Application Type	BLA, Original Application
STN	125692/0
CBER Received Date	February 1, 2019
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Division / Office	DVRPA/OVRR
Committee Chair	Brenda Baldwin
Clinical Reviewer(s)	Cynthia Nolletti
Project Manager	Edward Wolfgang
Priority Review	No
Reviewer Name	Ye Yang, Mathematical Statistician, VEB/DB
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Concurring Reviewer, VEB/DB
Supervisory Concurrence	Tsai-Lien Lin, Branch Chief, VEB/DB
Supervisory Concurrence	John Scott, Director, DB
Applicant	Seqirus Inc.
Established Name	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
(Proposed) Trade Name	AUDENZ
Pharmacologic Class	Influenza Vaccine
Dosage Form(s) and Route(s) of Administration	Injectable Suspension, containing 7.5 mcg HA per 0.5 mL dose, Intramuscular
Dosing Regimen	Administer two doses (0.5 mL each) 21 days apart
Indication(s) and Intended Population(s)	For active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine for persons six months and older

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GLOSSARY

aH5N1c	Cell culture-derived, MF59-adjuvanted H5N1
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Events of Special Interest
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
BIMO	Bioresearch Monitoring Program
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HI	Hemagglutination Inhibition
IM	Intramuscular
ISS	Integrated Summary of Safety
MedDRA	Medical Dictionary for Regulatory Activities
NOCD	New Onset of Chronic Disease
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
USA	United States of America

1. EXECUTIVE SUMMARY

Seqirus submitted a Biologics License Application (BLA) to seek approval of a pandemic influenza vaccine (aH5N1c) for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine for persons six months and older. The vaccine formulation includes 7.5 µg of hemagglutinin (HA) antigen and (b) (4) of MF59 adjuvant. Safety and immunogenicity data based on recommendations from the May 2007 FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines were obtained from five clinical studies to support licensure of this vaccine:

- V89P1: a Phase 1/2, randomized, double-blind trial was conducted to evaluate the safety and immunogenicity of 12 antigen-adjuvant dose combinations. Subjects were vaccinated on Day 1 and Day 22 and were assessed the following primary immunogenicity endpoints on Day 43: hemagglutination inhibition (HI) antibody titers, achievement of HI antibody titer ≥1:40, and seroconversion, defined as having HI ≥1:40 for subjects negative at baseline (HI <1:10) or a minimum of four-fold increase in HI titer for subjects positive at baseline (HI ≥1:10). Results showed that the adjuvanted formulations of the vaccine elicited significantly higher geometric mean titers (GMTs), seroconversion rates, and percentages of subjects achieving antibody titers ≥1:40 compared to the unadjuvanted formulation at the same antigen level. The results demonstrated the benefit of the adjuvant.

- V89_04, V89_11, V89_13: three Phase 2, randomized, double-blind studies were conducted separately for subjects aged 18 to 64 years, 6 months to 17 years, and 65 years and older, respectively. Subjects were randomized to one of the two formulations of the vaccine: a low dose containing 3.75 µg HA antigen and 0.125 mL MF59 adjuvant and a high dose containing 7.5 µg HA antigen and 0.25 mL MF59 adjuvant. Subjects were vaccinated on Day 1 and Day 22 and were evaluated for the achievement of HI antibody titer ≥1:40 and seroconversion on Day 43. In all three studies, the high dose met the prespecified immunogenicity objectives for rates of seroconversion and percentage of subjects with HI titer ≥1:40 (i.e., CBER criteria) according to recommendations in the FDA guidance.

- V89_18: a Phase 3, randomized, double-blind, placebo-controlled study was conducted to evaluate safety, immunogenicity, and lot-to-lot consistency of the aH5N1c vaccine containing 7.5 µg HA antigen and 0.25 mL MF59 adjuvant. Subjects were vaccinated on Day 1 and Day 22 with one of three lots of the aH5N1c vaccine or placebo and were evaluated on Day 43 for HI antibody titers and the achievement of HI antibody titer ≥1:40. Lot consistency based on Day 43 HI antibody titers was successfully demonstrated using a 1.5-fold equivalence margin, and superiority to 70% and 60% for the percentage of subjects achieving HI titers ≥1:40 were successfully demonstrated in the 18 to <65 years and ≥65 years age groups.

Overall, the 7.5 µg HA antigen + 0.25 mL MF59 vaccine formulation met all prespecified immunogenicity and lot consistency objectives evaluated in the Phase 2 and Phase 3 studies and no major statistical issues have been identified. While the aH5N1c vaccine appeared to elicit higher rates of local and systemic reactions than placebo, no practical differences in the rates of related SAEs, AESIs, NOCDs, AEs leading to withdrawal, and medically attended AEs were observed between the aH5N1c vaccine and placebo. No deaths occurred that were considered related to the vaccine. The clinical and immunogenicity data thus support licensure of the aH5N1c vaccine.

2. CLINICAL AND REGULATORY BACKGROUND

The BLA was submitted for a pandemic influenza vaccine intended to prevent illness caused by an A/H5N1 influenza strain. The Fast Track designation was granted in December 2015. The BLA is supported by clinical immunogenicity and safety data based on the May 2007 FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Data Integrity

During review of V89_11, it was found that serology results were missing for some samples that were indeed collected. During inspection by the Bioresearch Monitoring Program (BIMO), the applicant indicated that the serology results were missing in part due to a lack of sufficient serum to conduct analysis or inability to obtain a confirmatory result. Additional statistical analyses evaluating robustness of results to the missing serology data did not suggest a substantial impact on study conclusions.

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

Please refer to reviews of other review disciplines.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED

5.1 Review Strategy

All Phase I to Phase III clinical studies supporting aH5N1c are reviewed in this memo.

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

The following documents submitted to the BLA are reviewed:

125692/0.0 (submitted on 12/18/2018)

Module 2. Common Technical Document Summaries
Module 5. Clinical Study Reports

- V89P1 Clinical Study Protocol
- V89P1 Clinical Study Analysis Plan
- V89P1 Final Clinical Study Report
- V89_04 Clinical Study Protocol
- V89_04 Clinical Study Analysis Plan
- V89_04 Final Clinical Study Report
- V89_11 Clinical Study Protocol
- V89_11 Clinical Study Analysis Plan
- V89_11 Final Clinical Study Report
- V89_13 Clinical Study Protocol
- V89_13 Clinical Study Analysis Plan
- V89_13 Final Clinical Study Report
- V89_18 Clinical Study Protocol
- V89_18 Clinical Study Analysis Plan
- V89_18 Final Clinical Study Report

125692/0.1 (submitted on 12/27/2018)
Module 5. Clinical Study Reports

125692/0.18 (submitted on 7/8/2019)
Module 1. Regional

- 1.11.3 – Clinical Information Amendment

125692/0.21 (submitted on 8/2/2019)
Module 1. Regional

- 1.11.3 – Clinical Information Amendment

125692/0.37 (submitted on 11/20/2019)
Module 1. Regional

- 1.11.3 – Clinical Information Amendment

5.3 Table of Studies/Clinical Trials

Five clinical studies were conducted to support licensure of aH5N1c:

Table 1. Clinical Studies Supporting Licensure of aH5N1c

Study	N	Age	Description
V89P1	753	18 to 40 years	A Phase 1/2, randomized, double-blind, 12-arm study to select one of 12 antigen-adjuvant combinations
V89_04	979	18 to 64 years	A Phase 2, randomized, double-blind, two-arm study to select one of two (low vs. high) doses
V89_11	662	6 months to 17 years	A Phase 2, randomized, double-blind, two-arm study to select one of two (low vs. high) doses
V89_13	1393	≥65 years	A Phase 2, randomized, double-blind, two-arm study to select one of two (low vs. high) doses
V89_18	3196	≥18 years	A Phase 3, randomized, double-blind, placebo-controlled study to evaluate lot consistency and immunogenicity of vaccine dose (high dose) selected from the Phase 2 studies

Source: Adapted from V89P1, V89_04, V89_11, V89_13, and V89_18 Clinical Study Reports.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Clinical Study V89P1

V89P1 was a Phase 1/2, randomized, double-blind study to evaluate the safety and immunogenicity of 12 combinations of dose levels stemming from three levels of HA antigen (3.75 µg, 7.5 µg, or 15 µg) and four levels of MF59 adjuvant (0 mL, 0.0625 mL, 0.125 mL, or 0.25 mL corresponding to 0%, 25%, 50%, or 100%).

A total of 753 subjects were randomized equally to receive one of the 12 vaccine formulations given two doses three weeks apart at Day 1 and Day 22. The primary immunogenicity endpoints were Day 43 HI antibody titers, achievement of HI antibody titer ≥1:40, and seroconversion, defined as having HI ≥1:40 for subjects negative at baseline (HI <1:10) or a minimum of four-fold increase in HI titer for subjects positive at baseline (HI ≥1:10). Results showed that the adjuvanted formulations of the vaccine elicited significantly higher titers, seroconversion rates, and percentages of subjects achieving antibody titers ≥1:40 compared to the unadjuvanted formulation at the same antigen level. No SAEs or deaths were reported that were considered related to the study vaccine.

Reviewer Comment

- *Committee for Medicinal Products for Human Use (CHMP) immunogenicity criteria, required by other regulatory agencies, were also evaluated in V89P1 and subsequent studies. However, only information relevant to U.S. licensure were considered in this review.*

6.2 Clinical Study V89_04

Title of Study: A Phase II, Randomized, Observer-Blind, Multicenter, Study to Evaluate Safety, Tolerability and Immunogenicity of an Adjuvanted Cell Culture- Derived H5N1 Subunit Influenza Virus Vaccine at Two Different Formulations in Healthy Adult Subjects

Study Period: January 31, 2013 to May 20, 2014

6.2.1 Objectives

Primary Immunogenicity Objectives:

1. To select the vaccine (low dose or high dose aH5N1c) to be tested in Phase 3 based on CBER criteria three weeks after the second vaccine administration as measured by strain-specific HI assays.

