BLA Clinical Review Memorandum

Application Type	Original BLA for persons ≥6 months
STN	125692/0
CBER Received Date	February 1, 2019
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Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	No
Reviewer Name	Cynthia Nolletti, MD
Review Completion Date / Stamped Date	January 21, 2020
Supervisory Concurrence	Meghan Ferris, MD, MPH Team Leader CRB2 Andrea Hulse, MD Chief, CRB2
Applicant	Seqirus Pty Ltd
Established Name	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
(Proposed) Trade Name	Audenz
Pharmacologic Class	Vaccine
Formulation, including Adjuvants, etc.	Each 0.5 mL dose contains 7.5 mcg hemagglutinin (HA) from influenza A/H5N1 and (b) (4) MF59 adjuvant (containing 9.75 mg squalene).
Dosage Forms and Route of Administration	Sterile emulsified suspension for intramuscular (IM) injection supplied in single dose pre-filled syringes.
Dosing Regimen	Two 0.5 mL doses IM 21 days apart by needle-syringe.
Indication and Intended Population	Active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. Persons ≥6 months of age and older.
Orphan Designated	No

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GLOSSARY

aH5N1c	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted
ACIP	Advisory Committee for Immunization Practices
AE	adverse event
AES	All Enrolled Set
AESI	adverse event of special interest
BIMO	Bioresearch Monitoring
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CSR	complete study report
DBA	doing business as
DSMB	data safety monitoring board
ES	Exposed Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
GLP	good laboratory practice
GMT	geometric mean titer
HA	hemagglutinin
HI	hemagglutination inhibition
IAV	influenza A viruses
IBV	influenza B viruses
IIV	inactivated influenza vaccine
IIV3	trivalent inactivated influenza vaccine
IIV4	quadrivalent inactivated influenza vaccine
IM	intramuscular
IR	information request
ISS	integrated summary of safety
LAIV	live attenuated influenza vaccine
LB	lower bound
MAAE	medically-attended adverse event
MDCK	Madin Darby Canine Kidney
mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
NA	neuraminidase
NH	northern hemisphere
NI	non-inferiority
NOCD	new onset of chronic disease
OBE	Office of Biostatistics and Epidemiology
OBE/DE	Office of Biostatistics and Epidemiology/Division of Epidemiology

OSS	Overall Safety Set
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PMC	postmarketing commitment
PMR	postmarketing requirement
PPS	Per Protocol Set
PREA	Pediatric Research Equity Act
PSP	Pediatric Study Plan
PVP	Pharmacovigilance Plan
PT	Preferred Term
QIV	quadrivalent influenza vaccine
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCR	seroconversion rate
SH	southern hemisphere
SOC	system organ class
SSS	Solicited Safety Set
TEAE	treatment emergent adverse event
TIV	trivalent influenza vaccine
TIVc	cell culture-derived trivalent influenza vaccine
QIV	quadrivalent influenza vaccine
QIVc	cell culture-derived quadrivalent influenza vaccine
UB	upper bound
USS	Unsolicited Safety Set
VAERS	Vaccine Adverse Event Reporting System
VRBPAC	Vaccine and Related Biologics Products Advisory Committee
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Introduction

Seqirus, Inc, also referred to as "The Applicant" in this review, has submitted a Biologics License Application (BLA) for its Influenza A (H5N1) Monovalent Vaccine, Adjuvanted. The vaccine is a monovalent (influenza A/H5N1), inactivated subunit, cell culture-derived influenza vaccine that includes Seqirus' proprietary adjuvant MF59C.1 and is also referred to as the aH5N1c vaccine in this review. The proposed indication is for active immunization for prevention of disease caused by the influenza A/H5N1 virus subtype contained in the vaccine, for use in persons 6 months and older at increased risk of exposure to the influenza A/H5N1 virus subtype contained in the vaccine. The proposed dosing regimen in persons ≥6 months is two doses of 7.5 mcg H5N1 hemagglutinin (HA) (b) (4) MF59 adjuvant (total volume 0.5 mL per dose) administered intramuscularly (IM) 21 days apart. In this review the 7.5 mcg HA/0.25 mL MF59 dose is also referred to as "full" or "high" dose and a 3.75 mcg HA/0.125 mL MF 59 dose as "half" or "low" dose. The clinical review team recommends approval of the BLA based on demonstration of adequate safety and effectiveness and a favorable risk-benefit assessment. Evaluation of effectiveness is based on immunogenicity and inferred from the effectiveness of Seqirus' Flucelvax seasonal trivalent and quadrivalent influenza vaccines which are manufactured using the same process as is used to manufacture the influenza A/H5 HA antigen contained in the aH5N1c vaccine. Approval in adults ≥18

years will be granted according to the "traditional" approval pathway because seasonal Flucelvax (trivalent formulation, TIVc) and Flucelvax Quadrivalent (QIVc) have full or "traditional" approval in this age group. Because seasonal TIVc and QIVc were approved in children and adolescents 4 years to <18 years according to accelerated approval regulations (21 CFR 601.40-46) and are not approved in children<4 years, approval of the aH5N1c vaccine in persons 6 months to <18 years will be granted according to accelerated approval regulations.

The aH5N1c vaccine contains the influenza virus surface antigens HA (b) (4) derived from a reassortant virus produced by reverse genetics from an influenza A/turkey/Turkey/1/2005/ (b) (4) (H5N1) vaccine reference strain (b) (4) . Unlike egg-derived influenza vaccines, aH5N1c is grown in a Madin Darby Canine Kidney (MDCK) continuous mammalian cell culture line, following the same manufacturing process used for Seqirus' U.S.-licensed seasonal influenza vaccine Flucelvax. (b) (4) the HA (b) (4) antigens, the vaccine is (b) (4) MF59C.1 adjuvant (referred to as MF59 in this review) to augment the immune response. MF59 is an oil-in-water emulsion containing squalene oil (a liquid hydrocarbon intermediate in the synthesis of sterols, including cholesterol) and surfactants (polysorbate 80 and sorbitan trioleate) in a citrate buffer. MF59 is also contained in Seqirus' U.S.-licensed seasonal influenza vaccine Fluad. The United States Department of Health and Human Services (U.S. DHHS), Office of the Assistant Secretary for Preparedness and Response (ASPR), through its Biomedical Advanced Research and Development Authority (BARDA), contracted with Seqirus to develop the aH5N1c vaccine to respond to a potential influenza A/H5N1 pandemic. In the event of an influenza A/H5N1 pandemic, it is anticipated that the vaccine strain would be matched to the circulating A/H5N1 strain via a strain change supplement.

Effectiveness

Seqirus conducted five clinical studies to support the BLA: one pivotal Phase 3 placebo-controlled immunogenicity and lot-to-lot consistency study (V89_18), three Phase two dose confirmation studies (V89_04, V89_13, and V89_11), and one Phase 1/2 dose-finding study (V89P1), and performed an integrated summary of safety (ISS) in adults. Across the Phase 2 and 3 trials, the total primary immunogenicity population randomized to receive the full dose of aH5N1c vaccine selected for licensure (7.5 mcg H5N1 HA/0.25 mL MF59) included: n=1507 adults 18 through 64 years; n=1753 adults ≥65 years; and n=289 children and adolescents 6 months through 17 years. Immunogenicity was also evaluated in subjects randomized to receive a half dose of aH5N1c vaccine (3.75 mcg H5N1 HA/0.125 mL MF59): n=440 adults 18 through 64 years; n=664 adults ≥65 years; and n=288 children 6 months through 17 years.

In all five studies, the effectiveness of the aH5N1c vaccine was assessed by evaluating strain-specific neutralizing antibodies against HA which provide the main immunologic protective response against influenza infection and clinical disease. The anti-HA antibody response, as measured by the hemagglutination inhibition (HI) assay, specifically an HI titer of ≥1:40, is currently the best available surrogate marker of activity that is reasonably likely to predict clinical benefit. CBER concurred with the pre-specified primary immunogenicity endpoints used in the clinical studies because they are commonly used in studies of seasonal and pandemic influenza vaccines and follow CBER guidance. [17,18]

V89_18 (NCT02839330)
Study V89_18 was a Phase 3, age-stratified, randomized, observer-blind, multicenter, placebo-controlled study to evaluate the safety, immunogenicity and lot-to-lot consistency of aH5N1c in healthy adult subjects ≥18 years, conducted at 26 centers in the U.S. A total of 3196 subjects (planned n=3192) were enrolled, stratified by site and approximately equal age cohorts (18-64 and ≥65 years), and randomized 1:1:1:1 to receive two 0.5 mL doses (on Day 1 and Day 22) of one of three consecutively produced aH5N1c vaccine lots or placebo (Groups A, B, C and D), administered IM. Blood samples for HI titers were collected prior to each vaccination (Day 1 and Day 22) and on Days 43 and 183. Pre-specified solicited local and systemic reactogenicity events were collected for 7 days following each vaccination, and non-serious unsolicited adverse events (AEs) for 21 days following each vaccination. Serious adverse events (SAEs), Adverse Events of Special Interest (AESIs), New Onset of Chronic Diseases (NOCDs), AEs leading to study withdrawal, Medically-Attended Adverse Events (MAAEs), and concomitant medications and vaccinations were collected from Day 1 through Day 387.

The pre-specified co-primary immunogenicity endpoints for V89_18 were based on HI antibody responses to the homologous aH5N1c vaccine strain for subjects ≥18 years, in the aH5N1c vaccine groups:

- Geometric mean titers (GMTs) at Day 43 by lot.
- Percentage of subjects with a post-vaccination HI titer ≥1:40 (%HI ≥ 1:40) on Day 43 by age cohort (18 through 64 years and ≥65 years) in all lots, pooled.

Lot-to-lot consistency across three consecutively produced lots of aH5N1c vaccine was assessed by the ratio of GMTs of HI antibody responses to the H5N1 vaccine strain three weeks after the second vaccine administration (Day 43). Lot-to-lot consistency would be demonstrated if, for all subjects ≥18 years, the limits of the 2-sided 95% CIs for GMT ratio for all three pairwise comparisons [GMT Group A/GMT Group B, GMT Group A/GMT Group C, and GMT Group B/GMT Group C] were within the pre-specified equivalence range of 0.67 to 1.5.

After lot-to-lot consistency was demonstrated, the populations of all aH5N1c vaccine recipients were pooled to evaluate the %HI ≥1:40 at three weeks after the second vaccination (Day 43), measured by strain-specific HI assay, in each age cohort. The pre-defined success criteria for the % HI ≥1:40 were:

- Subjects 18 to <65 years: the LB of the adjusted 2-sided 95% CI must be ≥70%.
- Subjects ≥65 years: the LB of the adjusted 2-sided 95% CI must be ≥60%.

The Per Protocol Set (PPS) was used for the primary endpoint analyses and included all enrolled subjects who correctly received the assigned study vaccine at scheduled time points and had no protocol deviations leading to exclusion. The PPS included n=2249 aH5N1c vaccine and n=739 placebo recipients. Tables 1 and 2 show that V89_18 met the pre-specified co-primary endpoints for lot-to-lot consistency and %HI ≥1:40 in subjects ≥18 years. The LBs of the 2-sided 95% CI for %HI ≥1:40 in subjects 18-64 years and ≥65 years were 93.4% and 83.3%, respectively. Placebo recipients did not show an immune response.

Table 1: Adjusted HI GMTs and GMT Ratios for Lot-to-Lot Consistency following the Second Vaccination (Day 43), V89_18 (Per Protocol Set)*

-	Group A	Group B	Group C	GMT Ratio	GMT Ratio	GMT Ratio
-	aH5N1c Lot 1	aH5N1c Lot 2	aH5N1c Lot 3	Lot 1 / Lot 2	Lot 2 / Lot 3	Lot 1 / Lot 3
Day 43	-	-	-	-	-	-
N	729	710	717	-	-	-
GMT**	128.6	127.4	132.2	-	-	-
95% CI	118.9,139.1	117.6,138.0	122.2,143.1	-	-	-
GMT Ratio (95% CI)	-	-	-	1.01 (0.90,1.13)	0.96 (0.86,1.08)	0.97 (0.87,1.09)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 14 and 14.2.1.1.
Abbreviations: HI=hemagglutinin inhibition; GMT=geometric mean titers; N=number of subjects in the Per Protocol Set at Day 43; CI=confidence interval.
*ClinicalTrials.gov identifier: NCT02839330
**GMTs and 95% CIs were adjusted for the covariates of lot, age group (18-64 and ≥65 years), site, and pre-vaccination HI titer.

Table 2: Percentage of Subjects with HI Titer ≥1:40 (% HI ≥1:40) at Day 1 and Day 43 by Age Group, V89_18 (Per Protocol Set)*

Age Group	18 to <65 yrs	18 to <65 yrs	≥65 yrs	≥65 yrs
Treatment	**aH5N1c N=1116**	**Placebo N=372**	**aH5N1c N=1133**	**Placebo N=367**
Day 1, N	N=1116	N=372	N=1133	N=367
Day 1 % HI ≥1:40 (95% CI)	13.0 (10.7, 15.6)	15.0 (11.5, 19.4)	27.8 (24.9, 30.9)	24.5 (20.1, 29.6)
Day 43, N	N=1076	N=349	N=1080	N=351
Day 43 % HI ≥1:40 (95% CI)	95.0 (93.4, 96.2)	8.5 (5.9, 12.1)	85.7 (83.3, 87.9)	20.8 (16.6, 25.8)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR Tables 15 and 14.2.1.2.6.1.
Abbreviations: HI=hemagglutinin inhibition; %HI ≥1:40=percentage of subjects with post-vaccination HI titer of at least 1:40; N=number of subjects in the Per Protocol Set at the specified time points; CI=confidence interval.
*ClinicalTrials.gov identifier: NCT02839330
%HI ≥1:40 and 95% CIs were adjusted for site.
Success criteria for %HI ≥1:40: For subjects 18 to <65 years, the lower bound (LB) of the 95% CI for the % HI ≥40 must be ≥70%; for subjects ≥65 years, the LB of the 95% CI for the % HI ≥40 must be ≥60%.

Secondary immunogenicity endpoints, also based on HI antibody responses, included GMTs, %HI ≥1:40, and seroconversion rates (SCRs), measured in each treatment group (pooled aH5N1c or placebo), at different time points post-vaccination, overall, and by age sub-groups, sex, race, and ethnicity. Seroconversion was defined as either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a minimum 4-fold increase in post-vaccination HI titer. Pre-specified success criteria for secondary SCR endpoints in each age cohort were:

- 18 to <65 years: the LB of the 2-sided 95% CI for the SCR must be ≥40%.
- ≥65 years: the LB of the 2-sided 95% CI for the SCR must be ≥30%.

Subjects 18 to <65 years and ≥65 years met secondary endpoint criteria for the SCR after two vaccinations (LBs of the 2-sided 95% CI: 77.4% and 51.0%, respectively, at Day 43), but not after a single vaccination. GMTs, %HI ≥1:40, and SCRs all decreased toward baseline at six months after the first vaccination. Placebo recipients did not show an immune response.

V89_11 (NCT01776554)
One study was performed to support licensure in the pediatric population. V89_11 was a Phase 2, randomized, observer-blind, multicenter study to evaluate the safety and immunogenicity of two IM doses of either low dose (aH5N1c 3.75 mcg HA/0.125 mL MF59) or high dose (aH5N1c 7.5 mcg/0.25 mL MF59) aH5N1c vaccine in healthy subjects 6 months through 17 years, conducted at ten sites in the U.S. and two sites in Thailand. After obtaining informed consent, and assent in accordance with local Institutional Review Boards (IRB), a total of 662 subjects were enrolled, stratified by site and age cohort (6 through 35 months, 3 through 8 years, and 9 through 17 years), and randomized 1:1 to receive either low or high dose aH5N1c vaccine administered IM 21 days apart (Days 1 and 22). HI titers were collected before vaccination on Days 1 and 22, and on Days 43 and 387. Solicited AEs were collected for 7 days following each vaccination, non-serious unsolicited AEs for 21 days following each vaccination, and long-term safety data (SAEs, AESIs, NOCDs, MAAEs, AEs leading to study withdrawal), from Day 1 through Day 387.

Co-primary immunogenicity endpoints included SCRs and %HI ≥1:40 at Day 43 in each treatment group with the same success criteria as were used in study V89_18 for subjects 18 to <65 years. Secondary endpoints included GMTs, SCRs, and %HI ≥1:40 at different time points and according to age subgroups, sex, race, ethnicity, and country. The FAS, defined as all enrolled subjects who received at least one study vaccination and provided any evaluable immunogenicity data, included n=300 low dose and n=304 high dose recipients, and was used for the primary analyses. At 21 days after the second vaccination, subjects 6 months through 17 years in both low and high dose groups met both co-primary endpoints. Immune responses were higher in the high dose as compared to the low dose group. For the %HI ≥1:40, the LBs of the 2-sided 97.5% CI at Day 43 were 92% and 81%, respectively. For the SCR, the LBs of the 2-sided 97.5% CI at Day 43 were 93% and 81%, respectively. GMTs at Day 43 were 1356 and 431, respectively. In age subgroup analyses, children 6 to <36 months, 3 years to <9 years, and 9 to <18 years each met success criteria for the co-primary endpoints.

Secondary endpoints showed that only the high dose group met SCR criteria after a single vaccination (LB of the 2-sided 97% CI: 45%) or at twelve months following the second vaccination (LB of the 2-sided 97% CI: 40%). Neither group met the % HI ≥1:40 success criteria after a single vaccination or at twelve months after the second vaccination. At Day 387, GMTs in both low and high dose groups declined but remained ~5.6 and 12 times the baseline level, respectively. Based on an assumption that higher immune responses may be associated with greater effectiveness, the Applicant selected the 7.5 mcg HA/0.25 mL MF59 dose, which was associated with higher GMTs at all time points, for licensure in the pediatric population.

