (4) HI assays used in V118_18. The purpose of this study was to investigate the hypothesis that the differences in B-specific immunogenicity between V118_20 and V118_18 studies were associated with difference between the two assay methods. A random sample of (b) (4) subjects from each clinical study was selected for re-assessment of the immunogenicity of the B strains. Except for the (b) (4), the same testing protocol and same set of reagents used for the primary testing in the V118_18 study were used.

Reviewer's comment:

- *Table 10-1 of the "Report on the re-examination of antibody titers for influenza B strains in samples from two clinical studies using a single assay protocol" appears to show* (b) (4)

An (b) (4) test was used to evaluate whether the (b) (4) HI assays were (b) (4)



On August 5, 2019, CBER sent the following IR question to the applicant:

- "Please comment on why the equivalence of the HI titers between the primary V118_18 testing and the post-hoc testing results failed to meet the prespecified criterion for the B/Yamagata strain, but not for the B/Victoria strain, after using the same testing protocol and the same set of reagents (except (b) (4)) as

utilized for the V118_18 study. Please comment on whether this potential issue for the B/Yamagata strain affects the reliability of using the re-tested results of V118_20 to confirm the hypothesis that lower HI titers for B strains observed in V118_20 are associated with inter-laboratory variability."

On August 13, 2019, the applicant submitted a document entitled "Response to RFI Reanalysis of HI titers" to STN 125510/143.9. The applicant stated that because different (b) (4)

Reviewer's comment:

- *Equivalence of GMTs between the post-hoc and primary testing of V118_18 samples was demonstrated only for the B/Victoria strain (GMR:* (b) (4) *) but not for the B/Yamagata strain (GMR:* (b) (4) *). While a 2-fold difference in individual titer values may not suggest an assay shift since the measurements are step titers, a 2-fold difference in the GMTs appears to indicate some assay shift. Of note, it is typically required that the GMT ratios be within 0.67 to 1.5 to demonstrate lot consistency. That said, the shift appears to be large for the B/Yamagata strain and may indicate some degree of assay shift for this strain.*
- *For each strain, the reverse cumulative distribution curve (Figure 1) and* (b) (4) *regression analysis (Figure 2 and Table 12) suggest that the shift in (log-)titers between the post-hoc and primary testing results was larger for the V118_20 samples than for the V118_18 samples. Because of the clear differences in the magnitude of the shift, difference between the two assay methods appears to be one of the contributing factors for the difference in immune responses observed between the two studies. However, the post-hoc immunogenicity results of the B strains in V118_20 still did not meet the CBER immunogenicity criteria for seroconversion (Table 13).*

1 page has been determined to be not releasable: (b)(4)

Table 12. Results for slope and intercept estimates with 95% CIs from (b) (4) regression for each study and B strain - Randomly selected subsets of samples.

(b) (4)

Source. Table 10-1 of the "Response to RFI Reanalysis of HI titers" submitted to STN 125510.143.9.

The immune responses to the B strains based on post-hoc retests as well as original tests were summarized in Table 13. For the V118_20 samples, the percentages of subjects with post-vaccination HI titer ≥1:40 were much higher with the post-hoc testing results ((b) (4)] for B/Yamagata and (b) (4) for B/Victoria) than with the primary testing results ((b) (4) for B/Yamagata and (b) (4) for B/Victoria). However, the percentages of subjects achieving seroconversion with the post-hoc testing results remained low ((b) (4) for B/Yamagata and (b) (4) [95%CI: (b) (4)] for B/Victoria) and did not meet the CBER criteria.

Reviewer's comments:

- *For both B strains, the post-hoc testing results of the V118_20 post-vaccination samples passed the CBER criteria for the percentages of subjects achieving HI titer ≥1:40. Of note, the post-hoc testing results of the pre-vaccination samples also passed the CBER criteria for the percentages of subjects achieving HI titer ≥1:40 for both B strains.*
- *The point estimates of the primary testing results for the random subsets and those for the PPS in Table 13 appear to be similar, which further supports the assumption that the random subsets are likely representative of the subjects from the PPS.*

Table 13. Immune responses to each B Strain at baseline or post-vaccination for each study, using a randomly selected subset of subjects.