Secondary Immunogenicity Objectives:

1. For each aH5N1c vaccine (low dose or high dose), to evaluate achievement of CBER criteria three weeks after the first vaccine administration as measured by strain-specific HI assay.
2. To evaluate the immunogenicity of each aH5N1c vaccine (low dose or high dose) 12 months after the primary two-dose course.

Safety Objective:

1. To evaluate the safety and tolerability of low dose and high dose aH5N1c vaccine.

6.2.2 Design Overview

Subjects were randomized in a 1:1 ratio, stratified by site, to receive two injections of either a low or a high dose vaccine three weeks apart at Day 1 and Day 22. Serum samples were taken on Days 1, 22, 43, and 387 for the evaluation of immunogenicity. Solicited AEs were collected daily for seven days after each injection, unsolicited AEs were collected from Day 1 to Day 43, while SAEs, medically attended AEs, AEs of special interest (AESI), new onset of chronic disease (NOCD), and AEs leading to withdrawal were collected up to Day 387.

6.2.3 Population

Healthy adult subjects aged 18 to 64 years were enrolled.

6.2.4 Study Treatments or Agents Mandated by the Protocol

The vaccine formulations evaluated in this study consisted of a low (3.75 µg antigen + 0.125 mL MF59) and a high (7.5 µg antigen + 0.25 mL MF59) dose vaccine.

6.2.6 Sites and Centers

The study was conducted in 4 centers in the US, 3 centers in Australia, and 1 center in Thailand.

6.2.7 Surveillance/Monitoring

Please refer to the clinical review.

6.2.8 Endpoints and Criteria for Study Success

Primary Immunogenicity:

1. Achievement of seroconversion on Day 43 as defined in V89P1, with the following success criterion recommended in the FDA guidance:

    - The lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion met or exceeded 40%.

2. Achievement of Day 43 HI titer ≥1:40, with the following success criterion recommended in the FDA guidance:

    - The lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI titer ≥1:40 on Day 43 met or exceeded 70%.

Secondary Immunogenicity:

1. HI titer on Day 1, Day 22, and Day 387.
2. HI titer ratio for Day 22/Day 1, Day 43/Day 1, and Day 387/Day 1.
3. Achievement of seroconversion for HI on Day 22 and Day 387.
4. Achievement of HI titer ≥1:40 on Day 1, Day 22, and Day 387.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

Antibody titers were $\log_{10}$-transformed and modeled using Analysis of Covariance (ANCOVA) with main effects for vaccination group, center, and baseline titer. Geometric means and associated two-sided 95% CI were back-calculated based on least squares (LS) estimates from the models. For Day 43 seroconversion and HI ≥1:40, point estimates of proportions were obtained along with two-sided 97.5% CI estimated via the Clopper-Pearson method. The sponsor performed complete case analysis, which assumes missing data are missing completely at random. Values below the lower limit of quantification (LLOQ) were set to half that limit.

The main analysis set for immunogenicity was based on the Full Analysis Set (FAS) grouped as randomized, which included subjects who:

- Received at least one study vaccination and provided immunogenicity data at Day 1 and Day 43 (Day 43 FAS).
- Received at least one study vaccination and provided immunogenicity data at Day 1 and Day 22 (Day 22 FAS).
- Received at least one study vaccination and provided immunogenicity data at Day 1 and Day 387 (Day 387 FAS).

Analysis of Safety

All safety data were summarized descriptively. Safety endpoints were analyzed as treated based on subjects who received a study vaccination and provided post-baseline solicited (for Solicited Safety Set) or unsolicited (for Unsolicited Safety Set) AE data.

Multiplicity Adjustment

The family-wise Type I error rate for testing the primary endpoints was fixed at a one-sided $\alpha = 0.025$. No hypotheses were tested for the secondary endpoints. For each dose group, both hypotheses involving Day 43 seroconversion and percentage of subjects with HI ≥1:40 must be rejected simultaneously to claim success for that dose group. Multiplicity was adjusted for the two dose groups under the following testing procedure:

1. The two hypotheses in the low dose group were tested first, each under a one-sided 1.25% significance level.
2. If both hypotheses were rejected in the low dose group, each hypothesis in the high dose group would be tested at a one-sided 2.5% significance level. Otherwise, the hypotheses would be tested at a one-sided 1.25% significance level.

Sample Size Determination

In the V89P1 study, the 3.75 µg antigen + 0.125 mL MF59 formulation resulted in 77% subjects with HI ≥1:40 and 77% subjects achieving seroconversion on Day 43. Thus, a sample size of 437 subjects was chosen to yield 85% power to demonstrate superiority to a threshold of 70% of subjects with HI ≥1:40. This sample size also yields >99% power to demonstrate superiority to 40% for seroconversion under a one-sided $\alpha = 0.0125$. Assuming a dropout rate of 10%, 486 subjects per group were planned.

Reviewer Comment

- *The protocol did not specify the method used to test the hypotheses. I verified the sample size calculation using a Fisher's Exact test and the results appear to be consistent with the stated sample size.*

6.2.10 Study Population and Disposition

A total of 979 subjects were enrolled. Table 2 displays the demographics of the enrolled subjects. Overall, no major imbalances in age, gender, or ethnic origin were observed between the vaccine groups.

Table 2. Demographics – Enrolled set

-	Low Dose	High Dose	Total
Total, n	491	488	979
Age in years, mean (sd)	38.4 (14.2)	39.0 (13.7)	38.7 (14.0)
Gender	-	-	-
Male, n (%)	243 (47)	203 (42)	435 (44)
Female, n (%)	259 (53)	285 (58)	544 (56)
Ethnic Origin	-	-	-
Asian, n (%)	96 (20)	93 (19)	189 (19)
Black or African American, n (%)	99 (20)	97 (20)	196 (20)
American Indian or Alaskan Native, n (%)	1 (<1)	2 (<1)	3 (<1)
Native Hawaiian or Other Pacific Islander, n (%)	1 (<1)	0 (0)	1 (<1)
White, n (%)	290 (59)	291 (60)	581 (59)
Other, n (%)	4 (<1)	5 (1)	9 (<1)
Ethnicity	-	-	-
Hispanic/Latino, n (%)	99 (20)	107 (22)	206 (21)
Not Hispanic/Latino, n (%)	392 (80)	381 (88)	773 (79)

Source: Table 11.2-1 of V89_04 Clinical Study Report.

6.2.11 Immunogenicity Analyses

6.2.11.1 Analyses of Primary Endpoints

Immunogenicity results at each time point are shown in Table 3. The percentage of subjects meeting criteria for inclusion in the Day 43 FAS were 90% and 92% in the low and high dose groups, respectively. Both vaccine groups met the CBER criterion for seroconversion on Day 43, as the lower bounds of the two-sided 97.5% CI were all above 40%.

Percentages of subjects achieving HI ≥1:40 on Day 43 were similar to rates of seroconversion. On Day 43, the high dose group achieved the CBER criterion for percentage of subjects with HI ≥1:40 (85%, 97.5% CI: 81% - 88%), whereas the low dose group did not.

Table 3. Immunogenicity – FAS

-	Low Dose	High Dose
Enrolled, n	491	488
FAS - Day 1, n (%)	483 (98%)	478 (98%)
FAS - Day 22, n (%)	461 (94%)	464 (95%)
FAS - Day 43, n (%)	440 (90%)	451 (92%)
FAS - Day 387, n (%)	395 (80%)	411 (84%)
Seroconversion	-	-
Day 22, n (%, 97.5% CI)	124 (27, 22-32)	225 (48, 43-54)
Day 43, n (%, 97.5% CI)	269 (61, 56-66)	373 (83, 78-87)
Day 387, n (%, 97.5% CI)	35 (9, 6-13)	90 (22, 17-27)
HI ≥ 1:40	-	-
Day 1, n (%, 97.5% CI)	18 (4, 2-6)	20 (4, 2-7)
Day 22, n (%, 97.5% CI)	140 (30, 26-35)	239 (52, 46-57)
Day 43, n (%, 97.5% CI)	278 (63, 58-68)	382 (85, 81-88)
Day 387, n (%, 97.5% CI)	45 (11, 8-15)	109 (27, 22-32)
GMT	-	-
Day 1 (95% CI)	5.95 (5.63-6.29)	6.11 (5.78-6.46)
Day 22 (95% CI)	15 (13-17)	33 (28-39)
Day 43 (95% CI)	64 (53-77)	250 (208-302)
Day 387 (95% CI)	7.63 (6.79-8.57)	12 (11-14)
GMR	-	-
Day 22 / Day 1 (95% CI)	2.43 (2.07-2.84)	5.37 (4.6-6.27)
Day 43 / Day 1 (95% CI)	11 (8.68-13)	41 (34-49)
Day 387 / Day 1 (95% CI)	1.24 (1.1-1.4)	1.95 (1.73-2.19)

Source: Adapted from Tables 11.4.1-1 to 11.4.1-3 of V89_04 Clinical Study Report.

6.2.11.2 Analyses of Secondary Endpoints

The CBER criterion for seroconversion was met by the high dose three weeks after the first vaccination on Day 22, as 48% (97.5% CI: 43% - 54%) subjects seroconverted. Neither dose had greater than 40% seroconversion on Day 387. Neither group achieved the CBER criterion for the percentage of subjects with HI ≥1:40 on Day 22 or Day 387, as the point estimates were all less than 70%.

Adjusted immune responses were generally higher in the high dose group three weeks after the first and second vaccination as shown in Table 3. On Day 43, a GMR from baseline of 41 (95% CI: 34 – 49) was observed in the high dose group, while a GMR of 11 (95% CI: 9 – 13) was observed in the low dose group. On Day 387, HI titers appeared to decrease to near baseline levels in both vaccine groups.