<u>Safety</u>
Across trials, the overall safety database (total exposure) for the 7.5 mcg HA/0.25 mL MF59 (full) dose of aH5N1c vaccine selected for licensure was comprised of n=3579 adults, n=329 children and adolescents, for a total of n=3908 subjects exposed to full dose vaccine, and n=796 placebo recipients. An additional n=1179 adults and n=329 children and adolescents (total n=1508) were exposed to and contributed safety data for the 3.75 mcg HA/0.125 mL MF59 (half) dose vaccine. The Executive Summary will focus on safety data from the pivotal adult study V89_18 (the only study with a placebo control) and the pediatric study V89_11, briefly discuss adult studies V89_04 and

V89_13, and describe findings from the Applicant's Integrated Summary of Safety (ISS) which included the adult studies V89_18, V89_04 and V89_13.

V89_18 (adults ≥18 years)
The Overall Safety Set (OSS) was used to summarize all safety data. The OSS included all subjects in the Solicited Safety Set (SSS) and the Unsolicited Safety Set (USS), all enrolled subjects who received at least one dose of study vaccine (Exposed Set) and underwent any solicited and/or unsolicited safety assessments. The OSS was comprised of 3191 subjects (aH5N1c n=2395, placebo n=796). Most subjects (97.6%) received both vaccinations. Data were analyzed according to actual treatment received.

After a 30-minute post-vaccination observation period, solicited AEs were actively collected via a diary card through seven days following each vaccination (Days 1 through 7 and Days 22 through 28). The SSS was used to summarize solicited AEs which were analyzed by age group (18 through 64 years and ≥65 years). All solicited AEs were considered related to study product. The OSS included the same subjects as the USS and was used to summarize unsolicited AEs, overall and by age group. All unsolicited AEs (including SAEs, MAAEs, NOCDs, and AESIs) were passively collected through the end of the study, 12 months after the final vaccination (Day 387). This review will summarize all unsolicited AEs reported through 21 days after the second vaccination (Day 1 through Day 43), and all SAEs, AESIs, NOCDs, MAAEs, and AEs leading to discontinuation reported through the end of the study (Day 387).

Overall rates of any solicited local AE in subjects ≥18 years were higher in aH5N1c recipients than placebo (50.2% vs 14.7%), and among aH5N1c recipients, were higher in subjects 18-64 years (64.4%) than subjects ≥65 years (36.3%). In both age groups, injection site pain was the most frequently reported solicited local reaction and was reported more frequently by aH5N1c recipients as compared to placebo and by subjects in the younger age group (18 to <65 years: 64.1% vs 19.9%; ≥65 years: 35.9% vs 9.6%, respectively). Severe pain occurred in 0.3% of subjects 18 to <65 years and in no subjects ≥65 years. In both age groups, other local reactions (erythema, induration or ecchymosis) occurred in <1% of subjects in each treatment group and were mostly mild in severity. Local AEs occurred less frequently following the second vaccination. The majority of all solicited local AEs were <2 days in duration.

Overall rates of any solicited systemic AE following any vaccination in subjects ≥18 years were similar between aH5N1c and placebo groups (38.2% and 32.8%, respectively). Among subjects 18 to <65 years, the most common (≥10%) solicited systemic AEs reported by either aH5N1c or placebo recipients, respectively, were fatigue (24.8% vs 21.4%), headache (24.5% vs 22.7%), malaise (22.1% vs 12.1%), myalgia (14.4% vs 11.4%), arthralgia (10.4% vs 9.3%), and nausea (10.1% vs 10.9%). Fever was infrequent, occurring in 0.6% and 2.3% of aH5N1c and placebo recipients, respectively. Among subjects ≥65 years, the most common (≥10%) solicited systemic AEs reported by either aH5N1 or placebo recipients, respectively, were fatigue (19.7% vs 19.4%), malaise (16.1% vs 11.6%), and headache (15.5% vs 15.9%). Fever occurred in 0.7% and 0.3% of aH5N1c and placebo recipients, respectively. In both age groups, most solicited systemic AEs were mild to moderate in severity, began in the first three days following vaccinations, and were <3 days in duration. Rates of systemic AEs were generally lower following the second vaccination.

Rates of unsolicited AEs in subjects ≥18 years, reported in the 21 days following any vaccination (through Day 43), were similar between treatment groups (aH5N1c 23.4%, placebo 22.2%). Among aH5N1c recipients, the occurrence of any unsolicited AE through Day 43 was slightly higher in subjects ≥65 years than in subjects 18 to <65 years, (26.8% vs 20.0%, respectively). No unusual patterns or large imbalances in the rates of individual events or by organ system were observed between treatment groups. Across treatment and age groups, most unsolicited AEs were mild to moderate in severity, and most (≥92%) were assessed by the investigator as unrelated to study treatment.

A total of 12 deaths were reported in the 12 months following receipt of aH5N1c (n=11, 0.5%) or placebo (n=1, 0.1%). None were assessed by the investigator as related to study treatment.

SAEs occurred slightly less frequently in aH5N1c than placebo recipients ≥18 years overall (6.7% vs 9.3%, respectively), and were more frequent in both aH5N1c and placebo recipients ≥65 years (10.5% and 15.3%, respectively) as compared to subjects 18 to <65 years (2.9% and 3.3%, respectively). For all subjects ≥18 years, the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) categories with the highest frequencies of SAEs reported by aH5N1c or placebo groups, respectively, were: cardiac disorders (1.3% vs 2.8%), musculoskeletal and connective tissue disorders (1.3% vs 1.0%), infections and infestations (1.0% vs 1.1%), and neoplasms benign, malignant and unspecified, including cysts and polyps (0.9% vs 1.3%). No aH5N1c recipients had SAEs assessed by the investigator as related to study vaccine.

Adverse events of special interest (AESIs), including those assessed as SAEs, were reported in 7 (0.3%) aH5N1c and 7 (0.9%) placebo recipients. AESIs in aH5N1c recipients included PMR, ankylosing spondylitis, Basedow's disease, uveitis, worsening of sarcoidosis, chronic inflammatory demyelinating polyradiculopathy, and systemic lupus erythematosus rash. Relatedness between aH5N1c and these AESIs is unknown, and AESIs also occurred in placebo recipients, clearly without biological plausibility to support relatedness.

MAAEs (46.5% vs 46.0%) and NOCDs (9.5% vs 9.2%) occurred with similar frequencies between aH5N1c and placebo recipients, respectively, with larger proportions of events occurring in subjects ≥65 years. The most frequently reported SOC for MAAEs was infections and infestations (21.4% vs 24.7%). The most frequently reported SOC for NOCDs was musculoskeletal and connective tissue disorders (2.0% vs 1.8%). No large imbalances or unusual patterns of events were observed.

A total of six aH5N1c and five placebo recipients became pregnant during the study. Three pregnancies (aH5N1c n=1, placebo n=2) resulted in spontaneous abortions.

V89_11 (children and adolescents 6 months through 17 years)
The OSS (identical to the ES) was comprised of 658 subjects 6 months through 17 years, 329 of whom received low dose vaccine and 329 of whom received high dose vaccine. A total of 97% of subjects in each group received both vaccinations. A total of 57% and 56% of children 6 months to <6 years in the low (n=162) and high (n=160) dose groups, respectively, and 71% and 68% of children 6 years through 17 years in the low (n=161) and high (n=163) dose groups, respectively, reported any solicited local AE. Among children 6 months to <6 years, injection site tenderness was the most frequently

reported local AE following any vaccination (56% in both dose groups). Local erythema, induration and ecchymosis occurred in 1%-3% of younger subjects in either dose group. All local reactions were mild to moderate in severity except for three subjects who experienced severe tenderness (1% in each dose group). Among children 6 years through 17 years, injection site pain was the most frequently reported local AE following any vaccination (low dose 72%, high dose 68%). Local erythema, induration, and ecchymosis occurred in 0 to 2% of older subjects in either dose group. Local AEs were mild to moderate in severity except for three subjects (1% in each dose group) who reported severe injection site pain. In both age cohorts, rates of local AEs were lower following the second as compared to the first vaccination and most local reactions resolved within 3 days of onset.

A total of 40% and 43% of children 6 months to <6 years in the low (n=162) and high (n=160) dose groups, respectively, and 51% and 48% of children 6 years through 17 years in the low (n=161) and high (n=163) dose groups, respectively, reported any solicited systemic AE. Among children 6 months to <6 years, the most frequently reported solicited systemic AEs (≥10%) following any vaccination in low and high dose vaccine recipients, respectively, were irritability (28% vs 30%), sleepiness (25% in both groups), and change in eating habits (12% vs 18%). Most events were mild to moderate in severity. Severe solicited systemic AEs occurred in ≤1% of children. In both dose groups, lower proportions of subjects had systemic symptoms following the second vaccination as compared to the first. Most solicited systemic AEs resolved within 2-3 days of onset. Fever (≥38.0°C, ≥100.4°F) following any vaccination occurred in 8% of low dose and 16% of high dose vaccine recipients. Four (2%) low dose and 3 (2%) high dose recipients had fever ≥102.1°F. Most fevers occurred within two days of vaccinations and resolved within one to two days. A total of 26 (16%) and 37 (23%) of low and high dose recipients, respectively, used analgesics or antipyretics to treat pain or fever in the seven days following any vaccination.

Among children 6 years through 17 years, the most frequently reported solicited systemic AEs (≥10%) following any vaccination in low and high dose vaccine recipients, respectively, were fatigue (30% vs 27%), headache (29% vs 22%), myalgia (23% vs 30%), malaise (24% vs 25%), nausea (16% vs 13%), arthralgia (12% vs 13%), and loss of appetite (11% vs 14%). Most solicited systemic AEs were mild to moderate in severity. Severe solicited systemic AEs occurred in ≤1% of subjects in either group. In both dose groups, lower proportions of subjects had systemic symptoms following the second vaccination as compared to the first. Most systemic AEs resolved within 2-3 days of onset. Fever (≥38.0°C, ≥100.4°F) following any vaccination occurred in 3% of low dose and 4% of high dose vaccine recipients. One (1%) low dose and 1 (1%) high dose recipient had fever ≥102.1°F. Most fever occurred within 4 days of vaccinations and resolved within one day. A total of 23 (14%) and 24 (15%) of low and high dose recipients, respectively, used analgesics or antipyretics to treat pain or fever in the seven days following any vaccination.

Among all children 6 months through 17 years, the frequencies and types of unsolicited AEs occurring in the 21 days following any vaccination (through Day 43) were similar between low and high dose groups. Overall, 29% and 26% of subjects in each dose group, respectively, reported unsolicited AEs, with 1% of subjects in each group experiencing severe AEs and 4% in each group experiencing AEs assessed as at least possibly related to study vaccine. The most frequent unsolicited AEs, as categorized by system organ class (SOC), were infections and infestations (16% in both dose groups).

No febrile seizures or convulsions were reported in the 21 days following any vaccination. Overall, unsolicited AEs were typical of a pediatric population without unusual patterns.

Three subjects were discontinued from the second vaccination due to non-serious AEs assessed as possibly or probably related to study vaccine: irritability on Study Day 4; urticaria at the vaccination site (Day 1); and pyrexia (Day 3).

No deaths occurred during the study. A total of 24 non-fatal SAEs occurred from Day 1 through Day 387, including 14 SAEs reported by 11 subjects (3%) in the low dose group and 10 SAEs reported by 8 (2%) subjects in the high dose group. One subject (low dose) had an SAE of influenza with onset in the Day 1-43 post-vaccination period. The remaining SAEs began during the Day 44-387 follow-up period. SAEs consisted of events anticipated in a pediatric population, appeared unrelated to study vaccine, and did not reveal unusual patterns or safety concerns.

No AESIs were reported during the study. A total of three (0.4%) subjects, all low dose recipients, reported NOCDs during the study, all unrelated to study vaccine. A total of 223 (34%) of all subjects reported MAAEs with onset from Day 1 through Day 387, with 10% (n=68) of subjects experiencing onset of MAAEs in the 21 days after either vaccination (through Day 43). Across treatment groups, the most frequent MAAEs, as categorized by SOC, were infections and infestations (27%). Investigators assessed two MAAEs as possibly related to study vaccine: vomiting (Day 7) and dermatitis allergic (Day 2). Overall, MAAEs consisted of events that occur commonly in a pediatric population and did not reveal unusual patterns or safety concerns.

Phase 1 and Phase 2 Studies

Studies V89P1 (Phase 1/2, n=753 adults 18-40 years), V89_04 (Phase 2, n=979 adults 18 to <65 years), and V89_13 (Phase 2, n=1393 adults ≥65 years) supported the selection of two doses of the 7.5 mcg HA/0.25 mL MF59 vaccine to move into further clinical development and demonstrated acceptable safety.

Integrated Summary of Safety

The Integrated Summary of Safety (ISS) pooled data from the pivotal Phase 3 adult study V89_18 and two Phase 2 adult studies, V89_04 and V89_13. The three studies shared similarities in design, eligibility criteria, types and methods of safety data collection, and duration of follow-up. The exposed population in these studies included a total of 3579 adults ≥18 years who received at least one full dose aH5N1c vaccine, 1179 who received half dose vaccine, 4758 who received either full or half dose, and 796 who received saline placebo. The sponsor provided integrated analyses for full dose vaccine recipients (main pooled analysis) and for full and half dose vaccine recipients (expanded pool). Because an important objective of the ISS was to increase the likelihood of identifying potential large imbalances, safety signals or concerns in recipients of aH5N1c vaccine by increasing the number of exposed subjects in the safety database, the review team chose to focus equally on recipients of full dose and on full + half dose recipients combined but also considered that rates of events in main pooled analysis were more conservative due to smaller denominators in the aH5N1c treatment group (while the placebo group was constant).

Deaths
A total of 18 deaths were reported in the expanded pooled analysis of all subjects ≥18 years (full dose n=16, half dose n=1, and placebo n=1). The frequencies of deaths were low but were higher in the active treatment groups, 0.4% of all full or full + half dose aH5N1c recipients versus 0.1% of placebo recipients. Deaths occurred more frequently among aH5N1c recipients ≥65 years (0.5%, n=12) as compared to aH5N1c recipients 18-64 years (0.2%, n=5). Most deaths occurred >21 days after the last vaccination received, with an average time of death >7 months postvaccination, and in subjects with underlying medical conditions. No deaths were assessed as related to study treatment by the investigator or the Applicant. This reviewer agreed with the investigator and Applicant's assessments of relatedness. Among all aH5N1c recipients, the most frequently reported AEs leading to death were categorized as cardiac disorders (0.2%, n=7).

Serious Adverse Events
A total of n=286 (6.0%) of full and half dose aH5N1c recipients and n=74 (9.3%) placebo recipients in the expanded pooled analysis experienced SAEs. Most subjects had onset of SAEs during the follow-up period (full and half dose aH5N1c 5.5%; placebo 8.4%). Most SAEs occurred among subjects ≥65 years (full and half dose aH5N1c 8.6%; placebo 15.3%) as compared to 18-64 years (full and half dose aH5N1c 2.9%; placebo 3.3%). The most frequently reported SAEs (≥1%) by all full and half dose or placebo recipients ≥18 years, respectively, over the entire study period, as categorized by MedDRA SOC, were: cardiac disorders (1 vs 2.8%), musculoskeletal and connective tissue disorders (0.8% vs 1%), infections and infestations (0.8% vs 1.1%), neoplasms benign, malignant and unspecified (0.8% vs 1.3%), and gastrointestinal disorders (0.6% vs 1.1%). The only relatively large imbalance observed between treatment groups was among subjects who reported cardiac disorders: 1% vs 2.8% among aH5N1c/MF59 vs placebo recipients ≥18 years, respectively, driven by subjects ≥65 years, 1.5% vs 5%, respectively. No SAE, as categorized by MedDRA preferred term (PT), occurred with a frequency of ≥1% among full and half dose aH5N1c recipients, overall or in either age subgroup. SAEs assessed by the investigator as at least possibly related to study treatment were reported in one full dose aH5N1c (abortion spontaneous) and in no half dose aH5N1c recipients. In the opinion of the clinical reviewer, the SAE of abortion spontaneous, onset in a 30-year old full dose vaccine recipient (subject ID (b) (6) V89_04) on Study Day (b) (6) was unlikely to be related to study vaccine.

Adverse Events of Special Interest
In the expanded pooled analysis, a total of 18 subjects reported AESIs: 11 (0.2%) full dose aH5N1c, no half dose aH5N1c, and 7 (0.9%) placebo recipients. Rates of specific types of AESIs among subjects ≥18 years, whether categorized by MedDRA SOC or PT, were 0.0% (range of 0-2 subjects) for the aH5N1c groups and 0 to 0.4% (range 0-3 subjects) in the placebo group. All AESIs were reported during the follow-up period (after Day 43) except for one AESI of colitis ulcerative reported in the placebo group on Day 42 (20 days after the second vaccination). Among all AESIs, two were assessed by the investigator as possibly or probably related to study treatment: immune thrombocytopenic purpura and PMR, both in placebo recipients and, therefore, biologically implausible. Three AESIs occurred in full dose recipients 18 to <65 years (Raynaud's phenomenon, cardiomyopathy, and Basedow's disease) while eight occurred in full dose recipients ≥65 years (psoriasis [n=2], facial paralysis, uveitis, sarcoidosis, chronic inflammatory demyelinating polyradiculoneuropathy, ankylosing spondylitis, and PMR). After reviewing case narratives of AESIs in the individual study

reports, the clinical reviewer was unable to exclude a possible relationship between three AESIs and the aH5N1c vaccine: worsening of sarcoidosis, PMR, and facial paralysis. However, these cases highlighted the importance of a placebo group because the occurrence of AESIs was higher among placebo recipients and included AESIs similar to those in the vaccine group (e.g., PMR). Overall, the rates of AESIs were low and no patterns or clusters were observed that would strongly support an assessment of causality. No safety signals were identified.