-	V118_18	V118_18	V118_18	V118_20	V118_20	V118_20
-	The Random Subset	The Random Subset	Original report	The Random Subset	The Random Subset	Original report
Endpoints	**Post-hoc Testing**	**Primary Testing**	**PPS**	**Post-hoc Testing**	**Primary Testing**	**PPS**
-	(b) (4)		N=1256	(b) (4)		N=872
B/Yamagata			-			-
Pre-Vaccination GMT [95% CI]			12.83 [12.06, 13.64]			10.41 [9.86, 10.98]
Post-Vaccination GMT [95% CI]			87.40 [81.32, 93.94]			21.15 [19.75, 22.66]
GMR [95% CI]			6.81 [6.34, 7.31]			2.03 [1.92, 2.15]
Pre-Vaccination % HAI titer ≥ 1:40 [95% CI]			24.2% [21.83%, 26.65%]			11.12% [9.11%, 13.40%]
Seroconversion rate [95% CI]			60.6% [57.84%, 63.33%]			16.40% [14.00%, 19.03%]
Post-Vaccination % HAI titer ≥ 1:40 [95% CI]			79.3% [76.96%, 81.53%]			32.80% [29.69%, 36.03%]
B/Victoria			-			-
Pre-Vaccination GMT [95% CI]			11.78 [11.06, 12.56]			14.15 [13.30, 15.05]
Post-Vaccination GMT [95% CI]			103.42 [95.89, 111.54]			24.91 [23.21, 26.74]
GMR [95% CI]			8.78 [8.15, 9.47]			1.76 [1.66, 1.86]
Pre-Vaccination % HAI titer ≥ 1:40 [95% CI]			21.3% [19.01%, 23.63%]			19.72% [17.13%, 22.52%]
Seroconversion rate [95% CI]			65.0% [62.23%, 67.61%]			13.42% [11.22%, 15.86%]
Post-Vaccination % HAI titer ≥ 1:40 [95% CI]			81.4% [79.12%, 83.51%]			38.19% [34.95%, 41.51%]

Source: Tables 10-5 and 10-6 of the "Report on the Re-examination of Antibody Titers for Influenza B Strains in Samples from Two Clinical Studies Using a Single Assay Protocol" document submitted to STN 125510/143.6.

Reviewer's comment:

- *I verified the results presented in Table 13.*
- *The post-hoc testing results in V118_20 did not meet the CBER immunogenicity criteria for seroconversion rate for both B strains. I defer to the clinical team to evaluate the implication of these results.*

6.2.11 Safety Analyses

Solicited adverse events:
The percentages of subjects experiencing at least one solicited adverse events are summarized in Table 14. The percentages of subjects experiencing each type of solicited adverse event are summarized in Tables 15 and 16.

Table 14. Number (%) of subjects with at least one solicited adverse event reported from Day 1 through Day 7 by vaccination (Solicited Safety Set).

AE	**aQIV (N=883) n (%)**	**aTIV-1 (N=439) n (%)**	**aTIV-2 (N=438) n (%)**
Any solicited AE	457 (51.8%)	214 (48.7%)	211 (48.2%)
Any local solicited AE	385 (43.6%)	170 (38.7%)	167 (38.1%)
Any systemic solicited AE	231 (26.2%)	107 (24.4%)	110 (25.1%)
Other indicators of reactogenicity	48 (5.4%)	12 (2.7%)	17 (3.9%)

Source: Table 21 of "Clinical Study Report of V118_20" submitted to BLA 125510/143.0.

Reviewer's comment:

- *Overall, the aQIV group appears to have a similar percentage of subjects experiencing any solicited AE as the aTIV-1 and aTIV-2 groups.*

Table 15. Summary of solicited systemic adverse events by type from Day 1 to Day 7 (excluding the first 30 minutes after vaccination)

Symptom/Severity Grades	**aQIV - Any**	**aQIV - Grade 3**	**aTIV-1 - Any**	**aTIV-1 Grade 3**	**aTIV-2 Any**	**aTIV-2 Grade 3**
-	**N=883***	**N=883***	**N=439***	**N=439***	**N=438***	**N=438***
Headache	12.0%	0.5%	10.6%	0.7%	11.3%	0.7%
Generalized Myalgia	8.1%	0.5%	7.8%	0.0%	6.9%	0.9%
Generalized Arthralgia	9.1%	0.3%	8.5%	0.0%	7.1%	1.2%
Fatigue	16.0%	0.7%	15.4%	0.7%	11.5%	1.4%
Chills	4.7%	0.2%	3.4%	0.5%	4.4%	0.7%
Loss of Appetite	3.2%	0.2%	4.8%	0.0%	3.7%	0.5%
Nausea	4.0%	0.2%	4.1%	0.0%	4.6%	0.9%
Vomiting	0.8%	0.1%	0.5%	0.0%	2.1%	0.7%
Diarrhea	5.5%	0.6%	5.5%	0.5%	6.9%	0.7%
Body Temperature	-	-	-	-	-	-
≥38.0 (°C)	0.5%	-	0.2%	-	0.5%	-
>39.0 (°C)	0.1%	-	0.0%	-	0.0%	-
Other	5.4%	-	2.7%	-	3.9%	-