Reviewer Comment

- *No Analysis Data Model (ADaM) datasets were submitted. I repeated all analyses using the Study Data Tabulation Model (SDTM) datasets and the results were identical to those shown in Table 3.*
- *The CIs in Table 11.4.1-3 of the CSR, which displays GMTs by group and time point, were labelled as 97.5% CIs. The actual confidence level after verifying the results appear to be 95%.*

- *I re-estimated the GMTs and corresponding 95% CI by back-calculating the mean and corresponding 95% CI of the log-transformed titers assuming asymptotic normality. No substantial differences were found between the adjusted and unadjusted analysis.*

6.2.12 Safety Analyses

Percentages of subjects experiencing solicited local and systemic reactions after each and any vaccination are displayed in Table 4. The percentages of subjects reporting solicited local reactions after any vaccination were notably higher in the high dose group, while the percentages reporting systemic reactions were more similar between the two groups. Reporting of solicited reactions also tended to be lower after the second vaccination than the first.

Table 4. Solicited Reactions by Vaccination Group and Vaccination – Solicited Safety Set

	Low Dose	High Dose
Any Vaccination	-	-
N	471	473
Any, n (%)	295 (63)	359 (76)
Local, n (%)	236 (50)	322 (68)
Systemic, n (%)	209 (44)	223 (47)
First Vaccination	-	-
N	469	468
Any, n (%)	261 (56)	338 (72)
Local, n (%)	201 (43)	294 (63)
Systemic, n (%)	178 (38)	200 (43)
Second Vaccination	-	-
N	443	450
Any, n (%)	192 (43)	240 (53)
Local, n (%)	150 (34)	214 (48)
Systemic, n (%)	100 (23)	121 (27)

Source: Table 12.2.1-1 of V89_04 Clinical Study Report.

A total of four deaths, all in the high dose group, were reported during the study (Table 5). None of the deaths were determined to be related to the study vaccine. One subject in the high dose group experienced a spontaneous abortion (an SAE), which was assessed as possibly related to the vaccine. Percentages of subjects reporting medically attended AEs, AEs leading to withdrawal, AESIs, and AEs leading to NOCD were similar between the groups.

Table 5. Unsolicited Adverse Events from Day 1 to Day 387 – Unsolicited Safety Set

-	Low Dose	High Dose
Day 1 – Day 43	-	-
N	475	476
SAEs, n (%)	0 (0)	3 (1)
At least possibly related SAEs, n (%)	0 (0)	0 (0)
Deaths, n (%)	0 (0)	0 (0)
Medically attended AEs, n (%)	39 (8)	39 (8)
AEs resulting in withdrawal, n (%)	0 (0)	0 (0)
AESI, n (%)	0 (0)	0 (0)
AEs leading to NOCD, n (%)	1 (<1)	2 (<1)
Day 44 – Day 387	-	-
N	433	452
SAEs, n (%)	8 (2)	17 (4)
At least possibly related SAEs, n (%)	0 (0)	1 (<1)
Deaths, n (%)	0 (0)	4 (1)
Medically attended AEs, n (%)	131 (30)	145 (32)
AEs resulting in withdrawal, n (%)	0 (0)	4 (1)
AESI, n (%)	0 (0)	1 (<1)
AEs leading to NOCD, n (%)	13 (3)	10 (2)

Source: Adapted from Tables 12.2.1-3a and 12.2.1-3b of V89_04 Clinical Study Report.

6.3 Clinical Study V89_11

Title of Study: A Phase II, Randomized, Observer-Blind, Multicenter, Study to Evaluate Safety, Tolerability and Immunogenicity of an Adjuvanted Cell Culture-Derived H5N1 Subunit Influenza Virus Vaccine at Two Different Formulations in Healthy Pediatric Subjects

Study Period: January 31, 2013 to June 16, 2014

6.3.1 Objectives

The primary and secondary objectives for immunogenicity and safety were the same as those for V89_04.

6.3.2 Design Overview

The overall study design was similar to that for V89_04 with the exception of the target population and that randomization was stratified by age cohort (6 to 35 months, 3 to 8 years, and 9 to 17 years).

6.3.3 Population

Healthy pediatric subjects six months through 17 years of age were enrolled.

6.3.4 Study Treatments or Agents Mandated by the Protocol

The vaccine formulations evaluated in this study consisted of a low (3.75 µg antigen + 0.125 mL MF59) and a high (7.5 µg antigen + 0.25 mL MF59) dose vaccine.

6.3.6 Sites and Centers

The study was conducted in 10 centers in the US and 2 centers in Thailand.

6.3.7 Surveillance/Monitoring

Please refer to the clinical review.

6.3.8 Endpoints and Criteria for Study Success

The primary and secondary immunogenicity endpoints and criteria for study success were the same as those for V89_04.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

The analysis of immunogenicity was the same as that for V89_04.

Analysis of Safety

The analysis of safety was the same as that for V89_04.

Multiplicity Adjustment

The multiplicity adjustment strategy was the same as that for V89_04.

Sample Size Determination

A previous FLUAD-like H5N1 study (V87P6) suggested that approximately 89% of adolescents achieved seroconversion and HI ≥1:40 after vaccination with the high dose vaccine. Assuming an effect size of 84% for both seroconversion and percentage of subjects with HI ≥1:40, a sample size of 100 subjects yielded 84% power to demonstrate superiority to 70% for percentage of subjects with HI ≥1:40 and >99% power to demonstrate superiority to 40% for seroconversion under a one-sided $\alpha = 0.0125$ and a one-sample chi-square test. Assuming a dropout rate of 10%, 111 subjects per group and age cohort (666 subjects in total) were planned.

Reviewer Comment

- *No justification for the assumption of 84% was provided. Given that a similar high dose elicited 89% response in a previous study, the assumption of 84% may have been chosen for the low dose.*
- *Success criteria for the primary objectives were based on the overall sample, whereas the study was powered to meet the objectives within each of three age groups. Thus, the power of evaluation of the primary objective using the overall sample was likely greater than the calculated power provided by the applicant.*

6.3.10 Study Population and Disposition

A total of 662 subjects were enrolled. Table 6 presents demographics data for the enrolled subjects. Overall, the low and high dose groups appear to be comparable with respect to the distributions of age, gender, and ethnic origin.

Table 6. Demographics – Enrolled Set

-	Low Dose	High Dose	Total
Total, n	330	332	662
Age in months, mean (sd)	78.1 (55.6)	78.7 (55.9)	78.4 (55.7)
Gender	-	-	-
Male, n (%)	166 (50)	180 (54)	346 (52)
Female, n (%)	164 (50)	152 (46)	316 (48)
Ethnic Origin	-	-	-
Asian, n (%)	240 (73)	240 (72)	480 (73)
Black or African American, n (%)	18 (5)	13 (4)	31 (5)
American Indian or Alaskan Native, n (%)	0 (0)	2 (<1)	2 (<1)
White, n (%)	66 (20)	72 (22)	138 (21)
Other, n (%)	6 (2)	5 (2)	11 (2)
Ethnicity	-	-	-
Hispanic/Latino, n (%)	15 (5)	13 (4)	28 (4)
Not Hispanic/Latino, n (%)	314 (95)	319 (96)	633 (96)

Source: Table 11.2-1 of V89_11 Clinical Study Report.

6.3.11 Immunogenicity Analyses

6.3.11.1 Analyses of Primary Endpoints

Immunogenicity data are shown in Table 7. The percentages of subjects included in the Day 43 FAS were similar between the low (87%) and the high (87%) dose groups. Both vaccine groups met the CBER criterion for seroconversion on Day 43, with the lower bound of the two-sided 97.5% CI for seroconversion being 81% and 93% for the low and high dose groups, respectively.

Percentages of subjects achieving HI ≥1:40 on Day 43 were similar to those for seroconversion, as almost all subjects had baseline HI <1:40. Both dose groups met the CBER criterion for percentage with HI ≥1:40 on Day 43.

Table 7. Immunogenicity – FAS

-	Low Dose	High Dose
Enrolled, n	330 (100%)	332 (100%)
FAS - Day 1, n (%)	300 (91%)	304 (92%)
FAS - Day 22, n (%)	287 (87%)	283 (85%)
FAS - Day 43, n (%)	288 (87%)	289 (87%)
FAS - Day 387, n (%)	271 (82%)	271 (82%)
Seroconversion	-	-
Day 22, % (97.5% CI)	38 (31-44)	52 (45-58)
Day 43, % (97.5% CI)	86 (81-90)	96 (93-98)
Day 387, % (97.5% CI)	31 (25-38)	47 (40-54)
HI ≥1:40	-	-
Day 1, % (97.5% CI)	0 (0-2)	1 (0-3)
Day 22, % (97.5% CI)	38 (32-45)	51 (44-58)
Day 43, % (97.5% CI)	86 (81-90)	96 (92-98)
Day 387, % (97.5% CI)	31 (25-38)	47 (40-54)
GMT	-	-
Day 1 (97.5% CI)	5.15 (4.91-5.39)	5.23 (5-5.48)
Day 22 (97.5% CI)	34 (24-48)	64 (46-90)
Day 43 (97.5% CI)	431 (312-595)	1356 (985-1866)
Day 387 (97.5% CI)	29 (21-40)	62 (45-86)
GMR	-	-
Day 22 / Day 1 (97.5% CI)	6.63 (4.71-9.34)	13 (9-18)
Day 43 / Day 1 (97.5% CI)	84 (61-116)	262 (190-361)
Day 387 / Day 1 (97.5% CI)	5.62 (4.05-7.81)	12 (8.76-17)

Source: Adapted from Tables 11.4.1-1 to 11.4.1-3 of V89_11 Clinical Study Report.