New Onset of Chronic Diseases
Among subjects ≥18 years, a total of 9.6% (full dose n=348, half dose n=108) of aH5N1c and 9.2% (n=73) of placebo recipients reported NOCDs from Day 1 through Day 387. Most events occurred during the follow-up period after Day 43 (8.7% and 8.5%, respectively). Overall, NOCDs represented conditions commonly seen in adults. Frequencies were low and no large imbalances between treatment groups or unusual patterns were observed. No safety concerns were identified by these analyses.

Medically-Attended Adverse Events
Among subjects ≥18 years, a total of 46.9% (n=2230) of full and half dose aH5N1c and 46.0% (n=366) of placebo recipients reported MAAEs through study termination. Most MAAEs occurred after Day 43 during the follow-up period (aH5N1c 42.5%, placebo 42.5%). Overall and within age subgroups, no large imbalances in events as categorized by SOC or PTs were observed between treatment groups. Most events appeared to be medical conditions unrelated to study treatment. No new safety concerns were identified in the integrated analysis of MAAEs.

Common Adverse Events
The integrated analyses of unsolicited AEs with onset during the active treatment period (through 21 days after any vaccination) showed that similar proportions of full dose aH5N1c recipients and full or half dose recipients combined reported AEs, as categorized by MedDRA SOC and PT, as compared to placebo. Integrated analyses of solicited AEs showed patterns similar to those observed in the individual studies. Among subjects ≥18 years, solicited local AEs following any vaccination were reported by 51.6%, 48.5%, and 14.7% of full dose, full or half dose, and placebo recipients, respectively. Among full dose aH5N1c and placebo recipients, the most frequently reported local AE following any vaccination was pain (full dose aH5N1c 51.2%; placebo 14.7%). Solicited local AEs among full dose aH5N1c recipients were less frequent after the second vaccination (34.8%) as compared to the first (44.9%). Most local AEs were mild to moderate in severity (severe AEs ≤0.2%). Among subjects ≥18 years, solicited systemic AEs following any vaccination were reported slightly more frequently by full dose (39.0%) and full and half dose recipients combined (38.7%) as compared to placebo recipients (32.8%). The most frequent events following any vaccination in the full dose aH5N1c groups were fatigue (21.7%), headache (19.5%) and malaise (19.4%). Rates of solicited systemic AEs in placebo recipients were similar except for malaise which was lower (11.9%) as compared to the full dose aH5N1c group. Solicited systemic AEs among full dose aH5N1c recipients were less frequent after the second vaccination (21.6%) as compared to the first (31.8%). Most systemic AEs were mild to moderate in severity (severe AEs <1%).

<u>PREA Considerations</u>
Submission of STN 125692/0 triggered the Pediatric Research Equity Act (PREA) because it contained a new indication. The initial Pediatric Study Plan (iPSP) included a

request to defer studies in infants <6 months until after the declaration of an A/H5N1 pandemic at which time Seqirus would evaluate the safety and immunogenicity of two doses of 3.75 mcg H5N1 HA + 0.125 mL MF59 administered IM 3 weeks apart in this age group. The rationale for a deferred study was that the product would be ready for approval for use in persons ≥6 months before a pediatric study in infants <6 months was completed. FDA agreed to the iPSP on February 6, 2015. The BLA submission included a proposal to increase the proposed dose for the deferred study to 7.5 mcg H5N1 HA + 0.25 mL MF59, the same full dose as indicated for persons ≥6 months. To support this proposal, the sponsor provided age sub-group analyses of safety and immunogenicity from study V89_11 showing higher immune responses and acceptable safety data at the higher dose level. Except for fever, rates of local and systemic reactogenicity between dose groups were similar. Full dose aH5N1c was associated with higher rates of fever among children 6 months to <3 years as compared to half dose vaccine (21% vs 7%, respectively). However, given the high mortality associated with influenza A/H5N1 infection and an expectation that higher immune responses may be more protective, the higher rates of fever and only slightly higher rates of other systemic symptoms were acceptable to the review team and support the sponsor's proposal to increase the dose of aH5N1c for infants <6 months in the proposed deferred pediatric study V89_19 to full dose 7.5 mcg H5N1 HA/0.25 mL MF59.

On October 29, 2019, CBER presented the revised iPSP to the Pediatric Review Committee (PeRC) and the PeRC concurred with the review team's assessment that data from study V89_11 support licensure of the aH5N1c vaccine in children and adolescents 6 months through 17 years, and agreed with deferral of a postmarketing requirement (PMR) to evaluate the safety and effectiveness of the aH5N1c vaccine (7.5 mcg HA/0.25 mL MF59) in infants <6 months at the onset of an influenza A/H5N1 pandemic.

Pharmacovigilance Plan (PVP) – PMCs, PMRs

At the time the clinical review was completed, the OBE/DE review was ongoing and no specific recommendations for evaluations beyond routine postmarketing surveillance had been made. Please see the OBE/DE review for a full discussion of the PVP, PREA Considerations of this section, and Section 9.1.3 for further discussion of the pediatric PMR.

The sponsor agreed to develop a high-level concept protocol for a pregnancy registry and to work with FDA to finalize the protocol and initiate the registry at the onset of a pandemic. Please see the OBE/DE review for additional information.

Recommendation Based on Risk-Benefit

Immunogenicity and safety data submitted to this original BLA support traditional approval in adults ≥18 years and accelerated approval in children and adolescents 6 months to <18 years of the aH5N1c vaccine for active immunization to prevent disease caused by the influenza A/H5N1 virus subtype contained in the vaccine, for use in persons ≥6 months who are at risk for exposure to the A/H5N1 virus.

For traditional approval of the aH5N1c vaccine in children and adolescents 6 months to <18 years, the following postmarketing studies will be required to verify and describe clinical benefit: For traditional approval in children 6 months to < 4 years, the Applicant will need to 1) successfully complete and submit data from Flucelvax study V130_10 that demonstrate immunogenicity and safety of Flucelvax in children 6 months to < 4 years

(PMR #2 from 125408/127 approval letter dated May 23, 2016: Final Protocol Submission: June 30, 2019, Study Completion: August 30, 2020, Final Report Submission: February 28, 2021) and 2) demonstrate efficacy, safety and immunogenicity of Flucelvax in children 4 years to <18 years in the clinical disease endpoint study V130_12 (PMR #1 from 125408/127 approval letter dated May 23, 2016). Study V130_12 will also be the PMR to support traditional approval of the aH5N1c vaccine in children 4 years to <18 years.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

This section will summarize demographic data and subpopulation analyses of immunogenicity, solicited AEs, and non-serious unsolicited AEs performed on data from studies V89_18, the only pivotal Phase 3 adult study and the only study conducted solely in the U.S., and V89_11, the only pediatric study. Because subpopulation analyses of long-term safety data in study V89_18 were limited by small sample sizes and low rates of events, the reviewer chose to summarize subpopulation analyses of deaths, SAEs, AESIs, NOCDs, and MAAEs performed on the integrated safety population in adults (studies V89_18, V89_04 and V89_13) rather than on V89_18 alone.

V89_18

In study V89_18, distribution of demographic and baseline characteristics of the 3196 subjects in the All Enrolled Set (AES) across lots, treatment groups, overall, and within age cohorts was generally balanced. Females, whites, and non-Hispanic/Latinos comprised the majority of subjects in the overall study population (55.2%, 84.0%, and 91.6%, respectively). Black/African American and Hispanic/Latino subjects comprised 13.4% and 7.3% of the AES, respectively. American Indian/Alaskan Native (0.6%), Asian (1.1%), Native Hawaiian/Pacific Islander (0.3%), and racial groups identified as "other" (0.6%) comprised the remainder of the AES. Relative to the U.S. population (%), whites (75.7%) and non-Hispanic/non-Latinos (82.4%) were overrepresented, Asians (6.3%) were underrepresented, and blacks/African Americans (13.9%) approximated the U.S. population.

The mean age (SD) of all subjects was 57.7 (18.00) years, 43.0 (13.63) years for the 18 to <65 cohort, and 72.4 (5.55) years for the ≥65 years cohort. Equal proportions (50%) of subjects were enrolled in each age cohort. Similar proportions of subjects across treatment groups had received seasonal influenza vaccine in the prior 12 months (53.0% overall, 34.1% of subjects 18 to <65 years, and 71.9% of subjects ≥65 years).

<u>Subpopulation Analyses of Immunogenicity – V89_18</u>

Males and females comprised 44.5% and 55.5%, respectively, of subjects in the overall PPS (n=2988). Post-vaccination GMTs, % HI ≥1:40, and SCRs were similar between sexes in each treatment group and to the overall study population. The majority of subjects in the PPS were white (84.4%) or black/African American (13.2%) while other racial groups each comprised ≤1.2% of the PPS, precluding meaningful subananalyses. Blacks/African Americans showed numerically higher GMTs (207.0 vs 122.7), %HI ≥1:40 (95.3% vs 87.1%) and SCRs (77.2% vs 65.2%) at Day 43 as compared to whites. Non-Hispanic/Non-Latinos and Hispanic/Latinos comprised 91.7% and 7.3% of the PPS, respectively. Hispanic/Latino subjects had numerically higher GMTs (200.0 vs 126.5),

SCRs (80.0% vs 65.9%) and %HI ≥1:40 (91.3% vs 88.1%) as compared to non-Hispanic/Latinos.

Subpopulation Analyses of Solicited Adverse Events – V89_18
Overall, 55.8% and 43.3% of females and males, respectively, reported solicited local AEs and a total of 42.3% and 33.1%, respectively, reported solicited systemic AEs in the seven days following any vaccination with aH5N1c. The pattern of individual solicited AEs followed that observed in the overall study population.

Sample sizes were too small to make meaningful comparisons of solicited AEs among racial subgroups other than between whites and blacks/African Americans. Overall, whites reported slightly more solicited local and systemic AEs (50.2% and 37.8%, respectively) as compared to blacks/African Americans (48.9% and 40.8%, respectively), and rates of specific events were generally similar between the two racial groups.

A total of 172 (7.3%) of aH5N1c recipients (n=2352) in the Solicited Safety Set were Hispanic/Latino. Also limited by a relatively small sample, subanalyses showed slightly higher rates of solicited local (58.7% vs 49.4%) and systemic (44.2% vs 37.6%) AEs among Hispanic/Latino recipients of aH5N1c as compared to non-Hispanic/non-Latinos, respectively, in the seven days following any vaccination.

Subpopulation Analyses of Unsolicited Adverse Events – V89_18
Analyses of unsolicited AEs according to sex showed patterns similar to the overall study population. In the 21 days following any vaccination (through Day 43), a higher percentage of females reported unsolicited AEs as compared to males in both treatment groups (aH5N1c recipients 25.5% vs 20.9%, respectively, placebo recipients 27.2% vs 16.2%, respectively). Most events were mild to moderate in severity.

Racial subgroup analyses showed that more whites than blacks/African Americans reported unsolicited AEs in the 21 days following any vaccination, 24.7% and 15.5% white and black/African American aH5N1c recipients, respectively, and 22.9% and 18.8% of placebo recipients, respectively. Most AEs were mild to moderate in severity. Sample sizes of other racial subgroups were too small to make meaningful comparisons.

Analyses of unsolicited AEs according to ethnicity showed patterns similar to the overall study population with 53.1% of both Hispanic/Latino and non-Hispanic/non-Latino aH5N1c recipients reporting any unsolicited AE in the 21 days following any vaccination. Most events were mild to moderate in severity.

Subpopulation Analyses of Long-Term Safety – ISS (V89_18, V89_04 and V89_13)
Because small sample sizes and infrequent events in study V89_18 limited subpopulation analyses of long-term unsolicited adverse events (deaths, SAEs, AESIs, NOCDs, and MAAEs), a brief overview of subpopulation analyses of these events performed on the ISS are reported in this section. Subpopulations comprising the main pooled analysis of full dose aH5N1c vaccine recipients (n=3579) were as follows: males (n=1568, 43.8%), females (n=2011, 56.2%), whites (n=2752, 76.9%), blacks/African Americans (n=422, 11.8%), Asians (n=360, 10.1%), Hispanic/Latinos (n=298, 8.3%), non-Hispanic/non-Latinos (n=3257, 91.0%), U.S. (n=2976, 83.2%), Australia (n=198, 5.5%), New Zealand (n=82, 2.3%), and Thailand (n=323, 9.0%).

Integrated subpopulation analyses showed small differences but no large imbalances in rates of long-term safety events between male and female full dose aH5N1c recipients, respectively: Deaths (0.6% vs 0.3%), SAEs (6.7% vs 6.0%), AESIs (0.3% in both groups), NOCDs (8.9% vs 10.4%), and MAAEs (43.4% vs 50.0%). Analyses by race showed that numerically more white than black/African American or Asian recipients of aH5Nc vaccine reported unsolicited AEs, primarily more MAAEs, but without large or notable differences in specific types of AEs. Asians had lower rates of SAEs than the other two racial groups. Rates reported by white, black/African American and Asian full dose aH5N1c recipients, respectively, were as follows: Deaths (0.5%, 0.5% and 0), SAEs (6.9%, 5.0% and 3.6%), AESIs (0.3%, 0.2% and 0.3%), NOCDs (10.5%, 6.4% and 8.6%), and MAAEs (50.8%, 33.4% and 37.2%). ISS analyses of unsolicited AEs by ethnicity showed numerically lower rates of NOCDs (4.7% vs 10.2%) and MAAEs (34.2% vs 48.3%) among Hispanic/Latino vaccine recipients as compared to non-Hispanics/non-Latinos, respectively. ISS analyses by country showed no notable differences among subjects from different countries in the rates of deaths, SAEs, or AESIs. Higher rates of MAAEs and NOCDs occurred in the older study population from New Zealand. For example, as compared to the U.S., rates of NOCDs in adults from New Zealand were 22% vs 9.7% and MAAEs 74.5% vs 49.6%. Full and half dose aH5N1c ISS analyses showed very similar patterns as full dose alone. Interpretation of subpopulation analyses was limited by relative differences in sample sizes between the subgroups and the descriptive nature of the analyses. No safety concerns were identified in the integrated subpopulation analyses of long-term safety.

V89_11

The distribution of demographic and baseline characteristics of the AEs in study V89_11 (n=662) was balanced between treatment groups. Countries of enrollment included Thailand (73%) and the U.S. (27%). Males, Asians, and non-Hispanic/Latinos comprised the majority of subjects in the overall study population (52%, 73%, and 96%, respectively). Females (48%, whites (21%), blacks/African Americans (5%), American Indian/Alaskan Native (<1%), other racial groups (2%), and Hispanic/Latinos (4%) comprised the remainder of the AES. Relative to the total U.S. population (%), whites (73.0%) and blacks/African Americans (12.7%) were underrepresented, and Asians (5.4%) and non-Hispanics/Latinos (82.4%) were overrepresented. The mean age (SD) of all subjects was 78.4 (55.7) months. Overall, 19% of subjects reported ever having received an influenza vaccination, 11% within the previous 12 months, with nearly identical proportions between treatment groups.

Subpopulation Analyses of Immunogenicity - V89_11

Subanalyses of the %HI ≥1:40 at Day 43 among high (full) dose aH5N1c recipients by sex, race and ethnicity were as follows: females 96%, males 96%; Asians 95%, blacks/African Americans 100%, and whites 97%; Hispanic/Latinos 92% and non-Hispanic/non-Latinos 96%. SCRs showed patterns very similar to the %HI ≥1:40. GMTs were higher in females (1800) as compared to males (1185). GMTs among racial subgroups were similar: Asians (1095), blacks/African Americans (1036), and whites (1055). GMTs in Hispanic/Latinos were higher as compared to non-Hispanic/non-Latinos (2510 vs 1212), but the sample size of Hispanic/Latinos was small (n=12).

Subanalyses of the %HI ≥1:40 (95% CIs) at Day 43 among high (full) dose aH5N1c recipients by country showed the following: U.S. 98%, Thailand 95%. SCRs were nearly identical to the %HI ≥1:40. GMTs were higher in U.S. subjects (1440) as compared to Thai subjects (1095).

Overall, subanalyses of immunogenicity by sex, race, ethnicity and country followed patterns observed in the overall study population. Results were limited by the relatively small sample sizes and descriptive nature of the analyses.

Subpopulation Analyses of Solicited and Unsolicited Adverse Events – V89_11

Subpopulation analyses of solicited and unsolicited AEs were limited by small sample sizes, in particular for blacks/African Americans and Hispanic/Latinos who comprised 5% and 4% of enrolled subjects, respectively. Across both treatment and age groups, females and whites generally reported more solicited local reactions as compared to males or non-whites whereas no clear differences were observed in the rates of solicited systemic AEs between sexes or among racial groups. Rates of solicited local reactions among females as compared to males, respectively, were as follows: for subjects 6 months to <6 years, 63% vs 50%, and for subjects 6 years through 17 years, 74% vs 66%. In children 6 months to <6 years, the rates of any solicited local reactions after any vaccination across treatment groups among whites, blacks/African Americans, and Asians were 71%, 57%, and 53%, respectively. Hispanic subjects across both treatment and age groups reported more solicited local (71% vs 56%) and systemic (71% vs 40%) AEs as compared to non-Hispanics, respectively. Subpopulation analyses of unsolicited AEs across treatment groups showed higher rates of events among males, whites and Hispanics/Latinos [e.g., for females as compared to males, 43% vs 50%; for whites, blacks/African Americans, and Asians, 70%, 38%, and 40%, respectively; and for Hispanics/Latinos as compared to non-Hispanics/non-Latinos, 42.9% vs 26.7%]. Subanalyses by country showed that subjects from the U.S. reported more solicited and unsolicited AEs than subjects from Thailand, however, patterns of events were similar. The significance of these differences is unknown due to the descriptive nature of the analyses and small sample sizes. Because the study was not designed to demonstrate differences between subpopulations using inferential statistics, we cannot draw conclusions from the observed trends.