*Number of subjects in the Solicited Safety Set. The actual numbers of subjects who recorded the status for each AE type were ≥875, ≥435, and ≥434 in the aQIV, aTIV-1, and aTIV-2 groups, respectively.
Source: Adapted from Table 24 of the Clinical Study Report of V118_20 submitted to BLA 125510/143.0.

Table 16. Summary of solicited local adverse events by type from Day 1 to Day 7 (excluding the first 30 minutes after vaccination)

Symptom/Severity Grades	**aQIV N=883***	**aQIV N=883***	**aTIV-1 N=439***	**aTIV-1 N=439***	**aTIV-2 N=438***	**aTIV-2 N=438***
-	**Any**	**Severe**	**Any**	**Severe**	**Any**	**Severe**
Pain at Injection Site	31.9%	0%	29.1%	0.9%	25.7%	0.2%
-	**≥25mm**	**>100mm**	**≥25mm**	**>100mm**	**≥25mm**	**>100mm**
Erythema at Injection Site	7.6%	0%	7.4%	0.3%	8.6%	0%
Induration at Injection Site	7.0%	0%	5.4%	0%	5.3%	0%
Ecchymosis at Injection Site	2.5%	0.1%	1.5%	0%	1.5%	0%

*Number of subjects in the Solicited Safety Set. The actual numbers of subjects who recorded the status for each AE type were ≥794, ≥390, and ≥392 in the aQIV, aTIV-1, and aTIV-2 groups, respectively.
Source: Reviewer's analysis of Table 23 of the Clinical Study Report of V118_20 submitted to BLA 125510/143.0.

Reviewer's comment:

- *I verified the results presented in Tables 14-16.*

Unsolicited AEs:

Table 17 summarizes the unsolicited adverse events.

Table 17. Overall summary of unsolicited adverse events (percentage) in the unsolicited safety set

Unsolicited AEs	**aQIV (N=888)**	**aTIV-1 (N=444)**	**aTIV-2 (N=444)**
Subjects with any unsolicited AEs Days 1-181	176 (19.8)	76 (17.1)	91 (20.5)
Related Unsolicited AEs (Days 1-181)	39 (4.4)	17 (3.8)	19 (4.3)
Unsolicited AEs (Days 1-181) -Mild	100 (11.3)	38 (8.6)	57 (12.8)
-Moderate	49 (5.5)	15 (3.4)	22 (5.0)
-Severe	27 (3.0)	23 (5.2)	12 (2.7)
AEs leading to Study Discontinuation	0	0	0
-Serious Adverse Events (SAEs)	37 (4.2)	28 (6.3)	18 (4.1)
-Related SAEs	0	0	0
-Deaths	2 (0.2)	0	0
-Adverse Events of Special Interest (AESIs)	1 (0.1)	1 (0.2)	0
-Related AESIs	0	0	0
-AEs Leading to New Onset of Chronic Disease	23 (2.6)	16 (3.6)	14 (3.2)

Source: Table 22 of the Clinical Study Report of V118_20 submitted to BLA 125510/143.0.

Reviewer's comment:

- *The percentages of subjects experiencing each category of unsolicited AEs (Table 17) appear to be similar across the aQIV, aTIV-1, and aTIV-2 groups.*

The most commonly reported unsolicited AEs classified by Preferred Terms were Influenza-like-illness (2.0%-2.9% of subjects across groups), injection site bruising (1.1%-1.4% across groups), injection site erythema (0.7%-1.1% across groups), upper respiratory tract infection (0.7%-1.1% across groups), and headache (0.6%-1.8% across groups).

6.2.11.1 Deaths

There were 2 deaths in this study. Both deaths occurred in the aQIV vaccine group. The investigator did not consider these deaths to be related to the study vaccine.

- 1 death was reported with unknown cause. The 72-year-old white female subject received the vaccine approximately 3.5 months before she died. The applicant stated that the subject's death could be due to an acute event secondary to underlying comorbidities.
- A 72-year-old white male died 3 months after vaccination. The subject's cause of death was reported as suspected natural cause, and the actual cause of death was unknown because a death certificate was not available. No autopsy was performed.