6.3.11.2 Analyses of Secondary Endpoints

The high dose group met the CBER criterion for seroconversion on Day 22 and 387, whereas the low dose group did not. Neither group met the CBER criterion for the percentage of subjects with HI ≥1:40 on Day 22 or Day 387. Adjusted immune responses were generally higher in the high dose group after vaccination as shown in Table 7, while GMTs at Day 387 were similar to those at Day 22.

Reviewer Comment

- *No ADaM was submitted. I repeated all analyses using the SDTM and the results were consistent to those shown in Table 7. A minor discrepancy was found in the sample sizes included in the FAS and sample sizes actually used in some of the immunogenicity analysis. This was clarified with the applicant in the July 19, 2019 Information Request (IR). In the IR response, the applicant stated that the FAS included all subjects who had either the homologous or heterologous strain tested at baseline and the relevant time points. Thus, it was possible that a subject only had heterologous immunogenicity data at one of the time points, which would allow the subject to be included in the FAS but not the primary analysis.*
- *Laboratory data indicated that several serology results were missing for serum samples that were in fact collected. Specifically, there were 64 (10%) samples that were collected but not tested by the HI assay on Day 1 and 15 (2%) samples*

collected but not tested by the HI assay on Day 43. The applicant clarified that the serology results were missing in part due to a lack of sufficient serum to conduct analysis or an inability to obtain a confirmatory result. I performed a sensitivity analysis with conservative imputation of missing data, i.e. seroconversion was imputed as a "no" for subjects with missing serology result at Day 1 or Day 43, and HI ≥1:40 was imputed as a "no" for subjects with missing serology result on Day 43. This analysis was conducted to rule out the possibility of meaningful bias due to missing data, not because it is a scientifically plausible assumption that all missing values were "no."

- *For low dose, the percentage of subjects with HI ≥1:40 decreased from 86% (97.5% CI: 81% to 90%) to 83% (97.5% CI: 78% to 88%), while seroconversion decreased from 86% (97.5% CI: 81% to 90%) to 78% (97.5% CI: 72% to 83%).*
- *For high dose, the percentage of subjects with HI ≥1:40 decreased from 96% (97.5% CI: 92% to 98%) to 94% (97.5% CI: 90% to 96%), while seroconversion decreased from 96% (97.5% CI: 93% to 98%) to 85% (97.5% CI: 80% to 89%).*

Overall, imputing the worst case scenario for the missing serology results did not impact study success.

- *I obtained unadjusted estimates of GMTs by back-calculating the mean log-scale titers and corresponding CI obtained assuming asymptotic normality. The unadjusted results tended to be lower than the LS estimates adjusted for baseline titers and site. For example, the Day 43 GMTs and 97.5% CI were 359 (97.5% CI: 278 – 463) and 1143 (97.5% CI: 952 – 1372) for the low and high dose, respectively. Nevertheless, the vaccine appeared to elicit high Day 43 titers relative to baseline.*

6.3.12 Safety Analyses

The percentages of subjects reporting solicited local and systemic reactions after any vaccination, shown in Table 8, were similar between the two dose groups in both age groups (<6 years and 6 – 17 years). Reporting of solicited reactions tended to be lower after the second vaccination than the first.

Table 8. Solicited Reactions by Vaccination Group and Vaccination – Solicited Safety Set

-	<6 Years	<6 Years	6 – 17 Years	6 – 17 Years
-	Low Dose	High Dose	Low Dose	High Dose
Any Vaccination	-	-	-	-
N	162	160	161	163
Any, n (%)	116 (72)	112 (70)	122 (76)	122 (75)
Local, n (%)	92 (57)	89 (56)	115 (71)	111 (68)
Systemic, n (%)	65 (40)	68 (43)	82 (51)	79 (48)
First Vaccination	-	-	-	-
N	161	159	161	163
Any, n (%)	101 (63)	97 (61)	115 (71)	120 (74)
Local, n (%)	80 (50)	74 (47)	109 (68)	109 (67)
Systemic, n (%)	57 (35)	53 (33)	75 (47)	70 (43)
Second Vaccination	-	-	-	-
N	157	158	159	159
Any, n (%)	75 (48)	83 (53)	78 (49)	67 (42)
Local, n (%)	61 (39)	68 (43)	65 (41)	61 (38)
Systemic, n (%)	31 (20)	43 (27)	42 (26)	28 (18)

Source: Adapted from Tables 12.2.1-1 and 12.2.1-2 of V89_11 Clinical Study Report.

No deaths were reported during the study (Table 9). A total of 11 SAEs in the low dose and 8 SAEs in the high dose were reported, but none were considered related to the vaccine by investigators. One subject in high dose reported an AE leading to withdrawal while three subjects in low dose reported AEs leading to NOCD. No AESI in either dose group was observed during the study.

Table 9. Unsolicited Adverse Events from Day 1 to Day 387 – Unsolicited Safety Set

-	Low Dose	High Dose
N	324	326
SAEs, n (%)	11 (3)	8 (2)
At least possibly related SAEs, n (%)	0 (0)	0 (0)
Deaths, n (%)	0 (0)	0 (0)
Medically attended AEs, n (%)	113 (35)	110 (34)
AEs resulting in withdrawal, n (%)	0 (0)	1 (<1)
AESI, n (%)	0 (0)	0 (0)
AEs leading to NOCD, n (%)	3 (1)	0 (0)

Source: Table 12.2.1-4 of V89_11 Clinical Study Report.

6.4 Clinical Study V89_13

Title of Study: A Phase II, Randomized, Observer-Blind, Multicenter, Study to Evaluate Safety, Tolerability and Immunogenicity of an Adjuvanted Cell Culture-Derived H5N1 Subunit Influenza Virus Vaccine at Two Different Formulations in Healthy Elderly Subjects

Study Period: January 14, 2013 to June 30, 2014

6.4.1 Objectives

The primary and secondary objectives for immunogenicity and safety were the same as those for V89_04 and V89_11.

6.4.2 Design Overview

The overall study design was the same as that for V89_04 and V89_11 with the exception of the target population.

6.4.3 Population

Healthy subjects 65 years and older were enrolled.

6.4.4 Study Treatments or Agents Mandated by the Protocol

The vaccine formulations evaluated in this study consisted of a low (3.75 µg antigen + 0.125 mL MF59) and a high (7.5 µg antigen + 0.25 mL MF59) dose vaccine.

6.4.6 Sites and Centers

The study was conducted in 12 centers in the US, 5 centers in Australia, 4 centers in Thailand, and 2 centers in New Zealand.

6.4.7 Surveillance/Monitoring

Please refer to the clinical review.

6.4.8 Endpoints and Criteria for Study Success

Primary Immunogenicity:

1. Achievement of seroconversion on Day 43 as defined in previous studies, with the following success criterion recommended in the FDA guidance:

    - The lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion met or exceeded 30%.

2. Achievement of Day 43 HI titer ≥1:40, with the following success criterion recommended in the FDA guidance:

    - The lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI titer ≥1:40 on Day 43 met or exceeded 60%.

Secondary Immunogenicity:

1. HI titer on Day 1, Day 22, and Day 387.
2. HI titer ratio for Day 22/Day 1, Day 43/Day 1, and Day 387/Day 1.
3. Achievement of seroconversion for HI on Day 22 and Day 387.
4. Achievement of HI titer ≥1:40 on Day 1, Day 22, and Day 387.

6.4.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

The analysis of immunogenicity was the same as that for V89_04 and V89_11.

Analysis of Safety

The analysis of safety was the same as that for V89_04 and V89_11.

Multiplicity Adjustment

The multiplicity adjustment strategy was the same as that for V89_04 and V89_11.

Sample Size Determination

Based on previous FLUAD-like H5N1 studies, it was assumed that approximately 66% of subjects would achieve HI ≥1:40 and at least 50% would achieve seroconversion. Using a one-sample chi-square test, a sample of 624 subjects yielded 80% power to demonstrate superiority to 60% for percentage of subjects with HI ≥1:40 and >99% power to demonstrate superiority to 30% for seroconversion under a one-sided α = 0.0125. Assuming a dropout rate of 10%, 694 subjects per group were planned.

6.4.10 Study Population and Disposition

Demographics data are presented in Table 10. Overall, no major differences were observed between the low and high dose groups with respect to the distributions of age, gender, and ethnic origin.

Table 10. Demographics – Enrolled Set

-	Low Dose	High Dose	Total
Total, n	693	700	1393
Age in years, mean (sd)	70.7 (4.7)	71.2 (5.1)	71.0 (4.9)
Gender	-	-	-
Male, n (%)	275 (40)	293 (42)	568 (41)
Female, n (%)	418 (60)	407 (58)	825 (59)
Ethnic Origin	-	-	-
Asian, n (%)	237 (34)	240 (34)	477 (34)
Black or African American, n (%)	10 (1)	10 (1)	20 (1)
American Indian or Alaskan Native, n (%)	0 (0)	2 (<1)	2 (<1)
White, n (%)	444 (64)	445 (64)	889 (64)
Other, n (%)	2 (<1)	3 (<1)	5 (<1)
Ethnicity	-	-	-
Hispanic/Latino, n (%)	15 (2)	17 (2)	32 (2)
Not Hispanic/Latino, n (%)	678 (98)	683 (98)	1361 (98)

Source: Table 11.2-1 of V89_13 Clinical Study Report.

6.4.11 Immunogenicity Analyses

6.4.11.1 Analyses of Primary Endpoints

A total of 1393 subjects were enrolled (Table 11), of which 96% of subjects in both dose groups were included in the Day 43 primary immunogenicity analysis. The percentage of subjects achieving seroconversion on Day 43 in the low and high dose groups were 52% (97.5% CI: 48% - 56%) and 74% (97.5% CI: 70% - 77%), respectively, which met the CBER criterion for seroconversion.