1.2 Patient Experience Data

Patient experience data was not submitted as part of this application.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Influenza is an acute highly contagious respiratory viral infection that causes significant morbidity and mortality throughout the world. Influenza viruses are single-stranded, segmented, negative-sense RNA viruses belonging to the family Orthomyxoviridae, and are classified into three major genera or types, A, B, and C, based on their conserved internal proteins and major antigenic differences. Influenza types A and B (IAV and IBV, respectively) cause the majority of human disease and annual epidemics. IAV is a zoonosis that infects humans, wild aquatic birds, pigs, horses, dogs, whales, seals, and other animals, whereas IBV only infects humans. [27,44,49]

Structurally, influenza A and B viruses contain 8 RNA gene segments. The IAV genome encodes for 17 and the IBV genome for 11 different proteins, including the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). IAVs are classified into

multiple subtypes based on 18 antigenic variants of HA (H1-H18) and 11 variants of NA (N1-N11), but only subtypes H1N1, H2N2, and H3N2 have circulated widely in humans. Currently H1N1 and H3N2 co-circulate in humans. Most other IAV subtypes are found in wild aquatic birds, their natural host, or in land-based fowl (e.g., chickens). IAV subtypes can be further classified into two groups based on antigenic and structural characteristics, comprising distinct phylogenetic clades derived from different ancestral viruses. Group 1 IAVs include H1, H2, H5, H6, H8, H9, H11, H12, H13, H16, H17, and H18. Group 2 IAVs include H3, H4, H7, H10, H14, and H15. Unlike IAVs, IBV has only one known subtype which is comprised of two distinct antigenic lineages, B/Yamagata and B/Victoria, derived from the same ancestral IBV. These two IBV lineages have co-circulated in humans since the 1980s. [27,34,43,49]

Seasonal influenza may cause severe complications (e.g., primary viral or secondary bacterial pneumonia and exacerbations of underlying cardiopulmonary disease) that disproportionately affect children less than 2 years of age, the elderly, pregnant women, immunocompromised persons, and persons with cardiovascular and pulmonary co-morbidities. The CDC has estimated that annual seasonal influenza epidemics have caused between 9.3 and 49.0 million illnesses, 140,000 to 960,000 hospitalizations, and 12,000 to 79,000 deaths in the U.S. annually since 2010. Based on U.S. statistics, the WHO estimates the global burden of influenza as ~1 billion cases, 3-5 million severe illnesses, and 290,000-650,000 deaths annually. [4,5,8,9,11,47]

Unlike seasonal influenza which is mostly self-limited, influenza pandemics are much more deadly and recur at irregular, unpredictable intervals. The segmented nature of the influenza viral genome, multiple IAV HA and NA subtypes, and numerous animal reservoirs increase the likelihood of genetic reassortment (antigenic shift) and risk of human pandemics due to novel IAV subtypes. Alternatively, an avian influenza strain may acquire virulence factors that facilitate direct adaptation to the human host and pandemic potential. Continually emerging novel IAV subtypes represent a persistent pandemic threat, capable of infecting a large proportion of a mostly immunologically naïve global population. Examples of influenza A avian subtypes that have on occasion infected humans, with sometimes lethal outcomes and pandemic potential, include: H5N1, H7N9, H7N7, H7N3, H6N1, H5N6, H9N2, and H10N8. Of these avian subtypes, H5N1 and H7N9 currently represent the greatest pandemic threats. Because most influenza vaccines are manufactured by an egg-based time-consuming process (requiring approximately six months) and given the unpredictable nature of pandemics, a serious concern is that emergence of a novel pandemic strain due to antigenic shift may cause significant illness and death before an updated vaccine can be manufactured on a large scale and distributed widely. Based on the current vaccine industry infrastructure, it has been estimated that a future pandemic has the potential to cause 175-350 million deaths worldwide with an economic impact of ~8% of gross domestic product (GDP). [12,22,32,40,44,46]

Influenza A/H5N1 is a highly pathogenic avian influenza (HPAI) virus, very contagious in birds and lethal in poultry. It was first recognized to directly infect humans during a poultry outbreak in Hong Kong in 1997, and re-emerged in 2003 in Asia, Africa, the Middle East, and Europe. Outbreaks in poultry and sporadic direct transmission to humans occur under conditions of crowded populations and close contact with poultry. Between 2003 and June 2019, the World Health Organization (WHO) reported 861 human infections from 17 countries and 455 deaths, for a mortality rate of ~53%. Infection is characterized by abrupt onset of fever, headache, myalgia, severe fatigue,

non-productive cough, and sore throat. Complications include primary viral pneumonia, secondary bacterial pneumonia, and acute respiratory distress syndrome (ARDS). Approximately half of reported cases of A/H5N1 have occurred in persons less than 20 years. Severe lower respiratory infection and death due to H5N1 also disproportionately affects adolescents and young adults. While human-to-human spread is not efficient, rare cases of limited, non-sustained transmission have been described following prolonged direct contact between humans. However, influenza A/H5N1 represents a pandemic threat due to the potential for reassortment or mutation events that may result in enhanced transmission and/or virulence. An H5N1 pandemic would affect not only the usual high risk groups (children < 2 years, elderly, and those with chronic cardiopulmonary conditions) but also young healthy persons 20-40 years, and the U.S. healthcare system could be overwhelmed by the need for intensive care and ventilatory support for >2 million persons. [12,30,37,48]

As part of a national strategy for pandemic influenza preparedness and development of vaccines for the prevention of pandemic influenza, the U.S. Department of Health and Human Services (DHHS), through the Biomedical Advanced Research and Development Authority (BARDA), contracted with Novartis Vaccines and Diagnostics (now Seqirus, Inc.) prior to 2007 to develop a cell culture-derived monovalent pandemic influenza vaccine. Even if not perfectly matched to a future circulating strain, having a vaccine in the U.S. Strategic National Stockpile ready to deploy immediately at the onset of an H5N1 pandemic may elicit cross-reactive immune responses and save lives while manufacturers update the vaccine with a strain change supplement, produce and distribute a more closely-matched H5N1 vaccine. Thus, Seqirus has developed a monovalent inactivated influenza vaccine containing proteins from an influenza A/turkey/Turkey/1/2005 [H5N1] NIBRG-23 potential pandemic candidate strain and adjuvanted with its proprietary novel MF59C.1 (MF59) adjuvant. The MF59 adjuvant was included because previous clinical trials have shown that two doses of unadjuvanted egg-based H5N1 candidate vaccines are poorly immunogenic and addition of an adjuvant increases the magnitude and breadth of the immune response. The aH5N1c cell-culture based manufacturing process may also be advantageous during a pandemic because, unlike egg-grown vaccine production, manufacture of aH5N1c would be unaffected by shortages in the egg supply (e.g., due to highly pathogenic avian viruses), potentially making an updated aH5N1c vaccine more rapidly available for distribution.

2.2 Currently Available, Pharmacologically Unrelated Treatment for the Proposed Indication

Five licensed antiviral agents are available in the U.S. for the prevention or treatment of influenza in persons with confirmed or suspected severe, complicated, or progressive influenza, or in those at higher risk for complications. Because of widespread resistance, two older adamantane agents, amantadine and rimantidine, are no longer recommended for use against seasonal influenza viruses. Resistance to adamantanes among Asian H5N1 isolates ranges from 6% to 95% depending on geographic region. One of three neuraminidase (NA) inhibitors, oseltamivir is an oral antiviral indicated for the treatment of influenza A and B in persons ≥ 14 days of age and for chemoprophylaxis in persons ≥1 year of age. Frequent gastrointestinal side effects may limit its usefulness. Zanamivir, another NA inhibitor, is indicated for treatment of influenza in persons ≥ 7 years of age and for chemoprophylaxis in persons ≥ 5 years of age. It is administered as an orally inhaled powder and is associated with

bronchospasm especially in persons with underlying asthma or chronic obstructive pulmonary disease. The third NA inhibitor, peramivir, is a single dose intravenous antiviral indicated only for the treatment of acute uncomplicated influenza A and B infection in persons ≥2 years. Adverse effects include diarrhea. Postmarketing reports for NAs have also described serious cutaneous reactions and sporadic transient neuropsychiatric events. Emergence of resistance to oseltamivir during treatment of seasonal influenza is well-described and has also been reported in persons receiving oseltamivir for H5N1 infection. Zanamivir is much less frequently associated with resistance even in oseltamivir-resistant viruses. Overall, however, potential resistance and drug toxicities limit the use of antiviral agents and illustrate the need for effective prophylactic vaccines. [6,10,14,15,19,25,]

On October 24, 2018, FDA approved a new antiviral agent, baloxavir marboxil, which has a different mechanism of action than adamantanes and NA inhibitors. Baloxavir is an oral agent which inhibits the endonuclease activity of the polymerase acidic protein (PA), an enzyme within the viral RNA polymerase complex required for influenza A and B viral gene transcription and replication. Baloxavir is indicated for the treatment of acute uncomplicated influenza in persons 12 years and older who have been symptomatic for no more than 48 hours. In October 2019, the indication was expanded to specifically include persons 12 years and older who are at high risk for complications of influenza. As with other antiviral agents, emergence of resistance may occur during treatment. [3,23,42]

2.3 Safety and Efficacy of Pharmacologically Related Products

Two vaccines are approved in the U.S. for the prevention of pandemic influenza H5N1 in persons at risk for exposure to the influenza A/H5N1 subtype contained in the vaccine. Influenza Virus Vaccine, H5N1, is an unadjuvanted monovalent inactivated influenza A/H5H1/Vietnam/2004 vaccine manufactured by Sanofi Pasteur (STN 125244/0), approved in adults 18 through 64 years. Immunization consists of two doses of 90 mcg H5N1 HA antigen administered 28 days apart. Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted, is an AS03-adjuvanted influenza A/H5N1/Indonesia/05/2005 vaccine manufactured by ID Biomedical dba GlaxoSmithKline (GSK) (Q-Pan H5N1, STN 125419/0), and is approved in persons 6 months and older. Adult immunization consists of two doses of H5N1 HA antigen 3.75 mcg adjuvanted with AS03A (10.69 mg squalene and 11.86 mg DL-α-tocopherol), administered 21 days apart. The pediatric formulation, indicated in children and adolescents 6 months through 17 years, contains half of the adult dose of antigen and adjuvant (1.9 mcg HA/AS03B). Because clinical endpoint studies are not feasible in the absence of a pandemic, both vaccines were approved based on immunologic endpoints, i.e., hemagglutinin inhibition (HI) antibody titers. These vaccines are not licensed for commercial distribution but are kept in the National Stockpile for distribution by the U.S. government in the event of a pandemic.

Safety data for Sanofi's H5N1 vaccine were notable primarily for injection site pain and tenderness occurring in ~70% of subjects who received the approved dose. Safety concerns associated with GSK's Q-Pan relate primarily to increased reactogenicity and potential immune-mediated adverse events associated with the AS03 adjuvant. An increased risk of narcolepsy, predominantly in children and adolescents, was observed following vaccination with GSK's AS03-adjuvanted 2009 pandemic H1N1 vaccine Pandemrix (D-Pan H1N1). Limitations associated with studies of this safety signal make causality uncertain. Narcolepsy has not been reported in studies of other AS03-

adjuvanted pandemic vaccines but remains a theoretical concern as do other auto-immune or auto-inflammatory adverse events. Please see the clinical reviews of Q-Pan H5N1 for additional information (STN 125419 Amendments 0 and 39). [45]

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

No previous human experience exists for the MF59-adjuvanted cell culture-derived H5N1 vaccine (aH5N1c). However, the aH5N1c vaccine is related to other seasonal, pandemic and pre-pandemic vaccines manufactured by Seqirus. The manufacturing process for the monovalent (b) (4) H5N1c component of the aH5N1c vaccine is similar to Seqirus' MDCK cell culture-derived trivalent and quadrivalent inactivated seasonal influenza vaccines (Flucelvax and Flucelvax Quadrivalent). The trivalent formulation of Flucelvax (TIVc) was licensed in the EU in 2007 (as Optaflu) and in the U.S. in November 2012. For the annual reporting period from November 1, 2016 to November 11, 2017, total exposure to TIVc in the U.S. was (b) (4) doses (STN 125408/261). Flucelvax Quadrivalent (QIVc) was approved in adults and in children 4 years through 17 years on May 23, 2016 and will replace TIVc. The Applicant estimates a cumulative worldwide exposure to QIVc of 49.6 million persons through March 2019 (STN 125408/310). No unusual safety signals have been identified for TIVc or QIVc. Common adverse events (AEs) associated with TIVc and QIVc may be anticipated following vaccination with aH5N1c due to the similar pharmacologic class and manufacturing process. These include local injection site reactions, e.g., pain, erythema and induration, and systemic symptoms, e.g., fever, arthralgia, myalgia, and headache. Due to inclusion of the MF59 adjuvant, reactogenicity following aH5N1c may be more frequent and severe in comparison to the seasonal formulations. Anaphylaxis has been reported as a rare adverse reaction. Potential risks identified in the Applicant's Pharmacovigilance Plan (PVP) include uncommon or rare AEs associated with other influenza vaccines: convulsion, neuritis, encephalitis, vasculitis, Guillain Barre Syndrome (GBS), demyelination, Bell's palsy, and immune thrombocytopenia.

The MF59 adjuvant used in the aH5N1c vaccine is also used in Seqirus' egg-derived trivalent seasonal influenza vaccine Fluad (aTIV). Like aH5N1c, each 0.5 mL dose of Fluad contains a full or standard (b) (4) dose of MF59 containing 9.75 mg of squalene. Fluad was first approved in Italy on May 15, 1997. It is licensed in 30 countries including in the U.S. where it was approved in November 2015 for active immunization against seasonal influenza in persons 65 years and older. In Canada, Fluad is approved in children 6 to <24 months in addition to the elderly. Other non-U.S.-approved Seqirus MF59-adjuvanted influenza vaccines include: Focetria (egg-derived monovalent aH1N1 vaccine); Aflunov (pre-pandemic egg-derived aH5N1 vaccine); and Celtura (pandemic, cell culture-derived aH1N1c vaccine, licensed in Germany, Switzerland and Japan during the 2009 H1N1 pandemic).

Clinical review of the Fluad BLA (STN 125510/0) identified no safety concerns in the pivotal clinical trial (Fluad n=3541), 49 supportive studies (n~27,787), or from global post-marketing data following administration of ~85.1 million doses since 1997. Review of Seqirus' most recent Investigator's Brochure for the MF59 adjuvant, edition 11, dated July 2015, indicates that as of April 30, 2015, adult subjects (≥18 years) exposed to at least a single dose of antigen plus MF59 in clinical studies included: approximately 43,600 (influenza); 3,778 (HSV); 1,806 (HIV); 540 (CMV); 533 (HBV); and 84 (HCV). Pediatric subjects (<18 years) exposed to at least a single dose of antigen plus MF59 in clinical studies approximated 9,300 (influenza) and 18 (CMV). Integrated safety

analyses from these studies have shown increased reactogenicity as compared to unadjuvanted vaccines but a similar or decreased risk of all unsolicited AEs, autoimmune diseases, new onset of chronic diseases, SAEs, hospitalizations and deaths as compared to unadjuvanted vaccines. Finally, a recent Periodic Safety Update Report (PSUR #42) indicated a cumulative subject exposure to Fluad in clinical trials of 28,559 (including n=6811 subjects 6 months to <18 years), and a cumulative exposure from postmarketing experience (May 1997 to March 15, 2019) of 127,140,919 million individuals. No safety signals were reported. Identified and potential risks for Fluad are similar to those outlined in the PVP submitted for the proposed aH5N1c vaccine.