6.1.12.2 Nonfatal Serious Adverse Events

A total of 4.2%, 6.3%, and 4.1% of subjects from the aQIV, aTIV-1, and aTIV-2 groups, respectively, experienced serious adverse events. The most frequently occurring SAE in the aQIV group was Pneumonia (7 cases, 0.8%) and Osteoarthritis (3 cases, 0.3%). No SAEs were considered to be related to the vaccines.

Reviewer's comment:

- *The percentages of subjects experiencing each type of SAE appear to be similar across the aQIV, aTIV-1, and aTIV-2 groups. No noticeable imbalance in the percentage of subjects experiencing each specific preferred term of SAE was observed across groups.*

6.2.11.3 Adverse Events of Special Interest (AESI)

One case of AESI occurred in the aQIV vaccine group (Polymyalgia rheumatica) and one case occurred in the aTIV-1 vaccine group (Addison's disease).

6.2.11.4 Clinical Test Results

Not applicable since no laboratory assessments of hematology, blood chemistry, or urine chemistry were specified in the protocol.

6.2.11.5 Dropouts and/or Discontinuations

No AEs leading to study withdrawal occurred.

7. INTEGRATED OVERVIEW OF EFFICACY

This section is not applicable.

8. INTEGRATED OVERVIEW OF SAFETY

This section is not applicable.

9. ADDITIONAL STATISTICAL ISSUES

None.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

V118_18

- The pre-specified success criterion to demonstrate VE of aQIV (VE: 19.80% (adjusted 97.45% CI: -5.27%, 38.91%) in the FAS Efficacy) was not met. Of note, most influenza cases were antigenically unmatched to the vaccine strains.
- For all strains, the percentages of subjects achieving seroconversion for hemagglutination inhibition (HI) antibody and the percentages of subjects achieving an HI antibody titer ≥1:40 met the CBER immunogenicity criteria.
    - For all strains, the lower limit of the percentage of subjects achieving an HI antibody titer ≥1:40 was ≥77.0% and the lower limit of the percentage of subjects achieving seroconversion was ≥57.8% 21 days post-vaccination.

V118_20:

- For all strains, the success criteria for demonstrating non-inferiority of aQIV to aTIV-1 and aTIV-2 in terms of GMT ratios and differences between seroconversion rates were met.
- The CBER criteria (i.e., success criteria for percentages of subjects achieving seroconversion for HI antibody and percentages of subjects achieving an HI antibody titer ≥1:40 21 days post-vaccination) were met for the A/H1N1 and A/H3N2 strains, but not for the B/Yamagata and B/Victoria strains.
- The safety profiles appear to be comparable among the aQIV, aTIV-1, and aTIV-2 groups.

Exploratory study re-examining antibody titers for Influenza B strains in random subsets from V118_18 and V118_20 using the validated (b) (4) HI assays:

- Equivalence of GMTs between the post-hoc and primary testing of V118_18 samples was demonstrated only for the B/Victoria strain ((b) (4)) but not for the B/Yamagata strain ((b) (4)). The shift appears to be large and may indicate some degree of assay shift for the B/Yamagata strain. For each B strain, the reverse cumulative distribution curve and (b) (4) regression plot suggested that the shift in (log-)titers between the post-hoc and primary testing results was larger for the V118_20 samples than for the V118_18 samples. The difference

between the two assay methods appears to be one of the contributing factors for the difference in immune responses observed between the two studies.
In the re-tested (post-hoc) V118_20 samples, the percentages of subjects achieving HI titer ≥1:40 were high ((b) (4), with lower limits (b) (4)) and met the CBER criteria for both B/Yamagata and B/Victoria strains. However, the percentages of subjects achieving seroconversion were still low for the B/Yamagata ((b) (4)) and B/Victoria strains ((b) (4)) and did not meet the CBER criteria.

10.2 Conclusions and Recommendations

In summary, the safety profiles of subjects who received aQIV appear to be acceptable in both studies. The results of Fluad aQIV met the CBER immunogenicity criteria in V118_18. In V118_20, the CBER immunogenicity criteria for seroconversion rate were not met for the B/Yamagata and B/Victoria strains. I defer to the clinical review team to interpret the mixed conclusions from the two studies and determine whether the immunogenicity results are acceptable to support accelerated approval.