The high dose group met the CBER criterion for the percentage of subjects achieving HI ≥1:40 on Day 43 (81%, 97.5% CI: 77% - 84%), while the low dose group did not meet the criterion, as the lower bound of the 97.5% CI was less than 60%.

Table 11. Immunogenicity – FAS

-	Low Dose	High Dose
Enrolled, n	693 (100%)	700 (100%)
FAS - Day 1, n (%)	683 (99%)	693 (99%)
FAS - Day 22, n (%)	673 (97%)	681 (97%)
FAS - Day 43, n (%)	664 (96%)	673 (96%)
FAS - Day 387, n (%)	651 (94%)	658 (94%)
Seroconversion	-	-
Day 22, n (%, 97.5% CI)	144 (21, 18-25)	245 (36, 32-40)
Day 43, n (%, 97.5% CI)	345 (52, 48-56)	495 (74, 70-77)
Day 387, n (%, 97.5% CI)	64 (10, 7-13)	154 (23, 20-27)
HI ≥ 1:40		
Day 1, n (%, 97.5% CI)	68 (10, 8-13)	86 (12, 10-15)
Day 22, n (%, 97.5% CI)	213 (32, 28-36)	331 (49, 44-53)
Day 43, n (%, 97.5% CI)	415 (63, 58-67)	544 (81, 77-84)
Day 387, n (%, 97.5% CI)	104 (16, 13-19)	231 (35, 31-39)
GMT	-	-
Day 1 (97.5% CI)	7.67 (7-8.4)	8.29 (7.57-9.08)
Day 22 (97.5% CI)	16 (14-18)	26 (23-30)
Day 43 (97.5% CI)	45 (38-53)	129 (110-152)
Day 387 (97.5% CI)	10 (9.29-12)	16 (14-18)
GMR	-	-
Day 22 / Day 1 (97.5% CI)	2.01 (1.75-2.3)	3.21 (2.8-3.68)
Day 43 / Day 1 (97.5% CI)	5.72 (4.83-6.78)	16 (13-19)
Day 387 / Day 1 (97.5% CI)	1.3 (1.16-1.46)	1.97 (1.76-2.2)

Source: Adapted from Tables 11.4.1-1 to 11.4.1-3 of V89_13 Clinical Study Report.

6.4.11.2 Analyses of Secondary Endpoints

The high dose group also met the CBER criterion for seroconversion on Day 22 (36%, 97.5% CI: 32% - 40%), while neither dose achieved greater than 30% seroconversion on Day 387. Neither dose group had greater than 60% of subjects achieving HI ≥1:40 on Day 22 or Day 387.

The high dose on average yielded higher immune responses than the low dose group starting on Day 22 and later. The highest titers were observed on Day 43, where the low and high dose groups achieved GMRs of 5.7 (95% CI: 4.8 – 6.8) and 16 (95% CI: 13 – 19) relative to baseline, respectively.

Reviewer Comment

- *I repeated all analyses using the SDTM datasets and the results were identical to those shown in Table 11.*

6.4.12 Safety Analyses

Table 12 shows percentages of subjects reporting solicited local and systemic reactions after each and any vaccination. The high dose vaccine tended to result in higher solicited reactions, in particular solicited local reactions, than the low dose. Percentages of solicited reactions tended to be lower after the second vaccination compared to the first vaccination in either dose group.

Table 12. Solicited Reactions by Vaccination Group and Vaccination – Solicited Safety Set

-	Low Dose	High Dose
Any Vaccination	-	-
N	683	693
Any, n (%)	341 (50)	430 (62)
Local, n (%)	212 (31)	314 (45)
Systemic, n (%)	228 (33)	250 (36)
First Vaccination	-	-
N	681	692
Any, n (%)	264 (39)	363 (52)
Local, n (%)	147 (22)	266 (38)
Systemic, n (%)	177 (26)	194 (28)
Second Vaccination	-	-
N	665	676
Any, n (%)	188 (28)	264 (39)
Local, n (%)	110 (17)	197 (29)
Systemic, n (%)	114 (17)	129 (19)

Source: Table 12.2.1-1 of V89_13 Clinical Study Report.

There were a total of two deaths during the study with one in each dose group (Table 13). Neither death was considered related to the study vaccine. No SAEs at least possibly related to the vaccine were reported during the study. The percentages of subjects reporting medically attended AEs, AEs leading to withdrawal, and AEs leading to NOCD were also similar between the two groups.

Table 13. Unsolicited Adverse Events from Day 1 to Day 387 – Unsolicited Safety Set

-	Low Dose	High Dose
N	686	694
SAEs, n (%)	53 (8)	43 (6)
At least possibly related SAEs, n (%)	0 (0)	0 (0)
Deaths, n (%)	1 (<1)	1 (<1)
Medically attended AEs, n (%)	373 (54)	383 (55)
AEs resulting in withdrawal, n (%)	1 (<1)	1 (<1)
AESI, n (%)	0 (0)	2 (<1)
NOCD, n (%)	92 (13)	108 (16)

Source: Table 12.2.1-3 of V89_13 Clinical Study Report.

6.5 Clinical Study V89_18

Title of Study: A Phase 3 Randomized, Observer-Blind, Multi-center, Controlled Study to Evaluate Safety, Immunogenicity, and Lot-to-Lot Consistency of an Adjuvanted Cell Culture-Derived, H5N1 Subunit Influenza Virus Vaccine in Healthy Adult Subjects ≥18 years of Age

Study Period: July 11, 2016 to October 4, 2017

6.5.1 Objectives

Primary Immunogenicity Objectives:

1. To demonstrate lot-to-lot consistency across three consecutively produced lots of the aH5N1c vaccine, as assessed by the ratio of GMTs of HI antibody responses to the H5N1 vaccine strain three weeks after the second vaccine administration (Day 43) in healthy adult subjects ≥18 years of age.
2. After lot-to-lot consistency was demonstrated, the populations of all H5N1c vaccine recipients were pooled in order to evaluate immune responses to the aH5N1c vaccine according to CBER criteria in the FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines three weeks after the second vaccine administration (Day 43) as measured by age cohort.

Secondary Immunogenicity Objectives:

1. To evaluate immune responses to aH5N1c vaccine according to immunogenicity criteria defined by CBER three weeks after the first vaccine administration (Day 22) in healthy adult subjects ≥18 years of age by age cohort.
2. To evaluate immune responses to aH5N1c vaccine six months after the first vaccine administration (Day 183) in healthy adult subjects ≥18 years of age by age cohort.

Safety Objective:

1. To evaluate the safety and tolerability of aH5N1c vaccine and placebo in healthy adult subjects ≥18 years of age.

6.5.2 Design Overview

Subjects were randomized in a 1:1:1:1 ratio, stratified by site and age group (18 to <65 years and ≥65 years), to receive two injections of one of three lots of the aH5N1c vaccine or placebo three weeks apart at Day 1 and Day 22. Serum samples were taken on Days 1, 22, 43, and 183 for the evaluation of immunogenicity. Solicited AEs were collected daily for seven days after each injection, unsolicited AEs were collected from Day 1 to Day 43, while SAEs, medically attended AEs, AEs of special interest (AESI), new onset of chronic disease (NOCD), and AEs leading to withdrawal were collected up to Day 387.

6.5.3 Population

Healthy adult subjects 18 years of age and older were enrolled.

6.5.4 Study Treatments or Agents Mandated by the Protocol

The study treatments consisted of a saline placebo and three consecutively produced lots of an aH5N1c vaccine containing 7.5 µg H5 hemagglutinin antigen + 0.25 mL MF59 adjuvant.

6.5.6 Sites and Centers

The study was conducted at 26 centers in the US.

6.5.7 Surveillance/Monitoring

Please refer to the clinical review.

6.5.8 Endpoints and Criteria for Study Success

Primary Immunogenicity:

1. Day 43 HI antibody titers, using the following success criterion to demonstrate lot consistency:

    - The two-sided 95% CI for the GMT ratio of Day 43 HI titers were within 0.67 to 1.5 for all three pairwise comparisons.

2. Achievement of Day 43 HI titer ≥1:40, evaluated separately by age group using the following success criterion recommended in the FDA guidance:

    - Subjects 18 to <65 years of age: the lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI titer ≥1:40 on Day 43 met or exceeded 70%.
    - Subjects ≥65 years of age: the lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI titer ≥1:40 on Day 43 met or exceeded 60%.

Secondary Immunogenicity:

1. HI titer on Day 1, Day 22, Day 43, and Day 387.
2. HI titer ratio for Day 22/Day 1 and Day 43/Day 1.

3. Seroconversion on Day 22 and Day 43 as defined in previous studies, with the following success criterion recommend in the FDA guidance:

    - For subjects 18 to <65 years of age: the lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion met or exceeded 40%.
    - For subjects ≥65 years of age: the lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion met or exceeded 30%.

4. Achievement of HI titer ≥1:40 on Day 1, Day 22, and Day 183, with the following success criterion recommended in the FDA guidance:

    - For subjects 18 to <65 years of age: the lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI titer ≥1:40 met or exceeded 70%.
    - For subjects ≥65 years of age: the lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI titer ≥1:40 met or exceeded 60%.

6.5.9 Statistical Considerations & Statistical Analysis Plan

Analysis of Immunogenicity

To demonstrate lot consistency, antibody titers were $\log_{10}$-transformed and modeled using ANCOVA with main effects for lot, center, baseline titer, and age group (18 to <65, ≥65). Geometric means, between-lot geometric mean ratios, and associated two-sided 95% CI were back-calculated based on least squares estimates from the model.

After demonstration of lot consistency, data from the three lots were pooled. Achievement of Day 43 HI titer ≥1:40 was modeled separately by age group (18 to <65, ≥65) using a logistic regression with main effects for treatment group (aH5N1c vs. placebo) and center. Least squares mean and associated 95% CI for the proportion of subjects achieving HI titer ≥1:40 in each treatment group were obtained from the model. For all other binary endpoints, point estimates of proportions were obtained along with two-sided 95% CI estimated via the Clopper-Pearson method.