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

- September 28, 2007: FDA provided pre-IND meeting responses to Novartis that were deemed satisfactory and, therefore, no meeting was held.
- October 25, 2007: Submission of IND 13536. A Phase 1/2 study (V89P1) was initiated in the U.S. and Germany.
- June 22, 2011: Type B End-of-Phase 2 (EOP2) meeting (CRMTS 7996). Novartis indicated that cell culture-derived H5N1 antigens were used in the HI assay for Phase 1 and would be used in Phase 2 and 3 studies.
- May 7, 2014: Type C meeting (CRMTS 9354) to discuss results of Phase 2 studies (V89_04, V89_11, and V89_13) and plans for Phase 3 development and licensure. Because aH5N1c is manufactured by the same process as U.S.-licensed seasonal Flucelvax which was approved based on absolute and relative efficacy data, FDA agreed that a "traditional" approval pathway for aH5N1c based on immunogenicity and safety was acceptable, consistent with the May 2007 FDA guidance document "Clinical Data Needed to Support the Licensure of Pandemic Vaccines". CBER requested and the sponsor agreed to revise the Phase 3 protocol V89_18 to evaluate two co-primary endpoints sequentially: lot-to-lot consistency followed by the post-vaccination %HI ≥1:40. CBER stated that the proposed pivotal Phase 3 trial and supportive Phase 2 studies might provide a safety database sufficient to support licensure of the aH5N1c vaccine only for storage in the national stockpile for use in the event of a pandemic, but that a larger safety database would be required to support commercial development for a pre-pandemic indication. The actual size of an aH5N1c safety database necessary for a pre-pandemic indication would require further discussion including with the VRBPAC.
- January 9, 2015: Submission of an agreed Initial Pediatric Study Plan (iPSP) (IND 13536 SN41) followed by an FDA agreement letter dated February 2, 2015.
- October 15, 2015: Request for Fast Track designation (IND 13536 SN 45).
- December 14, 2015: Fast Track designation granted.
- November 2015: Applicant transitioned from Novartis Vaccines and Diagnostics, Inc. to Seqirus, Inc., and IND 13536 was transferred from Novartis to Seqirus.
- March and April 2016: Submission of draft Phase 3 protocol V89_18 and statistical analysis plan (SAP), respectively, for FDA comment. Updated V89_18 protocol submitted on July 11, 2016, SAP on February 16, 2018.
- November 17, 2016: FDA approved the HI assay validation plan.
- May 2017: Unblinded interim immunogenicity results from V89_18 (Day 43) submitted to FDA and BARDA to facilitate pandemic preparedness.
- June 21, 2018: Type B Pre-BLA meeting (CRMTS 11228). FDA indicated that we would consider traditional approval of aH5N1c for adults 18 years and older

and accelerated approval for the pediatric populations 4 years through 17 years and 6 months through 3 years but added that traditional approval of aH5N1c could be considered pending traditional approval of Flucelvax in these pediatric age groups. After reviewing immunogenicity results from the pediatric study V89_11, FDA acknowledged that both 3.75 and 7.5 mcg HA dose levels met pre-defined success criteria for immunogenicity endpoints and that either dose (3.75 or 7.5 mcg of HA adjuvanted with MF59) could support an indication in children 6 months through 17 years.

- May 23, 2016 – An efficacy supplement (sBLA) for seasonal Flucelvax Quadrivalent (STN 125408/127) supported the traditional approval of QIVc in adults ≥18 years based on a non-inferiority (NI) study (study V130_01) comparing QIVc to TIVc formulations containing one of two B lineage strains. Study V130_01 allowed immunobridging to a clinical endpoint study of TIVc in adults that demonstrated the clinical benefit of Flucelvax TIVc and supported traditional approval of the trivalent formulation in adults.
- STN 125408/127 also contained a pediatric study (V130_03) of QIVc in children 4 through 17 years to evaluate the safety and non-inferior immunogenicity of QIVc as compared to two formulations of TIVc containing one of two B lineage strains. Although study V130_03 met the NI co-primary endpoints for GMT ratios and SCR differences, clinical efficacy could not be inferred by immunobridging to TIVc, and traditional approval of QIVc could not be granted, because a prior NI study of TIVc as compared to U.S.-licensed Fluvirin in children 4 through 17 years had not meet pre-specified co-primary endpoints (STN 125408/101, V58_31). However, V130_03 did meet the secondary endpoints of SCRs and %HI ≥1:40 and supported the accelerated approval of QIVc in children 4 through 17 years (21 CFR 601.40-46).
- The accelerated approval of QIVc in children 4 through 17 years under STN 125408/127 was associated with a PMR to conduct a clinical endpoint study (V130_12) in that age group. A safety and immunogenicity study in children 6 months to <4 years (V130_10) was a deferred PREA PMR. A CSR for study V130_12 is expected in March/April 2020. Of note, the study was amended to collect data down to children 2 years of age to fulfill non-U.S. regulatory requirements and may be used to support an age extension. PREA PMR study V130_10 of QIVc in children 6 mos to <4 years is scheduled to begin in September 2019. Results from studies V130_12 and V130_10 will not be submitted to support traditional approval of QIVc or TIVc in the pediatric population until after the Action Due Date for STN 125692/0. Therefore, an accelerated approval of the aH5N1c vaccine in children 6 months to <18 years will be granted according to 21 CFR 601.40-46.
- Another efficacy study of QIVc in children 6 months to <4 years, V130_14, is not associated with U.S. licensure and is ongoing in the EU.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Submission Integrity

The sponsor stated that the clinical studies submitted to the BLA were conducted according to protocol and in compliance with Good Clinical Practice (GCP), as defined by the International Council on Harmonization (ICH), the principles outlined in the Declaration of Helsinki, and all applicable federal and local regulations.

Bioresearch Monitoring (BIMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, conducted an inspection of three adult (study V89_18, U.S. sites #111, #118, and #126) and two pediatric (study V89_11, Thailand, sites #75 and #76) clinical study sites representing 11.4% and 72.5% of subjects enrolled in studies V89_18 and V89_11, respectively, and 15.6% of all subjects enrolled in the four Phase 2 and 3 studies comprising the clinical trial database. BIMO inspections identified no deficiencies that would preclude approval.

3.3 Financial Disclosures

The Applicant provided a signed Form FDA 3454 and list of investigators for the clinical studies submitted to the sBLA, and certified that they had not entered into any financial agreements with the investigators that could potentially influence the outcome of the studies. The Applicant certified further that each listed investigator was required to disclose their financial interests and that no disclosable financial interests or arrangements as defined by 21 CFR 54.2 were reported.

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

4.1 Chemistry, Manufacturing, and Controls

During the review cycle, the Applicant discovered the presence of (b) (4) in all (b) (4) batches of (b) (4) and began a root cause investigation. This issue was discussed with the review team during the Late Cycle Meeting held on October 9, 2019. The investigation determined that the pre-filled syringe presentation was unaffected by (b) (4) and that the presence of (b) (4) might be related to an interaction between the drug product and (b) (4) stoppers. Because the investigation was ongoing and might not be complete prior to the Action Due Date, the Applicant proposed withdrawing the (b) (4) presentation from the BLA. The review team agreed with the Applicant's proposal. At the time the clinical review was completed, the CMC reviewers had identified no other issues that would preclude approval. Please see the CMC review for additional information.

4.2 Assay Validation

In response to the CMC assay reviewer's questions regarding the limits of the HI assay, the Applicant repeated lot-to-lot consistency analyses (study V89_18) using a lower upper limit of quantitation (ULOQ) for the assay (ULOQ changed from (b) (4)). The change had no clinical impact on immunogenicity results. The Day 43 GMT and UB

of the 95% CI were minimally changed only for Lot #3 (GMT from (b) (4) and UB from (b) (4)) and the GMT ratios for all (b) (4) comparisons were unchanged. Please see the CMC and statistical reviews for additional information.

4.3 Nonclinical Pharmacology/Toxicology

A GLP aH5N1c vaccine repeat-dose toxicology study was performed in rabbits. Three 0.5 mL doses (each containing 15 mcg H5N1 HA and (b) (4) MF59) were administered IM two weeks apart. Necropsies performed 2 days and 2 weeks after the third dose showed no evidence of local or systemic toxicity.

A GLP reproductive and developmental toxicity study was performed in female rabbits given aH5N1c vaccine (each 0.5 mL dose containing 7.5 mcg H5N1 HA and (b) (4) MF59) at 1 and 3 weeks prior to mating and at gestation days 7 and 20. One group of animals underwent caesarian section on day 29 of gestation and the other delivered offspring and were followed through day 29 of lactation. The vaccine elicited HI antibodies in vaccinated animals and antibodies were transferred to offspring. The vaccine did not cause maternal or embryofetal toxicity, was not teratogenic, and had no adverse effects on post-natal development.

Please see the Pharmacology/Toxicology review for additional information. No concerns were identified that would preclude approval.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Vaccination with inactivated influenza vaccines induces antibody responses primarily against HA and NA. Strain-specific neutralizing antibodies against HA provide the main protection against infection and clinical disease. The anti-HA antibody response, measured by the hemagglutination inhibition (HI) assay, is currently the best available surrogate marker of activity that is reasonably likely to predict clinical benefit. To date, prospective studies have not identified a specific HI titer associated with protection against culture confirmed seasonal influenza illness. Some studies have shown that HI titers ranging from 1:32 to 1:40 are associated with protection from illness due to seasonal influenza in approximately 50% of subjects, and that protection from illness generally correlates with higher titers. However, no single HI titer has been identified that predicts protection against seasonal or pandemic influenza. [4,5,13,19,20,21,24,38]

Reviewer comment: NA inhibits viral replication by preventing release of new virions from the infected cell surface. Anti-NA antibodies block this action and have been shown to independently correlate with protection and reduction in disease severity. However, the NA content of currently licensed influenza vaccines is not standardized. Other non-neutralizing antibodies, e.g., to the ectodomain of matrix protein (M2e), and/or cellular responses, e.g., to internal

nuclear protein (NP) and matrix protein M1, to vaccination may also contribute to protection but are not measured or standardized in approved IIVs. [16,26,29,32]

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

The statistical reviewer identified no issues that would preclude approval of the supplement. Please see the statistical review.

4.6 Pharmacovigilance

The OBE/DE reviewer recommended adding anaphylaxis to the Pharmacovigilence Plan (PVP) as an important potential risk associated with the aH5N1c vaccine. Please see the OBE/DE review and Sections 9.1.3 and 11.6 of this review for further discussion of the PVP and pregnancy postmarketing commitment.

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

5.1 Review Strategy

Seqirus conducted one pivotal Phase 3, one Phase 2 adult, one Phase 2 elderly, one Phase 2 pediatric, and one Phase 1/2 dose-finding study to support licensure of the aH5N1c vaccine. The Phase 1/2 study (V89P1) was reviewed to confirm dose justification and evaluate data contributing to long-term safety and is described briefly in Section 8. The remaining four studies were reviewed in greater depth in Section 6, focusing primarily on the pivotal study in adults ≥18 years (V89_18) which contributed the largest numbers of subjects (overall and from the U.S.) for evaluation of immunogenicity, lot consistency and safety of the dose intended for licensure, and was the only study to include a placebo control for comparison of adverse events. Evaluation of the Phase 2 adult studies was important in confirming the dose selected for licensure in two different age groups (18-64 years and ≥65 years) and contributed to understanding the safety profile of the aH5N1c vaccine in each age group. Study V89_11 was the only pediatric study supporting licensure and was reviewed individually with a focus on balancing the need for robust immunogenicity in a population that may have a disproportionately high risk of mortality due to A/H5N1 infection with confirming that full dose vaccine was associated with acceptable reactogenicity and safety. Study data were evaluated for consistency with information included in the proposed PI.

The Phase 3 adult, Phase 2 adult and Phase 2 elderly studies shared similarities in design, eligibility criteria, methods of safety data collection, duration of follow-up, and used the same strain of A/H5N1 in the study vaccine, allowing pooling of safety data in the Integrated Summary of Safety (ISS, Section 8). Review of the ISS was performed to increase the likelihood of detecting less common or unusual patterns of adverse events not apparent in the individual studies and to increase denominators of subpopulations for safety analyses.

The Phase 1/2 study, V89P1, was conducted with a vaccine manufactured with a different influenza A/H5N1 virus strain (A/Indonesia/5/2005) from the final vaccine formulation and evaluated 12 different combinations of antigen and adjuvant. Immunogenicity and safety data were reviewed in detail but are not presented in this review. Results from V89P1 supported further clinical evaluation of full dose (7.5 mcg HA + 0.25 mL MF59) and half dose (3.75 mcg HA + 0.125 mL MF59) formulations of the aH5N1c vaccine. Long-term safety data appeared acceptable and identified no unusual patterns or safety concerns.

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

- STN 125692/0 – Modules 1, 2, and 5.
- STN 125692/0/1 – Electronic datasets for clinical studies.
- STN 125692/0/5 – Partial response to 3/26/19 IR, Questions 1, 3, 4 and 9.
- STN 125692/0/8 – Response to 5/6/19 IR (V89_13 two MAAE case narratives).
- STN 125692/0/9 – Partial response to 3/26/19 IR, Questions 2, 6, and 9.
- STN 125692/0/10 – Corrected case narrative for V89_13, Subject (b) (6)
- STN 125692/0/12 – Partial response to 3-26-19 IR, Question 5.
- STN 125692/0/14 – Response to 1/24/19 IR, Questions 1-6.
- STN 125692/0/16 – Response to 6/6/19 IR, Question 1.
- STN 125692/0/17 – Partial response to 3/26/19 IR, Questions 7 and 8.
- STN 125692/18 – Response to CMC questions regarding the HI assay.
- STN 125692/0/19 – Response to 7/1/19 IR (V89_04 solicited fever; V89_13 disposition of subjects).
- STN 125692/0/21 – Response to statistical IR 7-19-19 regarding discrepant sample sizes between GMTs and GMRs in V89_11 CSR Table 11.4.1-3.
- STN 125692/0/22 – Corrected response to IR 7-1-19 (STN 125692/0/19).
- STN 125692/0/23 – Response to 7/25/19 IR: V89_11 subanalyses of solicited and unsolicited AEs by country.
- STN 125692/0/37 – Response to 11-6-19 and 11-8-19 IRs: PI Section 6.2, ISS solicited AEs, and pregnancy PMC.
- STN 125692/0/41 – Revised PI.
- STN 125692/0/43 – Revised PI.
- STN 125692/0/44 – PMR and PMC agreements.

5.3 Table of Studies/Clinical Trials

Table 3 summarizes the clinical trials submitted to the BLA in support of licensure and reviewed.

Table 3: Summary of Clinical Trials – STN 125692/0

Study NCT# Season Location	Design	Population	Objectives	Endpoints	Half Dose N/N*	Full Dose N/N*	Total Half or Full Dose N/N*	Saline Placebo N/N*
V89_18 NCT02839330 2016/2017 US	Phase 3, age-stratified, randomized, observer-blind, placebo-controlled, multicenter	Healthy adults ≥18 years	Lot-to-lot consistency Immunogenicity Safety	Co-primary: -GMTs by lot -%HI ≥1:40 Secondary: -SCR Safety: -Reactogenicity -Unsolicited AEs -SAEs -Other**	0	2398/ 2395	2398/ 2395	798/ 796
V89_04 NCT01776541 2013/2014 US,T,A	Phase 2 Randomized, OB, MC	Healthy adults 18 through 64 years	Dose confirmation Safety Immunogenicity	Co-primary: -%HI ≥1:40 -SCR Safety***	491/ 490	488/ 485	979/ 975	0
V89_13 NCT01766921 2013/2014 US,T,A,NZ	Phase 2, Randomized, OB, MC	Healthy adults ≥65 years	Dose confirmation Safety Immunogenicity	Co-primary: -%HI ≥1:40 -SCR Safety***	693/ 689	700/ 699	1393/ 1388	0
V89_11 NCT01776554 2013/2014 US,T	Phase 2, Randomized, OB, MC	Healthy children 6 months through 17 years	Dose confirmation Safety Immunogenicity	Co-primary: -%HI ≥1:40 -SCR Safety***	330/ 329	332/ 329	662/ 658	0
V89P1 NCT00812019 2008/2010 US, Germany	Phase 1/2, Randomized, OB, MC	Healthy adults 18-40 years	Safety Immunogenicity Dose finding	-GMTs -%HI≥1:40 -SCR Safety***	63/ 62	64/ 64	127/ 126	0
Total Adult/Elderly in ISS	-	-	-	-	1179	3579	4758	796
Total Exposure (as treated) – All Studies	-	-	-	-	1570	3972	5542	796

Source: Adapted from STN 125692/0, Module 2.5, Table 1; Module 5, V89_18 CSR Tables 14.1.1.2 and 14.1.1.2.1; V89_04 CSR Tables 14.1.1.1 and 14.1.1.1.1; V89_13 CSR Tables 14.1.1.1 and 14.1.1.1.2; V89_11 CSR Tables 14.1.1.1 and 14.1.1.1.2; and V89P1 CSR Tables 14.1.1.1.1.1, 14.1.1.1.1.2, 14.1.1.1.2.1, and 14.1.1.1.2.2.

Abbreviations: NCT=ClinicalTrials.gov identifier; ISS=Integrated Summary of Safety; OB=observer-blind; MC=multicenter; GMT=geometric mean titer; HA=hemagglutinin; HI=hemagglutination inhibition; %HI≥1:40=percentage of subjects with post-vaccination HI titer ≥1:40; SCR=seroconversion rate; AE=adverse event; SAE=serious adverse event; AESI=adverse events of special interest; NOCD=new onset of chronic diseases; MAAEs=medically-attended adverse events; US=United States; T=Thailand; A=Australia; NZ=New Zealand.

Half dose: 3.75 mcg H5N1 HA/0.125 mL MF59; Full dose: 7.5 mcg H5N1 HA/0.25 mL MF59.

*N/N represents the number of subjects: Enrolled (as randomized)/Exposed (as treated).

**Other long-term safety endpoints: AESIs, NOCDs, MAAEs, AEs leading to discontinuation.

***Safety monitoring the same for Phase 2 and 3 studies: Solicited AEs for 7 days after each injection; Unsolicited AEs through 21 days after each injection (Day 43); SAEs, AESIs, NOCDs, MAAEs, and AEs leading to discontinuation through 12 months after the last injection (Day 387). Long-term safety for V89P1 extended through 18 months after the first injection (Day 546).

5.4 Consultations

5.4.1 Advisory Committee Meeting

CBER consulted the Vaccines and Related Biological Products Advisory Committee (VRBPAC) during the review of another adjuvanted H5N1 vaccine (please see the clinical review of STN 125419/0 for details of that discussion). Because relevant issues have been discussed, CBER determined that a VRBPAC was not necessary for this application.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

"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".

Protocol ID: V89_18
ClinicalTrials.gov ID: NCT02839330
Date of First Subject Enrolled: July 11, 2016
Date of Last Subject Completed: October 4, 2017
Database Lock Point: December 1, 2017
Date of Final Study Report: September 20, 2018

6.1.1 Objectives

Co-Primary Immunogenicity Objectives

- To demonstrate lot-to-lot consistency across three consecutively produced lots of 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 subjects ≥18 years of age.
- After lot-to-lot consistency was demonstrated, to evaluate immune responses (%HI ≥1:40) in all aH5N1c recipients (pooled lots) at three weeks after the second vaccination by age cohort, as measured by strain-specific HI assay.

Secondary Immunogenicity Objectives

After lot-to-lot consistency was demonstrated, to evaluate immune responses to the aH5N1c vaccine, as measured by strain-specific HI assay:

- According to immunogenicity criteria defined by the Committee for Medicinal Products for Human Use (CHMP) recommendations three weeks after the second vaccine administration in healthy adults ≥18 years, by age cohort.
- According to immunogenicity criteria defined by CBER and CHMP recommendations three weeks after the first vaccination (Day 22) in healthy subjects ≥18 years, by age cohort.
- Six months after the first vaccination (Day 183) in healthy subjects ≥18 years, by age cohort.

CBER and CHMP criteria were evaluated separately for each age cohort (18 to <65 years and ≥65 years, and 18 to <60 years and ≥60 years, respectively).

Safety Objective

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

6.1.2 Design Overview

V89_18 was a Phase 3, age-stratified, randomized, observer-blind, multicenter, placebo-controlled study to evaluate the safety, immunogenicity and lot-to-lot consistency of aH5N1c in healthy adult subjects ≥18 years, conducted at 26 centers in the United States. A total of 3196 subjects (planned n=3192) were enrolled, stratified by site and approximately equally by age cohort (18-64 and ≥65 years), and randomized 1:1:1:1 to receive two 0.5 mL doses (on Day 1 and Day 22) of one of three consecutively produced aH5N1c vaccine lots or placebo (Groups A, B, C and D) administered intramuscularly (IM). Subjects were observed for at least 30 minutes after each vaccination for immediate AEs. After the second vaccination, subjects were monitored for ~six months for immune responses and ~12 months for safety, for a total study duration of ~13 months per subject. The study was divided into a Treatment Period (Day 1 through Day 42), consisting of two clinic visits and four reminder calls, and a Follow-up Period (Day 43 through Day 387), consisting of three clinic visits and eight safety calls.

Blood samples for HI titers were collected prior to each vaccination (Day 1 and Day 22) and on Days 43 and 183. A subject Diary Card was used to collect solicited AEs (pre-specified local and systemic reactogenicity events), unsolicited AEs, medications, and other vaccinations received during the 7 days following each vaccination (Days 1-7 and Days 22-28, inclusive). For Days 8-21 and 29-42, inclusive, unsolicited AEs, solicited AEs continuing beyond Days 7 and 28, medications, and other vaccinations were collected at the return clinic visits on Days 22 and 43, respectively. Additionally, from Day 1 through Day 387, SAEs, AESIs, NOCD, AEs leading to study withdrawal, and MAAEs, any medications received for these events, and all vaccinations were collected via the Diary Card, subject interviews, and review of all available medical records.

A Data Monitoring Committee (DMC) was not used for the study, according to the SAP, because prior studies identified no safety signals and procedures ensured monitoring of important safety issues in real-time.

Reviewer comment: Study V89_18 was similar in design to studies supporting licensure of other influenza vaccines, seasonal and pandemic, and was agreed on following discussion of a draft protocol during a May 7, 2014 meeting held with the Applicant, followed by FDA reviews of revised versions of the protocol and SAP (IND 13536 Amendments 49, 54, and 67). The sponsor agreed to analyze the co-primary endpoints sequentially, demonstrating lot-to-lot consistency before pooling data for vaccine lots (Groups A, B and C) for the analysis of % HI ≥1:40. Eligible subjects were randomized by means of a computer-generated program to ensure balance among treatment groups. Unblinded personnel responsible for preparation and administration of the investigational products (IP) did not participate in safety assessments or collection of study data following IP administration. A formal interim analysis of immunogenicity through Day 43 was conducted by an independent statistician and programmer to preserve the blind. This analysis was considered the final analysis of the primary immunogenicity endpoints and was provided in aggregate form to BARDA and FDA for planning purposes. Investigators, other site, CRO, and Sponsor personnel, and the serology laboratory remained blinded until completion of the study, database lock, and final review of Day 387 data. Please see Section 6.1.9, Statistical Considerations and Statistical Analysis Plan, for additional information. The randomization and blinding procedures were deemed adequate by the clinical and statistical reviewers.

6.1.3 Population

Inclusion Criteria

- Adults ≥18 years who provided written informed consent and were in good health as determined by medical history, physical examination and the clinical judgment of the Investigator.

Selected Exclusion Criteria (please see CSR Section 9.3.2 for a complete list)

- Individuals with known or suspected impairment of the immune system (inhaled, intranasal, or topical corticosteroids were allowed).
- Progressive or severe neurologic disorder, seizures, or history of Guillain Barre Syndrome (GBS).
- Suspected or confirmed diagnosis of an AESI.
- History or ongoing illness for which participation, in the opinion of the investigator, might pose a risk to the subject.
- Body temperature of 38.0°C (100.4°F) or history of acute illness in the 3 days prior to vaccination.
- Pregnant or breastfeeding individuals. Females of childbearing potential must have a negative pregnancy test prior to each study vaccine administration.
- Females of childbearing potential who refused to use an acceptable method of birth control from Day 1 (first vaccination) to three weeks after the second study vaccination, and, if sexually active, who were not using a reliable birth control method for at least two months prior to study entry.
- Individuals who received any type of influenza vaccine (e.g., “seasonal”) within seven days prior to enrollment in the study or who were planning to receive any

type of influenza vaccine within seven days (before or after) receipt of the study vaccines.
- Receipt of any other licensed vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in the study or who were planning to receive any (non-influenza) vaccine within 28 days (before or after) from (receipt of) study vaccines.
- Previous confirmed or suspected illness from avian flu caused by an H5N1 virus.
- Household contact with and/or intimate exposure to an individual with culture-proven H5N1 infection, or exposure to infected household poultry or contaminated environments with sick and dead poultry within 60 days prior to enrollment.
- Receipt of any prior H5N1 vaccine.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Investigational Product:
H5N1 influenza vaccine, cell culture-derived (using Madin Darby Canine Kidney [MDCK] cells), inactivated, adjuvanted with MF59C.1, abbreviated in this review as aH5N1c.

- The active ingredients of the aH5N1c subunit vaccine are the hemagglutinin (HA) and neuraminidase (NA) surface antigens of an MDCK-derived influenza virus A/turkey/Turkey/1/2005 NIBRG-23, a reverse genetics-derived reference strain. The potency of the vaccine is based on HA protein content.
- The MF59C.1 adjuvant (abbreviated as MF59 in this review) is an oil-in-water emulsion composed of squalene, with surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer. A standard or full dose of MF59 contains 9.75 mg squalene in a volume of 0.25 mL.
- Each 0.5 mL total dose of aH5N1c contains 7.5 mcg HA and 0.25 mL MF59.
- Supplied in preservative-free single dose pre-filled syringes. The vaccine appears as a milky-white homogenous fluid.

The dosage of aH5N1c vaccine used in study V89_18 was two 0.5 mL doses (each containing 7.5 mcg HA + 0.25 mL MF59) administered IM into the deltoid muscle 21 days apart.

Lot numbers:

- Lot 1 (Group A): #181053
- Lot 2 (Group B): #181054
- Lot 3 (Group C): #181675

Saline Placebo
The placebo control (Group D) consisted of a 0.9% NaCl (saline) solution. Each 0.5 mL dose was administered IM into the deltoid 21 days apart. Lot number: #035385.

6.1.5 Directions for Use

Not applicable.

6.1.6 Sites and Centers

The study was conducted at 26 centers in the U.S. Study sites and the principal investigator for each site are presented in Table 4.

Table 4: Study Sites, Investigators, and Number of Subjects* - V89_18**
(All Enrolled Set [Full Analysis Set])

Site	Investigator	Location	#Subjects*
101	Stephan Bart, MD (PI)	Rockville, MD, USA	84 (81)
102	Daniel Brune, MD	Peoria, IL, USA	110 (110)
103	Shane Christensen, MD	Salt Lake City, UT, USA	139 (139)
104	Patrick Yassini, MD	San Diego, CA, USA	112 (110)
106	Katie Ann Julien, MD	South Jordan, UT, USA	104 (102)
108	Randle Middleton, MD	Huntsville, AL, USA	150 (148)
109	James Peterson, MD	Salt Lake City, UT, USA	146 (140)
110	Stephanie Plunkett, MD	Salt Lake City, UT, USA	116 (115)
111	Murray Kimmel, MD	Melbourne, FL, USA	163 (160)
112	Samir Arora, MD	Columbus, OH, USA	107 (102)
113	Donald Brandon, MD	San Diego, CA, USA	145 (141)
114	Matthew Davis, MD	Rochester, NY, USA	180 (179)
115	Frank Eder, MD	Binghamton, NY, USA	110 (106)
116	John Ervin, MD	Kansas City, MO, USA	87 (84)
117	Charles Fogarty, MD	Spartanburg, SC, USA	155 (154)
118	Donald Hurley, MD	Charleston, SC, USA	101 (96)
119	Terry Poling, MD	Wichita, KS, USA	121 (118)
120	Randall Severance, MD	Chandler, AZ, USA	149 (146)
121	Susann Varano, MD	Milford, CT,USA	125 (122)
122	Enrique Cifuentes, MD	Tempe, AZ, USA	93 (88)
123	John La Vaccare, MD	Chicago, IL, USA	70 (65)
124	John Rubino, MD	Raleigh, NC, USA	125 (122)
125	Robert Lee Jacobs, MD	San Antonio, TX, USA	113 (113)
126	Miguel Trevino, MD	Clearwater, FL, USA	101 (100)
127	Larkin Wadsworth, MD	St. Louis, MO, USA	129 (126)
128	Jonathan Wilson, MD	Winston-Salem, NC, USA	161 (154)

Source: STN 125692/0, Module 5, V89_18 CSR, Appendix 16.1.4, and electronic datasets.
*Number of subjects enrolled (number of subjects in the Full Analysis Set).
**ClinicalTrials.gov identifier: NCT02839330

6.1.7 Surveillance/Monitoring

The schedule of study procedures, including safety monitoring, is presented in Table 5.

Table 5: Schedule of Procedures, V89_18*

Period	**Tx**	**Tx**	**Tx**	**Tx**	**Tx**	**Tx**	**FU**	**FU**	**FU**	**FU**	**FU**	**FU**	**FU**	**FU**	**FU**	**FU**	**FU**
Visit	**V1**	**-**	**-**	**V2**	**-**	**-**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**13**
Call	**-**	**RC**	**RC**	**-**	**RC**	**RC**	**-**	**SC**	**SC**	**SC**	**-**	**SC**	**SC**	**SC**	**SC**	**SC**	**-**
Study Day	**D1**	**D3**	**D5**	**D22**	**D24**	**D26**	**D43**	**D91**	**D122**	**D152**	**D183**	**D217**	**D251**	**D285**	**D319**	**D353**	**D387**
Informed consent[1]	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Review of systems	X	-	-	X	-	-	X	-	-	-	X	-	-	-	-	-	X
General physical exam	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Symptom-directed exam	-	-	-	X	-	-	X	-	-	-	X	-	-	-	-	-	X
Urine pregnancy test[2]	X	-	-	X	-	-	X	-	-	-	-	-	-	-	-	-	-
Body temperature (oral preferred)	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Eligibility criteria	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Enrollment/randomization	X	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serologies	X	-	-	X	-	-	X	-	-	-	X	-	-	-	-	-	-
Review criteria for repeat vaccination	-	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Vaccination	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
30 minute post-vaccination observation for vital signs and AEs	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Issue diary card and instructions[3]	X	-	-	X	-	-	-	-	-	-	-	-	-	-	-	-	-
Diary card reminder call	-	X	X		X	X	-	-	-	-	-	-	-	-	-	-	-
Diary card review, collection	-	-	-	X	-	-	X	-	-	-	-	-	-	-	-	-	-
Assess all AEs	X	-	-	X	-	-	X	-	-	-	-	-	-	-	-	-	-
Assess solicited AEs	-	-	-	X	-	-	X	-	-	-	-	-	-	-	-	-	-
Assess SAEs, AESIs, MAAEs, NOCD, AEs leading to withdrawal	X	-	-	X	-	-	X	X	X	X	X	X	X	X	X	X	X
Assess medications	X	-	-	X	-	-	X	X	X	X	X	X	X	X	X	X	X
Study termination	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	X

Source: STN 125692/0, Module 5, CSR V89_18,Table 5.

Abbreviations: Tx=Treatment Period; FU=Follow-up Period; V=Visit; RC=reminder call; SC=safety call; D=Day; AE=adverse event; AESI=adverse event of special interest; NOCD=new onset chronic disease; SAE=serious adverse event.

*ClinicalTrials.gov identifier: NCT02839330

[1]The informed consent process could be conducted prior to Visit 1.

[2]Pregnancy test in females of childbearing potential.

[3]Diary card completion to begin ~6 hours post-vaccinations on Days 1 and 22 and through the following 6 days (Days 7 and 28).

Definitions and Criteria for the Assessment of Severity and Causality of AEs

Definitions of AEs and SAEs and reporting requirements were consistent with those in 21 CFR 312.32. AEs were followed to resolution or stabilization. Solicited AE parameters and the severity grading scales for both solicited and unsolicited AEs including SAEs are presented in Table 6:

Table 6: Severity Grading Scales for Solicited and Unsolicited Adverse Events – V89_18*

Solicited Local Reactogenicity	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
Pain	None	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Induration, erythema, or ecchymosis	<25 mm	25 to 50 mm	51 to 100 mm	>100 mm
Solicited Systemic Symptoms	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
Fever	<100.4°F (<38.0°C)	100.4°F-101.1°F (38.0°C-38.4°C)	101.2°F-102°F (38.5°C-38.9°C)	102.1-104°F (39.0°C-40°C)
Nausea	None	Present; does not interfere with oral intake	Leading to decreased oral intake	Leading to minimal to no oral intake
Myalgia	None	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Arthralgia	None	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Headache	None	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity
Chills	None	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Loss of appetite	None	Loss of appetite without decrease in oral intake	Decreased oral intake without weight loss	Decreased oral intake with weight loss
Malaise	None	No interference with activity	Some interference with activity	Significant; prevents daily activity
Unsolicited Adverse Events	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
Event	n/a	Transient; no limitation in normal daily activity	Some limitation in normal daily activity	Unable to perform normal daily activity

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR Section 9.5.1.3.1 and protocol Appendix 16.1.1, sub-Appendices B and C.
*ClinicalTrials.gov identifier: NCT02839330
Grade 4 toxicity was not defined in the grading scale but, according to the protocol Appendix 16.1.1, sub-Appendix C, was to be defined in the statistical analysis plan (SAP) as necessary.
n/a=not applicable.

Reviewer comment: Solicited AEs and severity grading scales were consistent with those collected in the Applicant's other influenza vaccine studies.

Reviewer comment: The V89_18 protocol (Appendix 16.1.1, sub-Appendix C) and the Integrated Summary of Safety (ISS) defined Grade 3 fever as 102.1°F to ≤104°F (39.0°C to ≤40°C), and Grade 4 fever as >104°F (>40°C). However, the protocol, statistical analysis plan (SAP), and CSR indicated that body temperature would be analyzed by two methods: 1) as None (<38.0°C, <100.4°F) or Any (≥38.0°C, ≥100.4°F); and 2) in 0.5°C increments. The 0.5°C increments, as defined in the SAP and reported in Section 14 of the CSR, included the categories of ≥39.0°C to

<39.5°C, ≥39.5°C to <40.0°C, and ≥40.0°C, which differs slightly from the toxicity grading scale with respect to 40.0°C. This review will use the toxicity grading scale as pre-defined and categorize temperatures of 40.0°C (104.0°F) as Grade 3. The discrepancy between the toxicity grading scale and actual categorization of a body temperature of 40.0°C (104.0°F) in the safety analyses was not an issue because no subject had a maximum solicited temperature of exactly 40.0°C.

AEs were also categorized according to whether they met the following criteria:

- MAAE: An AE that led to an unscheduled visit to a healthcare professional.
- NOCD: An AE that led to a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to enrollment.
- AESI: An AE that represented a potential immune-mediated disease, prospectively defined in the protocol according to a list provided by FDA prior to study start. Please see V89_18 CSR protocol Appendix 16.1.1, Appendix A, for the full list of AESIs.

Assessment of Causality

Solicited AEs were considered related to study treatment. The relationship of all other AEs to study treatment was determined by the investigator as follows:

- Not related: There was evidence that clearly indicated an alternative explanation and/or the timing of exposure and onset of the AE were not reasonably related in time.
- Possibly related: The administration of study treatment and the AE were considered reasonably related in time and the AE could be explained by exposure to the treatment or by other causes.
- Probably related: Exposure to study treatment and the AE were reasonably related in time and no alternative explanation was identified.

If the AE met the regulatory definition of serious (21 CFR 312.32), the relationship of study treatment to the SAE was determined by the investigator as follows:

- Related/suspected: The SAE had been assessed as possibly or probably related on the AE case report form (CRF).
- Not related: The SAE was not related if exposure to study treatment had not occurred, or the occurrence of the SAE was not reasonably related in time, or the SAE was considered unlikely to be related to use of the study treatment, i.e., there were no evidence or arguments to suggest a causal relationship.