The main analysis set for immunogenicity was based on the Per Protocol Set (PPS), which included subjects who correctly received both doses of the randomized vaccine at the scheduled time points, have no major protocol deviations, and provided immunogenicity result at Day 1 and the respective analysis time point. Missing data were treated as missing completely at random and were not imputed. Values below LLOQ were set to half that limit, while values above the upper limit of quantification (ULOQ) were set to the limit.

Analysis of Safety

All safety data were summarized descriptively. Safety endpoints were analyzed as treated based on subjects who received a study vaccination and provided post-baseline solicited (for Solicited Safety Set) or unsolicited (for Unsolicited Safety Set) AE data.

Multiplicity Adjustment

Demonstration of lot consistency required that the two-sided 95% CIs fall within 0.67 to 1.5 for all pairwise comparisons of Day 43 GMTs. In addition, study success required that the criterion for the percentage of subjects achieving Day 43 HI titer ≥1:40 be met for both age groups (18 to <65, ≥65). Thus, no multiplicity adjustments were made.

Sample Size Determination

Sample size determination was based on data from the V89_04 and V89_13 studies. Assuming a between-lot mean difference of 0 and a standard deviation of 0.85 for the log-scale Day 43 HI titers, and a sample of 718 subjects per group, the power to demonstrate equivalence for each pairwise comparison under a 1.5-fold equivalence margin was 95%. Thus, the overall power to demonstrate lot consistency was 86%. Accounting for 10% dropout, a sample size of 798 subjects per lot was planned.

Assuming that 86% of subjects in the 18 to <65 age group and 81% of subjects in the ≥65 age group achieved an HI titer ≥1:40 on Day 43, a pooled sample of 1077 subjects per age group provided 98% power to meet success criteria for percent achieving HI titer ≥1:40.

6.5.10 Study Population and Disposition

6.5.10.1 Populations Enrolled/Analyzed

A total of 3196 subjects were enrolled in the study as shown in Table 14. The percentages of subjects included in the PPS on Day 22, Day 43, and Day 183 were similar between the four vaccine groups. Overall, approximately 87.7% to 90.7% of enrolled subjects in each group were included in the Day 43 primary immunogenicity analyses.

Table 14. Analysis Sets

-	Lot 1	Lot 2	Lot 3	Lots 1–3	Placebo	Total
Enrolled	804 (100%)	799 (100%)	795 (100%)	2398 (100%)	798 (100%)	3196 (100%)
PPS - Day 22	761 (94.7%)	744 (93.1%)	740 (93.1%)	2245 (93.6%)	736 (92.2%)	2981 (93.3%)
PPS - Day 43	729 (90.7%)	710 (88.9%)	717 (90.2%)	2156 (89.9%)	700 (87.7%)	2856 (89.4%)
PPS - Day 183	698 (86.8%)	689 (86.2%)	692 (87.0%)	2079 (86.7%)	687 (86.1%)	2766 (86.5%)

Source: Table 9 of V89_18 Clinical Study Report.

6.5.10.1.1 Demographics

Demographics data for each group are presented in Table 15. Roughly half of all subjects enrolled were 18 to less than 65 years of age, while half were 65 years of age and older.

Overall, all four vaccine groups appeared to be similar in terms of age and distributions of gender, race, and ethnicity.

Table 15. Demographics – Enrolled Set

-	Lot 1	Lot 2	Lot 3	Lots 1–3	Placebo	Total
Total, n	804	799	795	2398	798	3196
Age in years, mean (sd)	58.1 (17.7)	57.5 (17.8)	57.5 (18.2)	57.7 (17.9)	57.7 (18.3)	57.7 (18.0)
Age Group per CBER	-	-	-	-	-	-
18 to <65 years, n (%)	403 (50.1)	399 (49.9)	397 (49.9)	1199 (50.0)	498 (49.9)	1597 (50.0)
≥65 years, n (%)	401 (49.9)	400 (50.1)	398 (50.1)	1199 (50.0)	500 (50.1)	1599 (50.0)
Gender						
Male, n (%)	360 (44.8)	365 (45.7)	348 (43.8)	1073 (44.7)	360 (45.1)	1433 (44.8)
Female, n (%)	444 (55.2)	434 (54.3)	447 (56.2)	1325 (55.3)	438 (54.9)	1763 (55.2)
Race	-	-	-	-	-	-
American Indian/Alaskan Native, n (%)	6 (0.7)	4 (0.5)	5 (0.6)	15 (0.6)	3 (0.4)	18 (0.6)
Asian, n (%)	12 (1.5)	7 (0.9)	9 (1.1)	28 (1.2)	7 (0.9)	35 (1.1)
Black/African American, n (%)	110 (13.7)	102 (12.8)	104 (13.1)	316 (13.2)	112 (14.0)	428 (13.4)
Native Hawaiian/Pacific Islander, n (%)	3 (0.4)	2 (0.3)	1 (0.1)	6 (0.3)	4 (0.5)	10 (0.3)
White, n (%)	668 (83.1)	679 (85.0)	674 (84.8)	2021 (84.3)	665 (83.3)	2686 (84.0)
Other, n (%)	5 (0.6)	5 (0.6)	2 (0.3)	12 (0.5)	7 (0.9)	19 (0.6)
Ethnicity	-	-	-	-	-	-
Hispanic/Latino, n (%)	53 (6.6)	61 (7.6)	64 (8.1)	178 (7.4)	55 (6.9)	233 (7.3)
Not Hispanic/Latino, n (%)	746 (92.8)	729 (91.2)	721 (90.7)	2196 (91.6)	732 (91.7)	2928 (91.6)
Not reported/Unknown, n (%)	5 (0.6)	9 (1.1)	10 (1.3)	24 (1.0)	11 (1.4)	35 (1.1)

Source: Table 11 of V89_18 Clinical Study Report.

6.5.11 Immunogenicity Analyses

6.5.11.1 Analyses of Primary Endpoints

Lot Consistency (Adjusted)

Baseline and Day 43 antibody titers for each vaccine group are displayed in Table 16. On Day 43, the adjusted GMTs ranged from 127.4 (95% CI: 117.6 – 138.0) in Lot 2 to 132.2 (95% CI: 122.1 – 143.1) in Lot 3. The adjusted GMT ratios and the corresponding 95% CIs were within the prespecified equivalence margins of 0.67 to 1.5 for all pairwise comparisons among the three lots. Thus, the primary objective for lot consistency was demonstrated.

Table 16. Adjusted* Geometric Mean Titer and Ratio for Lot Consistency – Per Protocol Set

-	Lot 1	Lot 2	Lot 3
Day 1	-	-	-
N	761	747	741
GMT	16.1	17.0	17.0
95% CI	(15.1, 17.2)	(15.9, 18.2)	(15.9, 18.2)
Day 43	-	-	-
N	729	710	717
GMT	128.6	127.4	132.2
95% CI	(118.9, 139.1)	(117.6, 138.0)	(122.1, 143.1)
-	-	-	-
Day 43	Lot 1 vs. Lot 2	Lot 2 vs. Lot 3	Lot 1 vs. Lot 3
GMT Ratio	1.01	0.96	0.97
95% CI	(0.90, 1.13)	(0.86, 1.08)	(0.87, 1.09)

*LS Means adjusted for lot (1, 2, 3), age group (18 to <65, 65+), and baseline titer.
Source: Table 14 of V89_18 Clinical Study Report.

Percentage of Subjects with HI ≥1:40 (Adjusted)

The analysis results for the co-primary endpoint of percentage of subjects achieving HI titers ≥1:40 on Day 43 are shown in Table 17 by age group. The adjusted percentage of subjects ages 18 to <65 years achieving HI titer ≥1:40, pooled across the three lots, was 95% with 95% CI 93.4% - 96.2%, which met the CBER criterion of ≥70% for the lower bound. For subjects ≥65 years of age, 85.7% achieved HI titers ≥1:40 on Day 43 with 95% CI 83.3% - 87.9%, which also met the CBER criterion of ≥60% for the lower bound. Thus, the co-primary objective for the percentage of subjects achieving HI titers ≥1:40 on Day 43 was met in both age groups.

Table 17. Adjusted* Percentage with HI ≥ 1:40 by Age Group – Per Protocol Set

-	18 to <65 Years	18 to <65 Years	≥65 Years	≥65 Years
-	Active Treatment	Placebo	Active Treatment	Placebo
Day 1	N = 1116	N = 372	N = 1133	N = 367
n	194	73	320	94
% HI ≥ 1:40	13.0	15.0	27.8	24.5
95% CI	(10.7, 15.6)	(11.5, 19.4)	(24.9, 30.9)	(20.1, 29.6)
-	-	-	-	-
Day 43	N = 1076	N = 349	N = 1080	N = 351
n	1002	38	902	80
% HI ≥ 1:40	95.0	8.5	85.7	20.8
95% CI	(93.4, 96.2)	(5.9, 12.1)	(83.3, 87.9)	(16.6, 25.8)

*LS Means adjusted for site.
Source: Table 15 of V89_18 Clinical Study Report.

Reviewer Comment

- *Primary analyses were verified using the SDTM datasets and the results were identical.*
- *Unadjusted analyses as well as analyses using the FAS did not affect study conclusions.*

- *During review, the upper limit of quantification (ULOQ) was changed from* (b) (4) *the value used in the original analysis, to* (b) (4) *There was one subject in Lot 3 at Day 43 with HI titer greater than* (b) (4) *Day 43 GMT for Lot 3 was re-estimated and no practical difference was found in the results.*

6.5.11.2 Analyses of Secondary Endpoints

GMT (Adjusted)

Adjusted GMTs by time point, treatment, and age group are shown in Table 18. Active treatment elicited higher immune responses than placebo at all post-baseline time points. The highest GMTs were observed on Day 43 under active treatment, with the 18 to <65 year-old age group achieving higher GMTs than the 65+ year-old age group. On Day 183, titers in subjects 65 years and older appeared to have decreased to near-baseline values.