SAEs were also evaluated by the sponsor for expectedness. An unexpected AE was one that was not listed in the current summary of product characteristics or the Investigator Brochure (IB), or was an event that was by nature more specific or more severe than a listed event.

6.1.8 Endpoints and Criteria for Study Success

Co-Primary Immunogenicity Endpoints

The co-primary immunogenicity endpoints were based on HI antibody responses to the H5N1 vaccine strain for subjects ≥18 years, in the aH5N1c vaccine groups only.

- GMTs at Day 43 by lot.
- Percentage of subjects with HI titer ≥1:40 on Day 43 by age cohort (18 through 64 years and ≥65 years) in all lots, pooled.

Lot-to-lot consistency across three consecutively produced lots of aH5N1c vaccine was assessed by the ratio of GMTs of HI antibody responses to the H5N1 vaccine strain three weeks after the second vaccine administration (Day 43). Lot-to-lot consistency would be demonstrated if, for subjects ≥18 years, the limits of the 2-sided 95% CIs for GMT ratio for all three pairwise comparisons [GMT Group A/GMT Group B, GMT Group A/GMT Group C, and GMT Group C/GMT Group B] were within the predefined equivalence range of 0.67 to 1.5.

After lot-to-lot consistency was demonstrated, the populations of all aH5N1c vaccine recipients were pooled to evaluate the% HI ≥1:40 at Day 43 by age cohort and strain-specific HI assay. The pre-defined success criteria for the %HI ≥1:40 were:

- 18 to <65 years: the LB of the adjusted 2-sided 95% CI must be ≥70%
- ≥65 years: the LB of the adjusted 2-sided 95% CI must be ≥60%

Reviewer comment: The immunogenicity endpoints followed CBER guidance, are commonly used in studies of influenza vaccines, and were acceptable to the review team.

Secondary Immunogenicity Endpoints

Secondary immunogenicity endpoints included the following:

- GMT at Days 1, 22, 43, and 183 by treatment and age group.
- % HI ≥1:40 at Days 1, 22, and 183 by treatment and age group.
- SCR on Days 22 and 43 by treatment and age group.

CBER pre-defined success criteria for secondary immunogenicity endpoints in subjects 18 through 64 years:

- The LB of the adjusted 2-sided 95% CI for % HI ≥1:40 must be ≥70%.
- The LB of the 2-sided 95% CI for the SCR must be ≥40%.

CBER pre-defined success criteria for secondary immunogenicity endpoints in subjects ≥65 years:

- The LB of the adjusted 2-sided 95% CI for % HI ≥1:40 must be ≥60%.
- The LB of the 2-sided 95% CI for the SCR must be ≥30%.

Seroconversion was defined as either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a minimum 4-fold increase in post-vaccination HI titer.

Secondary endpoints also included GMTs, %HI ≥1:40, SCRs, and GMT ratios of HI titers, Day 22/Day 1 and Day 43/Day 1, evaluated by slightly different criteria as required by the European Medicines Agency (EMA) Committee for Human Medicinal Products (CHMP), according to treatment and age cohorts.

Reviewer comment: Study V89_18 evaluated both CBER and EMA's CHMP criteria separately for each age cohort. This clinical review will focus on the CBER pre-defined immunogenicity objectives, endpoints and success criteria.

Safety Endpoints

Safety endpoints included the following:

- Percentages of subjects with solicited local, solicited systemic, and other AEs that occurred in the seven days (inclusive) following each vaccination (first and second) and any vaccination (first or second) by treatment group, and calculated for the following time intervals post-vaccination: 30 minutes; 1 to 3 days (without 30 minutes); 4 to 7 days; 1 to 7 days (without 30 minutes); 1 to 3 days (including 30 minutes); and 1 to 7 days (including 30 minutes).
- Percentages of subjects with any unsolicited AEs reported through 21 days after each (first and second) and any (first or second) vaccination by treatment group.
- Percentages of subjects reporting SAEs, AESIs, NOCD, AEs leading to vaccine/study withdrawal, MAAEs, and concomitant medications associated with these events as collected from Day 1 to Day 387, by treatment group.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please see the statistical review for a complete discussion of the statistical analysis plan (SAP). The statistical analyses were based on the final SAP, version 3.0, dated 15 November 2017, finalized before unblinding.

The co-primary immunogenicity objectives V89_18 were to: 1) demonstrate lot-to-lot consistency across three consecutively produced lots of aH5N1c vaccine as assessed by GMT ratios of HI titers three weeks after the second vaccination (Day 43); and 2) after lot-to-lot consistency was demonstrated, to evaluate the % HI ≥1:40 by age cohort at three weeks after the second vaccination (Day 43), using data pooled from subjects assigned to all three lots of aH5N1c.

The statistical equivalence hypotheses for lot-to-lot consistency were tested simultaneously. In mathematical notation, the null (H_0) and alternative (H_1) hypotheses were as follows:

H_0: (μLot A - μLot B) ≤ -0.176 or (μLot A - μLot B) ≥ 0.176 or
(μLot A - μLot C) ≤ -0.176 or (μLot A - μLot C) ≥ 0.176 or
(μLot B - μLot C) ≤ -0.176 or (μLot B - μLot C) ≥ 0.176
versus

H_1: (μLot A - μLot B) > -0.176 and (μLot A - μLot B) < 0.176 and
(μLot A - μLot C) > -0.176 and (μLot A - μLot C) < 0.176 and
(μLot B - μLot C) > -0.176 and (μLot B - μLot C) < 0.176

H_1 refers to the alternative hypothesis of pairwise equivalence (consistency) transformed to the log10 scale. μLotA, μLot B, and μLot C denote the means of log10-transformed Day 43 titers of the corresponding lot groups. Lot-to-lot consistency was demonstrated if the two-sided 95% CIs of all three pairwise comparisons were within the equivalence ranges. The significance level for all the tests was $\alpha = 0.05$ and did not need adjustment for multiple comparisons because all three hypotheses had to be rejected for success.

Reviewer comment: The pre-specified equivalence range for the GMT ratio of >0.667 to <1.5 corresponded to testing ratios of log10-transformed GMTs at an equivalence range of > -0.176 and < 0.176.

The second co-primary hypothesis of %HI ≥1:40 was evaluated according to pre-defined success criteria stating that the LB of the adjusted two-sided 95% CI must be ≥70% and

60%, respectively, for the two age cohorts 18 through 64 and ≥65 years. The null (H_0) and alternative (H_1) hypotheses were as follows:

H_0: $(\pi_i - \pi_0) \leq 0$ vs. H1: $(\pi_i - \pi_0) > 0$

π_0 refers to the success criteria thresholds, $\pi_0 = 0.7$ for subjects 18 through 64 years and $\pi_0 = 0.6$ for subjects ≥65 years. π_i denotes the actual % HI ≥1:40 for each age cohort. For success, the endpoint % HI ≥1:40 for both age cohorts must be met at significance levels of $\alpha = 0.05$. Adjustment for multiplicity was not necessary as all hypotheses needed to be rejected for success.

Reviewer comment: The co-primary hypotheses were acceptable to the statistical reviewer and review team.

The primary analysis population was the Per Protocol Set (PPS). If the percentage of subjects excluded from the PPS for analysis of immunogenicity was >5%, a supporting analysis based on the Full Analysis Set (FAS) was to be performed for comparison. Please see Section 6.1.10.1 for definitions of the analysis populations.

The primary immunogenicity analyses were adjusted for the following covariates: lot, age group, study site, and pre-vaccination HI titer.

The sponsor calculated that a sample size of n=798 subjects per lot would provide each lot-to-lot equivalence test with a power of 95% and α level of 0.025. For three comparisons, the overall power was ~86% (0.95 x 0.95 x 0.95). The sample size also accounted for a dropout rate of 10%. For the % HI ≥1:40 calculation, the sponsor used data from previous studies (V89_04 and V89_13) to assume that ~86% and ~81% of subjects in the two respective age cohorts (18 to <65 years and ≥65 years) would achieve success criteria. The minimum sample size of evaluable subjects from three pooled lots required to meet the %HI ≥1:40 endpoint with a power of ~98% was n=1077 (0.99 x 0.99), and to allow for a dropout rate of 10%, an n=1197. The overall power to demonstrate both co-primary endpoints of lot-to-lot consistency and % HI≥1:40 was ~84% (0.86 x 0.98).

For safety endpoints, descriptive statistics were used to summarize the number and percentage of subjects experiencing at least one adverse event by treatment group, overall and by age cohort. Unsolicited AEs were coded according to MedDRA preferred terms (PT) using version 20.0. Only treatment-emergent AEs (those occurring after exposure to study treatment) were summarized. In the event that the same unsolicited AE occurred more than once in a subject, the event was counted only once for the subject using the maximum severity grade and strongest relationship. Safety analyses were based on the study treatment actually received.

<u>Protocol Deviations</u>

Prior to unblinding, a report of all protocol deviations was provided to a clinical study team that included medical and clinical members from the sponsor and contract research organization (CRO) to identify deviations that may have had significant impact on safety and immunogenicity data. These were considered major deviations and were used to determine exclusions from the safety and immunogenicity analysis populations.

<u>Missing Data</u>

Missing safety and immunogenicity data were not imputed. To minimize the effect of dropouts and missing data, the study period was divided into intervals for immunogenicity and safety analyses. Subjects without any solicited AE data for an individual parameter were removed from the denominator for that parameter. The number and percentage of subjects with missing solicited AE assessments were reported for each follow-up time period (e.g., Day 1-7, Day 1-3, Day 4-7). Similarly, for unsolicited AEs, the study period was divided into intervals: Day 1-22; Day 23-43; Day 44-387; and Day 1-387.

Exclusion of Implausible Solicited Adverse Events

The following solicited AE measurements were considered biologically implausible, and were excluded from the analyses but were included in listings:

- Body temperature: ≤33°C (91.4°F) or ≥42°C (107.6°F).
- Erythema: <0 mm or ≥900 mm.
- Induration or Ecchymosis: <0 or ≥500 mm.

Changes in the Conduct of the Study or Planned Analyses

The original SAP was issued on June 28, 2016 and was amended twice. The final SAP, version 3.0, was finalized prior to the database lock and unblinding on December 1, 2017. Significant clarifications or changes in the conduct of the study or planned analyses included:

- Incorporation of an interim analysis of immunogenicity to be conducted after immunogenicity data from Day 43 was available for all subjects (Protocol v 2.0, January 11, 2016; SAP v 2.0, October 3, 2016). FDA agreed to the interim analysis provided that the data were cleaned and locked prior to unblinding and the interim analysis would be considered final.
- Clarification that the occurrence of at least one solicited AE would be defined as "any" for a subject if he/she reported greater than "none" for qualitatively assessed solicited systemic AEs and/or ≥25 mm for erythema, ecchymosis or induration, and "none" otherwise.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Analysis populations were defined as follows:

- All Enrolled Set (AES): All screened subjects who provided informed consent and demographic and/or other baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a subject identification (ID).
- Exposed Set (ES): All subjects in the AES who received a study vaccination.
- Full Analysis Set (FAS), Immunogenicity Set: All subjects in the AES who received at least one dose of study vaccination, and provided at least one immunogenicity result (evaluable serum sample) at relevant time points.
    - FAS-1: All subjects who provided at least one immunogenicity result at Day 1 and Day 43.
    - FAS-2: All subjects who provided at least one immunogenicity result at Day 1 and Day 22.
    - FAS-3: All subjects who provided at least one immunogenicity result at Day 1 and Day 183.

In case of vaccination error, subjects in the FAS were analyzed according to randomization, i.e., assigned treatment rather than actual treatment. Subjects randomized to the wrong age stratum were analyzed according to the randomized stratum (i.e., assigned rather than correct stratum).

- Per Protocol Set (PPS), Immunogenicity Set: All subjects in the FAS who: correctly received the vaccine to which the subject was randomized and at the scheduled time points; had no major protocol deviation leading to exclusion as defined prior to unblinding/analysis; and were not excluded due to other reasons (e.g., subjects who withdrew informed consent) defined prior to unblinding or analysis. The PPS-1, PPS-2, and PPS-3 corresponded to time intervals defined for the FAS-1, FAS-2, and FAS-3, respectively. The PPS excluded subjects who received the wrong study vaccine or who were randomized to the wrong age stratum. Exclusions were considered by objective and time point, i.e., sometimes not all data but only part of the subject's data were removed from the PPS analysis.
- Overall Safety Set (OSS): All subjects in the Solicited Safety Set and/or in the Unsolicited Safety Set. In case of vaccination error, subjects were analyzed as treated, i.e., according to actual treatment received rather than treatment to which they were randomized. Subjects randomized to the wrong age stratum were re-assigned to the correct age stratum and analyzed using the corrected stratum for all safety analyses. Subjects providing only 30 minutes post-vaccination safety data were reported separately in a 30-minute post-vaccination safety analysis.
- Solicited Safety Set (SSS): All subjects in the Exposed Set (ES), as treated, who underwent any assessment of local and systemic site reaction and/or assessment of any use of analgesics/antipyretics.
- Unsolicited Safety Set (USS): All subjects in the ES, as treated, who underwent any AE assessment (but did not need to have an AE to be included).

6.1.10.1.1 Demographics

Table 7 presents demographic and baseline characteristics of the All Enrolled Set (AES) according to treatment group. Distribution of characteristics across lots, treatment groups, overall, and within age cohorts (data not shown) was generally balanced. Females, whites, and non-Hispanic/Latinos comprised the majority of subjects in the overall study population (55.2%, 84.0%, and 91.6%, respectively). The mean age (SD) of all subjects was 57.7 (18.00) years, 43.0 (13.63) years for the 18 to <65 cohort, and 72.4 (5.55) years for the ≥65 years cohort (data not shown in table). Equal proportions (50%) of subjects were enrolled in each age cohort. The proportion of subjects stratified by age in each treatment group was similar across study sites (data not shown). Overall and within age cohorts, similar proportions of subjects across treatment groups had received seasonal influenza vaccine in the prior 12 months (53.0% overall, 34.1% of subjects 18 to <65 years, and 71.9% of subjects ≥65 years, data not shown in table).

Table 7: Demographic and Baseline Characteristics – V89_18 (All Enrolled Set)*

Treatment	**aH5N1c Lot 1 N=804**	**aH5N1c Lot 2 N=799**	**aH5N1c Lot 3 N=795****	**aH5N1c Pooled N=2398****	**Placebo N=798**	**Total N=3196****
Mean Age (yrs) (SD)	58.1 (17.67)	57.5 (17.83)	57.5 (18.24)	57.7 (17.91)	57.7 (18.29)	57.7 (18.00)
18 to <65 yrs, n (%)	403 (50.1)	399 (49.9)	397 (49.9)	1199 (50.0)	398 (49.9)	1597 (50.0)

Treatment	aH5N1c Lot 1 N=804	aH5N1c Lot 2 N=799	aH5N1c Lot 3 N=795**	aH5N1c Pooled N=2398**	Placebo N=798	Total N=3196**
≥65 yrs, n (%)	401 (49.9)	400 (50.1)	398 (50.1)	1199 (50.0)	400 (50.1)	1599 (50.0)
Sex – Male, %	44.8	45.7	43.8	44.7	45.1	44.8
Sex – Female, %	55.2	54.3	56.2	55.3	54.9	55.2
Race, %	-	-	-	-	-	-
American Indian or Alaskan Native	0.7	0.5	0.6	0.6	0.4	0.6
Asian	1.5	0.9	1.1	1.2	0.9	1.1
Black or African American	13.7	12.8	13.1	13.2	14.0	13.4
Native Hawaiian or Pacific Islander	0.4	0.3	0.1	0.3	0.5	0.3
White	83.1	85.0	84.8	84.3	83.3	84.0
Other	0.6	0.6	0.3	0.5	0.9	0.6
Ethnicity, %	-	-	-	-	-	-
Hispanic/Latino	6.6	7.6	8.1	7.4	6.9	7.3
Non-Hispanic/Latino	92.8	91.2	90.7	91.6	91.7	91.6
Not reported/unknown	0.6	1.1	1.3	1.0	1.4	1.1
BMI (kg/m2)**						
Mean	27.40	27.86	27.41	27.56	27.60	27.57
(SD)	4.213	4.080	4.227	4.177	4.199	4.182
Seasonal Influenza Vaccine in Last 12 Months?						
Yes	53.5	52.1	53.6	53.0	52.9	53.0
No	46.5	47.9	46.4	47.0	47.1	47.0

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 11 and 14.1.1.3.
Abbreviations: SD=standard deviation; BMI=body mass index.
*ClinicalTrials.gov identifier: NCT02839330
**For BMI, N=794 for aH5N1c Lot 3, N=2397 for aH5N1c All lots, and N=3195 for Total.
Percentages are based on the number of subjects in each treatment group.

Reviewer comment: Differences in demographic and baseline characteristics were small between treatment groups and were not likely to impact interpretation of study results. In this study, the proportion of whites (84%) and non-Hispanics/Latinos (91.6%) were slightly overrepresented relative to the U.S. population (75.7% and 82.4%, respectively), and Asians (1.1%) were underrepresented (6.3%). The proportions of females (55.2%) and blacks/African Americans (13.4%) in the study approximated the U.S. population (50.8% and 13.9%, respectively). [41]

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Medical History

Pre-existing medical conditions or events were reported by 90.4% of all subjects in the AES, in 89.8% and 91.9% of aH5N1c vaccine and placebo recipients, respectively, 81.2% and 85.7% of subjects 18 to <65 years, respectively, and 98.4% and 98.0% of subjects ≥65 years, respectively. Overall, the Applicant's summary tables indicated that similar percentages of subjects ≥18 years in the aH5N1c vaccine and placebo groups reported pre-existing medical conditions as categorized by MedDRA SOC and PT, including the SOC categories of immune system disorders (34.5% vs 32.9%) and neoplasms benign, malignant and unspecified (13.8% vs 12.5%).