Table 18. Adjusted* Geometric Mean Titer by Age Group and Day – Per Protocol Set

-	18 to <65 Years	18 to <65 Years	≥65 Years	≥65 Years	All	All
-	Active Treatment	Placebo	Active Treatment	Placebo	Active Treatment	Placebo
Day 1	-	-	-	-	-	-
N	1116	372	1133	367	2249	739
GMT	13.5	13.7	20.5	20.6	16.6	16.7
95% CI	(12.8, 14.2)	(12.5, 15.0)	(19.4, 21.8)	(18.6, 22.7)	(16.0, 17.3)	(15.6, 17.9)
Day 22	-	-	-	-	-	-
N	1115	370	1130	366	2245	736
GMT	50.6	11.6	42.4	14.5	46.4	13.0
95% CI	(47.6, 53.8)	(10.4, 12.9)	(40.0, 45.0)	(13.1, 16.0)	(44.5, 48.4)	(12.1, 14.0)
Day 22 / Day 1	-	-	-	-	-	-
N	1115	370	1130	366	2245	736
GMR	3.81	0.87	2.14	0.73	2.86	0.80
95% CI	(3.58, 4.05)	(0.79, 0.97)	(2.02, 2.27)	(0.66, 0.81)	(2.74, 2.98)	(0.74, 0.86)
Day 43	-	-	-	-	-	-
N	1076	349	1080	351	2156	700
GMT	170.7	11.0	97.9	16.7	130.6	13.7
95% CI	(160.5, 181.6)	(9.9, 12.2)	(92.1, 104.1)	(15.0, 18.5)	(124.8, 136.6)	(12.6, 14.8)
Day 43 / Day 1	-	-	-	-	-	-
N	1076	349	1080	351	2156	700
GMR	12.70	0.82	4.90	0.83	7.96	0.83
95% CI	(11.94, 13.51)	(0.73, 0.91)	(4.61, 5.20)	(0.75, 0.92)	(7.61, 8.33)	(0.77, 0.90)
Day 183	-	-	-	-	-	-
N	1025	341	1054	346	2079	687
GMT	20.4	6.8	19.3	8.6	20.0	7.7
95% CI	(19.3, 21.6)	(6.1, 7.4)	(18.2, 20.4)	(7.8, 9.5)	(19.2, 20.8)	(7.2, 8.2)
Day 183 / Day 1	-	-	-	-	-	-
N	1025	341	1054	346	2079	687
GMR	1.53	0.51	0.97	0.43	1.22	0.47
95% CI	(1.44, 1.61)	(0.46, 0.56)	(0.91, 1.02)	(0.39, 0.47)	(1.17, 1.27)	(0.44, 0.50)

*LS Means with dependent variables treatment group (active vs. placebo), site, and baseline titer.
Source: Adapted from Tables 16 and 17 of V89_18 Clinical Study Report.

Percentage of Subjects with HI ≥1:40 (Unadjusted)

Unadjusted percentages of subjects achieving HI titers ≥1:40 at each time point are shown in Table 19. Overall, higher percentages of subjects achieving titers ≥1:40 were observed in the active treatment than placebo at all post-baseline time points, while percentages of subjects 18 to <65 years old achieving titers ≥1:40 were higher than those observed among subjects 65 years and older. Consistent with the primary adjusted analysis, the active treatment met the CBER criterion for the percentage of subjects achieving titers ≥1:40 on Day 43 in both age groups.

Table 19. Unadjusted Percentage with HI ≥ 1:40 by Age Group – Per Protocol Set

-	18 to <65 Years	18 to <65 Years	≥65 Years	≥65 Years	All	All
-	Active Treatment	Placebo	Active Treatment	Placebo	Active Treatment	Placebo
-	-	-	-	-	-	-
Day 1	N = 1116	N = 372	N = 1133	N = 367	N = 2249	N = 739
% HI ≥ 1:40	17.4	19.6	28.2	25.6	22.9	22.6
95% CI	(15.2, 19.7)	(15.7, 24.0)	(25.6, 31.0)	(21.2, 30.4)	(21.1, 24.6)	(19.6, 25.8)
Day 22	N = 1115	N = 370	N = 1130	N = 366	N = 2245	N = 736
% HI ≥ 1:40	63.0	13.5	55.6	16.4	59.3	14.9
95% CI	(60.1, 65.9)	(10.2, 17.4)	(52.6, 58.5)	(12.7, 20.6)	(57.2, 61.3)	(12.4, 17.7)
-	-	-	-	-	-	-
Day 43	N = 1076	N = 349	N = 1080	N = 351	N = 2156	N = 700
% HI ≥ 1:40	93.1	10.9	83.5	22.8	88.3	16.9
95% CI	(91.4, 94.6)	(7.8, 14.6)	(81.2, 85.7)	(18.5, 27.5)	(86.9, 89.6)	(14.2, 19.8)
-	-	-	-	-	-	-
Day 183	N = 1025	N = 341	N = 1054	N = 346	N = 2079	N = 687
% HI ≥ 1:40	34.2	2.1	30.9	8.4	32.6	5.2
95% CI	(31.3, 37.2)	(0.8, 4.2)	(28.1, 33.8)	(5.7, 11.8)	(30.6, 34.6)	(3.7, 7.2)

Source: Adapted from Tables 19 and 20 of V89_18 Clinical Study Report.

Seroconversion (Unadjusted)

Percentages of subjects achieving seroconversion, as shown in Table 20, were higher in the active treatment group and among 18 to <65 year-olds than in placebo and 65+ year-olds, respectively. The highest percentages achieving seroconversion were observed on Day 43, where the active treatment met the CBER criterion for seroconversion in the respective age groups.

Table 20. Unadjusted Percentage Achieving Seroconversion by Age Group – Per Protocol Set

-	18 to <65 Years	18 to <65 Years	≥65 Years	≥65 Years	All	All
-	Active Treatment	Placebo	Active Treatment	Placebo	Active Treatment	Placebo
-	-	-	-	-	-	-
Day 22	N = 1115	N = 370	N = 1130	N = 366	N = 2245	N = 736
% Seroconversion	40.4	1.9	24.2	0.3	32.2	1.1
95% CI	(37.6, 43.4)	(0.8, 3.9)	(21.7, 26.8)	(0.0, 1.5)	(30.3, 34.2)	(0.5, 2.1)
-	-	-	-	-	-	-
Day 43	N = 1076	N = 349	N = 1080	N = 351	N = 2156	N = 700
% Seroconversion	79.9	0.3	54.0	1.7	66.9	1.0
95% CI	(77.4, 82.3)	(0.0, 1.6)	(51.0, 57.0)	(0.6, 3.7)	(64.9, 68.9)	(0.4, 2.0)
-	-	-	-	-	-	-
Day 183	N = 1025	N = 341	N = 1054	N = 346	N = 2079	N = 687
% Seroconversion	16.2	0.3	8.0	1.2	12.0	0.7
95% CI	(14.0, 18.6)	(0.0, 1.6)	(6.4, 9.8)	(0.3, 2.9)	(10.7, 13.5)	(0.2, 1.7)

Source: Adapted from Tables 22 and 23 of V89_18 Clinical Study Report.

6.5.11.3 Subpopulation Analyses

The applicant performed subgroup analysis for the Day 43 percentage of subjects with HI titer ≥1:40. Unadjusted estimates and corresponding 95% CI were obtained according to baseline titer (<1:10 or ≥1:10), use of seasonal influenza vaccine in last 12 months (yes or no), sex (male or female), and age group (18 to 49, 50 to 64, 65 to 74, or ≥75). The lower bounds of the 95% CI were >70% in all subgroups defined by baseline titer, use of seasonal influenza vaccine, sex, and age group. In addition, subgroup analyses did not suggest practical differences within race or ethnicity in the percentage of subjects with Day 43 HI titers ≥1:40.

With respect to unadjusted estimates of the percentage of subjects achieving seroconversion on Day 43, the lower bounds of the corresponding 95% CI were >40% in all subgroups defined by baseline titer, use of seasonal influenza vaccine, sex, and age group.

6.5.12 Safety Analyses

The percentage of subjects reporting solicited reactions was generally higher in the active treatment than placebo, particularly for solicited local reactions as shown in Table 21. Overall, the percentages of subjects reporting solicited reactions were lower after the second vaccination compared to after the first vaccination in both treatment groups.

Table 21. Solicited Reactions by Vaccination Group and Vaccination – Solicited Safety Set

-	Active Treatment	Placebo
Any Vaccination	-	-
N	2352	784
Any, n (%)	1403 (59.7)	298 (38.0)
Local, n (%)	1181 (50.2)	115 (14.7)
Systemic, n (%)	898 (38.2)	257 (32.8)
First Vaccination	-	-
N	2346	782
Any, n (%)	1230 (52.4)	236 (30.2)
Local, n (%)	1013 (43.2)	80 (10.2)
Systemic, n (%)	720 (30.7)	203 (26.0)
Second Vaccination	-	-
N	2303	770
Any, n (%)	94.6 (41.1)	172 (22.3)
Local, n (%)	782 (33.9)	57 (7.4)
Systemic, n (%)	491 (21.3)	143 (18.6)

Source: Table 32 of V89_18 Clinical Study Report.

Table 22 displays percentages of subjects reporting selected unsolicited AEs from baseline to study termination. Overall, no substantial differences were observed between the treatment groups with respect to the reporting of unsolicited AEs, SAEs, AEs leading to withdrawal, medically attended AEs, and AEs leading to NOCD. A total of 12 deaths (11 in active treatment and 1 in placebo) were reported during the study, but none were considered related to study treatment.

Table 22. Unsolicited Adverse Events from Day 1 to Study Termination – Unsolicited Safety Set

-	Active Treatment	Placebo
N	2395	796
Unsolicited AEs, n (%)	1271 (53.1)	416 (52.3)
At least possibly related unsolicited AEs, n (%)	172 (7.2)	52 (6.5)
Unsolicited SAEs, n (%)	161 (6.7)	74 (9.3)
At least possibly related unsolicited SAEs, n (%)	0 (0.0)	2 (0.3)
Unsolicited AEs leading to withdrawal, n (%)	13 (0.5)	3 (0.4)
Medically attended unsolicited AEs, n (%)	1114 (46.5)	366 (46.0)
Unsolicited AEs leading to NOCD, n (%)	228 (9.5)	73 (9.2)
Unsolicited AESIs, n (%)	7 (0.3)	7 (0.9)
Unsolicited AEs leading to death, n (%)	11 (0.5)	1 (0.1)

Source: Table 33 of V89_18 Clinical Study Report.

7. INTEGRATED OVERVIEW OF EFFICACY

No integrated analysis of efficacy was performed.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety data were summarized descriptively according to the study vaccine received. The following safety analysis sets were used:

Solicited Safety Set: consists of all subjects who received at least one dose of the study vaccine and provided post-vaccination solicited safety data.

Unsolicited Safety Set: consists of all subjects who received at least one dose of the study vaccine and provided post-vaccination unsolicited safety data.

8.2 Safety Database

Data from studies V89_04, V89_13, and V89_18 were pooled for the integrated summary of safety.

8.3 Pooling of Data Across Studies/Clinical Trials

Two pooled datasets were generated:

1. Full Dose vs. Placebo: all subjects in the V89_04, V89_13, and V89_18 studies who received the 7.5 µg HA + 0.25 mL MF59 dose vaccine or placebo and provided solicited (for Solicited Safety Set) or unsolicited (for Unsolicited Safety Set) AE data.
2. Full + Half Dose vs. Placebo: all subjects in the V89_04, V89_13, and V89_18 studies who received the 7.5 µg HA + 0.25 mL MF59 or 3.75 µg HA + 0.125 mL MF59 dose vaccine or placebo and provided solicited (for Solicited Safety Set) or unsolicited (for Unsolicited Safety Set) AE data.

As the study designs were similar with the exception of the introduction of a placebo arm in V89_18, there does not appear to be major concerns in the pooling of safety data. As only subjects in V89_18 received a placebo, the placebo population was the same in both pooled sets.

8.4 Safety Results

Table 23 shows pooled solicited AE data seven days within each and any vaccination (excluding the first 30 minutes) for subjects who received the full dose, full or half dose, and placebo across V89_04, V89_13, and V89_18. Overall, occurrence of solicited local and systemic reactions were higher among subjects under the active treatment than placebo. In all vaccine groups, fewer subjects reported solicited local or systemic reactions after the second vaccination than the first.

Table 23. Solicited Reactions from Day 1 (Excluding the first 30 minutes) to Day 7

-	Full Dose	Full + Half Dose	Placebo
Any Vaccination	-	-	-
N	3518	4672	784
Any, n (%)	2177 (61.9)	2795 (59.8)	298 (38.0)
Local, n (%)	1817 (51.6)	2265 (48.5)	115 (14.7)
Systemic, n (%)	1371 (39.0)	1808 (38.7)	257 (32.8)
First Vaccination	-	-	-
N	3506	4656	782
Any, n (%)	1922 (54.8)	2437 (52.3)	236 (30.2)
Local, n (%)	1573 (44.9)	1921 (41.3)	80 (10.2)
Systemic, n (%)	1114 (31.8)	1469 (31.6)	203 (26.0)
Second Vaccination	-	-	-
N	3430	4538	770
Any, n (%)	1438 (41.9)	1807 (39.8)	172 (22.3)
Local, n (%)	1193 (34.8)	1453 (32.0)	57 (7.4)
Systemic, n (%)	741 (21.6)	955 (21.0)	143 (18.6)

Source: Adapted from Tables 15 and 20 of Final Integrated Summary of Safety.

Reviewer Comment

- *In the Full Dose group, the total number of subjects with any local (n = 1817) and with any systemic (n=1371) reaction after any vaccination appear to be consistent with the data from the individual studies. However, the number of subjects in the Full Dose with any local or systemic reaction (n = 2177) after any vaccination in Table 23 do not appear to equal the values summed from the individual studies in Tables 4, 12, and 21 (n = 359 + 430 + 1403 = 2192). This was clarified with the applicant, who responded in Amendment 37 that "use of analgesic/antipyretic medications" was included under "Any Solicited AEs" in V89_04 and V89_13 but was not included in the Integrated Summary of Safety, hence the difference.*

The occurrence of at least one related unsolicited AE from Day 1 to Day 43 was slightly higher in the full dose (8.2%) than in placebo (6.2%), as shown in Table 24. A total of 6.3% of subjects under the full dose and 9.3% of subjects under placebo reported at least one SAE, of which one (<0.1%) subject under the full dose and two (0.3%) subjects under placebo had a possibly related SAE. There were 16 deaths in the full dose and one death in placebo from Day 1 to study termination on Day 387 across the studies, though none were considered related to the study treatment. No practical differences were found in the rates of AESIs, NOCDs, AEs leading to withdrawal, and medically attended AEs between the full dose and placebo.

Table 24. Unsolicited AEs from Day 1 to Study Termination

-	Full Dose	Full + Half Dose	Placebo
N	3579	4758	796
Any unsolicited AE (Day 1 – 43), n (%)	920 (25.7)	1283 (27.0)	180 (22.6)
Any related unsolicited AE (Day 1 – 43), n (%)	294 (8.2)	424 (8.9)	49 (6.2)
Any SAE, n (%)	225 (6.3)	286 (6.0)	74 (9.3)
Any related SAE, n (%)	1 (0.0)	1 (0.0)	2 (0.3)
Any AE with outcome death, n (%)	16 (0.4)	17 (0.4)	1 (0.1)
Any AESI, n (%)	11 (0.3)	11 (0.2)	7 (0.9)
Any NOCD, n (%)	348 (9.7)	456 (9.6)	73 (9.2)
Any AE leading to withdrawal, n (%)	18 (0.5)	19 (0.4)	3 (0.4)
Any medically attended AE, n (%)	1687 (47.1)	2230 (46.9)	366 (46.0)

Source: Adapted from Tables 16 and 21 of Final Integrated Summary of Safety.

Reviewer Comment

- *The total numbers of treatment-emergent related SAEs, deaths, AESIs, NOCDs, and AEs leading to withdrawal in Table 24 appear to be consistent with the data from the individual studies. The number of subjects with any SAE in the Full Dose, however, was 225 in Table 24, whereas the number of subjects with any SAE summed from Table 5, 13, and 22 was n = 20 + 43 + 161 = 224. This was noted by the Clinical Reviewer, who clarified that there was one subject in V89_13 with an onset of an SAE after Day 387 that was not included in the V89_13 study report.*

8.5 Additional Safety Evaluations

Please refer to the clinical review for additional safety evaluations.

8.6 Safety Conclusions

Compared to placebo, the aH5N1c vaccine appeared to elicit higher rates of solicited local and systemic reactions after vaccination. No deaths occurred that were considered related to the vaccine, and no practical differences in the rates of related SAEs, AESIs, NOCDs, AEs leading to withdrawal, and medically attended AEs were observed between the aH5N1c vaccine and placebo. Acceptability of the safety profile of the vaccine is deferred to the Clinical Reviewer.

9. ADDITIONAL STATISTICAL ISSUES

There are no additional statistical issues.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Immunogenicity of the aH5N1c vaccine has been evaluated in five clinical studies: V89P1, V89_04, V89_11, V89_13, and V89_18.

In V89P1, a Phase 1/2 study, adjuvanted formulations of the vaccine showed significantly higher GMTs, seroconversion rates, and percentages of subjects achieving HI antibody titers ≥1:40 compared to the unadjuvanted formulation at the same antigen level at Day 43, three weeks after the second dose of the two-dose regimen.

Two formulations of the vaccine, a "high" dose containing 7.5 µg HA antigen and 0.25 mL MF59 adjuvant and a "low" dose containing 3.75 µg HA antigen and 0.125 mL MF59 adjuvant, were subsequently evaluated in three Phase 2 studies: V89_04 consisting of 18 to 64 year-old subjects, V89_11 consisting of 6-month to 17 year-old subjects, and V89_13 consisting of ≥65 year-old subjects. In all three studies, for the "high" dose, the lower bounds of the multiplicity-adjusted 97.5% CI for seroconversion and percentage achieving HI titers ≥1:40 were above the age-specific CBER criteria included in the FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines.

The selected dose of 7.5 µg HA antigen + 0.25 mL MF59 was further evaluated in V89_18, a Phase 3 safety, immunogenicity, and lot consistency study in healthy adult subjects ≥18 years of age. In this study, lot consistency based on HI titers was successfully demonstrated under a 1.5-fold equivalence margin and the lower bound of the 95% CI for the percentage of subjects with Day 43 HI titer ≥1:40, the co-primary endpoint, met the age-specific CBER criteria included in the FDA guidance.

While the aH5N1c vaccine appeared to elicit higher rates of local and systemic reactions, no practical differences in the rates of related SAEs, AESIs, NOCDs, AEs leading to withdrawal, and medically attended AEs were observed between the aH5N1c vaccine and placebo. No deaths occurred that were considered related to the vaccine.

10.2 Conclusions and Recommendations

No major statistical or safety issues have been identified. All prespecified immunogenicity objectives across the Phase 2 and Phase 3 studies have been met by the proposed vaccine formulation. The clinical and immunogenicity data thus support licensure of the aH5N1c vaccine.