Concomitant Medications

A total of 31.1% and 31.3% of aH5N1c vaccine and placebo recipients, respectively, ≥18 years in the Overall Safety Set, reported any medication use in the two months prior to the first vaccination. Concomitant medications, defined as medications taken or vaccines administered at any time from enrollment through the end of the study, were reported by 88.1% and 88.2% of aH5N1c and placebo recipients, respectively. Review of the Applicant's summary tables identified no large imbalances between treatment groups in the use of specific types of medications.

6.1.10.1.3 Subject Disposition

Tables 8 and 9 present the disposition of subjects and selected analysis populations for immunogenicity and safety, overall and by age and treatment group. Analysis populations are defined in Section 6.1.10.1 and table footnotes.

Table 8: Disposition of Subjects and Analysis Populations for Immunogenicity by Age and Treatment Group – V89_18, (All Enrolled Set, as Randomized)*

≥18 years	**aH5N1c Lot 1 N=804**	**aH5N1c Lot 2 N=799**	**aH5N1c Lot 3 N=795**	**aH5N1c Pooled N=2398**	**Placebo N=798**	**Total N=3196**
All Enrolled Set, n (%)	804 (100)	799 (100)	795 (100)	2398 (100)	798 (100)	3196 (100)
FAS, Immunogenicity	787 (97.9)	783 (98.0)	775 (97.5)	2345 (97.8)	776 (97.2)	3121 (97.7)
FAS-1	778 (96.8)	773 (96.7)	769 (96.7)	2320 (96.7)	766 (96.0)	3086 (96.6)
PPS, Immunogenicity	761 (94.7)	747 (93.5)	741 (93.2)	2249 (93.8)	739 (92.6)	2988 (93.5)
PPS-1	729 (90.7)	710 (88.9)	717 (90.2)	2156 (89.9)	700 (87.7)	2856 (89.4)
Total number enrolled	804 (100)	799 (100)	795 (100)	2398 (100)	798 (100)	3196 (100)
Total number exposed	804 (100)	797 (99.7)	793 (99.7)	2394 (99.8)	797 (99.9)	3191 (99.8)
Completed protocol	746 (92.8)	741 (92.7)	747 (94.0)	2234 (93.2)	747 (93.6)	2981 (93.3)
Primary reason for discontinuation	--	--	--	--	--	--
Adverse event	0	1 (0.1)	2 (0.3)	3 (0.1)	2 (0.3)	5 (0.2)
Death	4 (0.5)	6 (0.8)	1 (0.1)	11 (0.5)	1 (0.1)	12 (0.4)
Withdrawal by subject	27 (3.4)	19 (2.4)	11 (1.4)	57 (2.4)	13 (1.6)	70 (2.2)
Lost to follow-up	22 (2.7)	27 (3.4)	29 (3.6)	78 (3.3)	25 (3.1)	103 (3.2)
Administrative reason	0	0	0	0	1 (0.1)	1 (0.0)
Protocol deviation/violation	1 (0.1)	2 (0.3)	2 (0.3)	5 (0.2)	3 (0.4)	8 (0.3)
Other	4 (0.5)	3 (0.4)	3 (0.4)	10 (0.4)	6 (0.8)	16 (0.5)
18 to <65 years	**aH5N1c Lot 1 N=403**	**aH5N1c Lot 2 N=399**	**aH5N1c Lot 3 N=397**	**aH5N1c Pooled N=1199**	**Placebo N=398**	**Total N=1597**
All Enrolled Set, n (%)	403 (100)	399 (100)	397 (100)	1199 (100)	398 (100)	1597 (100)
FAS, Immunogenicity	392 (97.3)	387 (97.0)	383 (96.5)	1162 (96.9)	383 (96.2)	1545 (96.7)
FAS-1	386 (95.8)	378 (94.7)	378 (95.2)	1142 (95.2)	376 (94.5)	1518 (95.1)
PPS, Immunogenicity	379 (94.0)	376 (94.2)	361 (90.9)	1116 (93.1)	372 (93.5)	1488 (93.2)
PPS-1	364 (90.3)	359 (90.0)	353 (88.9)	1076 (89.7)	349 (87.7)	1425 (89.2)
Total number exposed	403 (100)	398 (99.7)	397 (100)	1198 (99.9)	398 (100)	1596 (99.9)
Completed protocol	363 (90.1)	359 (90.0	360 (90.7)	1082 (90.2)	363 (91.2)	1445 (90.5)
Primary reason for discontinuation	--	--	--	--	--	--
Adverse event	0	0	2 (0.5)	2 (0.2)	1 (0.3)	3 (0.2)
Death	1 (0.2)	0	0	1 (0.1)	0	1 (0.1)
≥65 years	**aH5N1c Lot 1 N=401**	**aH5N1c Lot 2 N=400**	**aH5N1c Lot 3 N=398**	**aH5N1c Pooled N=1199**	**Placebo N=400**	**Total N=1599**
All Enrolled Set, n (%)	401 (100)	400 (100)	398 (100)	1199 (100)	400 (100)	1599 (100)
FAS, Immunogenicity	395 (98.5)	396 (99.0)	392 (98.5)	1183 (98.7)	393 (98.3)	1576 (98.6)
FAS-1	392 (97.8)	395 (98.8)	391 (98.2)	1178 (98.2)	390 (97.5)	1568 (98.1)
PPS, Immunogenicity	382 (95.3)	371 (92.8)	380 (95.5)	1133 (94.5)	367 (91.8)	1500 (93.8)
PPS-1	365 (91.0)	351 (87.8)	364 (91.5)	1080 (90.1)	351 (87.8)	1431 (89.5)
Total number exposed	401 (100)	399 (99.8)	396 (99.5)	1196 (99.7)	399 (99.8)	1595 (99.7)
Completed protocol	383 (95.5)	382 (95.5)	387 (97.2)	1152 (96.1)	384 (96.0)	1536 (96.1)

Primary reason for discontinuation	--	--	--	--	--	--
Adverse event	0	1 (0.3)	0	1 (0.1)	1 (0.1)	2 (0.1)
Death	3 (0.7)	6 (1.5)	1 (0.3)	10 (0.8)	1 (0.3)	11 (0.7)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 14.1.1.1, 14.1.1.2, and 14.1.1.2.2, and electronic datasets.
Abbreviations: FAS=Full Analysis Set; PPS=Per Protocol Set; FAS-1 and PPS-1=subjects in FAS at Day 43 and PPS at Day 43, respectively.
*ClinicalTrials.gov identifier: NCT02839330
All Enrolled Set (AES): All screened subjects who provided informed consent and demographic and/or other baseline screening assessments, regardless of the subject's randomization and treatment status in the study, and received a subject identification (ID).
Exposed Set (ES): All subjects in the All Enrolled Set who received a study vaccination.
Full Analysis Set (FAS) for immunogenicity: All subjects in the AES who received at least one dose of study vaccination, and provided at least one immunogenicity result (evaluable serum sample) at relevant time points. FAS-1 provided immunogenicity results for Days 1 and 43.
Per Protocol Set (PPS) for immunogenicity: All subjects in the FAS who correctly received the vaccine to which the subject was randomized and at the scheduled time points; had no major protocol deviation leading to exclusion as defined prior to unblinding/analysis; and were not excluded due to other reasons. PPS-1 provided immunogenicity results for Days 1 and 43.
Percentages are based on the numbers of subjects in the All Enrolled Set, as randomized, in each treatment group.

Table 9: Disposition of Subjects and Analysis Populations for Safety by Age and Treatment Group – V89 18, (Exposed Set, as Treated)*

≥18 years	**aH5N1c Lot 1 N=805**	**aH5N1c Lot 2 N=797**	**aH5N1c Lot 3 N=793**	**aH5N1c Pooled N=2395**	**Placebo N=796**	**Total N=3191**
Exposed Set, n (%)	805 (100)	797 (100)	793 (100)	2395 (100)	796 (100)	3191 (100)
Vaccination 1	805 (100)	797 (100)	793 (100)	2395 (100)	796 (100)	3191 (100)
Vaccination 2	783 (97.3)	782 (98.1)	770 (97.1)	2335 (97.5)	779 (97.9)	3114 (97.6)
Solicited Safety Set, Any	791 (98.3)	786 (98.6)	775 (97.7)	2352 (98.2)	784 (98.5)	3136 (98.3)
Vaccination 1	789 (98.0)	785 (98.5)	772 (97.4)	2346 (98.0)	782 (98.2)	3128 (98.0)
Vaccination 2	771 (95.8)	771 (96.7)	762 (96.1)	2304 (96.2)	770 (96.7)	3074 (96.3)
Unsolicited Safety Set, Any	--	--	--	--	--	--
Day 1 – Day 43	805 (100)	797 (100)	793 (100)	2395 (100)	796 (100)	3191 (100)
Day 1 – Day 387	805 (100)	797 (100)	793 (100)	2395 (100)	796 (100)	3191 (100)
Overall Safety Set (solicited and unsolicited)	805 (100)	797 (100)	793 (100)	2395 (100)	796 (100)	3191 (100)
Completed protocol**	747 (92.8)	741 (93.0)	747 (94.2)	2235 (93.3)	746 (93.7)	2981 (93.3)
Randomized but not treated	0	2	2	4	1	5
18 to <65 years	**aH5N1c Lot 1 N=403**	**aH5N1c Lot 2 N=398**	**aH5N1c Lot 3 N=397**	**aH5N1c Pooled N=1198**	**Placebo N=398**	**Total N=1596**
Exposed Set, n (%)	403 (100)	398 (100)	397 (100)	1198 (100)	398 (100)	1596 (100)
Solicited Safety Set, Any	393 (97.5)	388 (97.5)	382 (96.2)	1163 (97.1)	387 (97.2)	1550 (97.1)
Unsolicited Safety Set, Any	--	--	--	--	--	--
Day 1 – Day 43	403 (100)	398 (100)	397 (100)	1198 (100)	398 (100)	1596 (100)
Day 1 – Day 387	403 (100)	398 (100)	397 (100)	1198 (100)	398 (100)	1596 (100)
Overall Safety Set	403 (100)	398 (100)	397 (100)	1198 (100)	398 (100)	1596 (100)
≥65 years	**aH5N1c Lot 1 N=402**	**aH5N1c Lot 2 N=399**	**aH5N1c Lot 3 N=396**	**aH5N1c Pooled N=1197**	**Placebo N=398**	**Total N=1595**
Exposed Set, n (%)	402 (100)	399 (100)	396 (100)	1197 (100)	398 (100)	1595 (100)
Solicited Safety Set, Any	398 (99.0)	398 (99.7)	393 (99.2)	1189 (99.3)	397 (99.7)	1586 (99.4)
Unsolicited Safety Set, Any	402 (100)	399 (100)	396 (100)	1197 (100)	398 (100)	1595 (100)
Day 1 – Day 43	402 (100)	399 (100)	396 (100)	1197 (100)	398 (100)	1595 (100)
Day 1 – Day 387	402 (100)	399 (100)	396 (100)	1197 (100)	398 (100)	1595 (100)
Overall Safety Set	402 (100)	399 (100)	396 (100)	1197 (100)	398 (100)	1595 (100)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 14.1.1.1.1 and 14.1.1.2.1, and electronic datasets.

*ClinicalTrials.gov identifier: NCT02839330
Exposed Set (ES): All subjects in the All Enrolled Set who received a study vaccination.
Solicited Safety Set (SSS): All subjects in the ES who underwent any assessment of solicited local and systemic site reaction and/or assessment of any use of analgesics/antipyretics within seven days post-vaccination (Days 1-7 and/or Days 22-28). In this table, the SSS after any vaccination, vaccination 1 and vaccination 2 exclude the 30-minute post-vaccination observation period. During the 30-minute observation period following any vaccination, a total of n=2395 (100%) and n=796 (100%) of exposed subjects in the pooled aH5N1c and placebo groups, respectively, provided safety data. The SSS for the 30-minute observation periods post-vaccinations were analyzed separately and not shown in the table.
Unsolicited Safety Set (USS): All subjects in the ES who underwent any AE assessment (but did not need to have an AE to be included).
Overall Safety Set (OSS): All subjects in the Solicited Safety Set and/or in the Unsolicited Safety Set.
**Numbers of exposed subjects ≥18 years who completed protocol were the same as for those in the All Enrolled Set except that one subject randomized to placebo actually received aH5N1c, Lot 1. Reasons for discontinuation in exposed subjects ≥18 years (total n=3191) were the same as for the All Enrolled Set (total n=3196) except for n=5 enrolled subjects who were not treated/exposed.
Percentages are based on the numbers of subjects in the All Exposed Set, as treated, in each treatment group.

Of a total of n=3196 enrolled subjects, n=2398 and n=798 were randomized to receive aH5N1c vaccine or placebo, respectively. Five subjects were enrolled and randomized in error due to not meeting eligibility criteria, did not receive any study treatment, were considered protocol deviations, and were excluded from the FAS, PPS, and Safety populations. One subject (≥65 years) randomized to receive placebo actually received aH5N1c vaccine, Lot #1.

A total of 2981 (93.3%) of enrolled subjects completed the protocol while 6.7% terminated early. The primary reasons for subject discontinuation were lost to follow-up (3.2%) and withdrawal by subject (2.2%). Many withdrawals by subject and "other" discontinuations were due to subject relocation. Discontinuations due to AEs occurred in 0.1% and 0.3% of aH5N1c and placebo recipients, respectively. Discontinuations due to deaths occurred in 0.5% and 0.1% of aH5N1 and placebo recipients, respectively.

Protocol Deviations occurred in a total of 384 (12.0%) enrolled subjects and were generally balanced across treatment groups as were the proportions of subjects excluded from immunogenicity analysis populations due to deviations. The most frequent deviation (8.1% of enrolled subjects) was not complying with the blood draw schedule (e.g., drawn outside the pre-specified window). A total of 34 subjects (1.1%) did not meet eligibility criteria, 2.5% did not comply with the vaccination schedule, and 1.2% received either a prohibited concomitant medication or vaccine.

The most common reasons for exclusion from the immunogenicity analyses were "serological results not available" (6.0%) for the Full Analysis Set (FAS) and "did not comply with blood draw schedule" (8.1%) for the Per Protocol Set (PPS).

Reviewer comment: Evaluation of listings and the electronic datasets confirmed the Applicant's report of subject disposition and protocol deviations. Overall, 6.7% of subjects discontinued the study, small percentages due to AEs (0.1%) or death (0.5%). The dropout/discontinuation rates were relatively low, similar across treatment groups, and were unlikely to have significantly impacted the interpretation of immunogenicity or safety results. No individual study site appeared to have a disproportionate number of major protocol deviations.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

A total of 99.8% and 97.4% of enrolled subjects received the first and second vaccinations, respectively. Please see Section 6.1.10.1.3 for a discussion of analysis populations. The PPS-1 was the primary analysis population for the co-primary immunogenicity endpoints. In accordance with the SAP and discussions between the Applicant and CBER, analyses based on the FAS were not conducted because the difference in numbers of subjects between the PPS and FAS was <5%.

Lot-to-Lot Consistency

Lot-to-lot consistency across three consecutively manufactured lots was assessed by comparing the ratios of GMTs of aH5N1c HI titers three weeks after the second vaccination (Day 43). Table 10 shows that lot-to-lot consistency was demonstrated for all three lots (the 2-sided 95% CIs of pairwise comparisons between all three lots fell within the pre-specified equivalence range of >0.667 and <1.5).

Table 10: Adjusted HI GMTs and GMT Ratios for Lot-to-Lot Consistency following the Second Vaccination (Day 43), V89_18 (Per Protocol Set)*

-	Group A	Group B	Group C	GMT Ratio	GMT Ratio	GMT Ratio
-	aH5N1c Lot 1	aH5N1c Lot 2	aH5N1c Lot 3	Lot 1 / Lot 2	Lot 2 / Lot 3	Lot 1 / Lot 3
Day 43	-	-	-	-	-	-
N	729	710	717	-	-	-
GMT**	128.6	127.4	132.2	-	-	-
95% CI	118.9,139.1	117.6,138.0	122.2,143.1	-	-	-
GMT Ratio (95% CI)	-	-	-	1.01 (0.90,1.13)	0.96 (0.86,1.08)	0.97 (0.87,1.09)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 14 and 14.2.1.1.
Abbreviations: HI=hemagglutinin inhibition; GMT=geometric mean titers; N=number of subjects in the Per Protocol Set at Day 43; CI=confidence interval.
*ClinicalTrials.gov identifier: NCT02839330
**GMTs and 95% CIs were adjusted for the covariates of lot, age group (18-64 and ≥65 years), site, and pre-vaccination HI titer.

Percentage of Subjects with HI ≥1:40 at Day 43

Study V89_18 also met the second co-primary endpoint of % HI ≥1:40 against the aH5N1c vaccine strain at Day 43. Table 11 shows that, for aH5N1c recipients (all lots pooled), the LB of the 2-sided 95% CI for subjects 18 to <65 years was 93.4% and for subjects ≥65 years was 83.3%. Subjects in the placebo group did not meet the endpoint (the LB of the 2-sided 95% CI in placebo recipients was 5.9% for subjects 18 to <65 years and 16.6% for subjects ≥65 years).

Table 11: Percentage of Subjects with an HI Titer ≥1:40 at Day 1 and Day 43 by Age Group, V89_18 (Per Protocol Set)*

Age Group	18 to <65 yrs	18 to <65 yrs	≥65 yrs	≥65 yrs
Treatment	**aH5N1c N=1116**	**Placebo N=372**	**aH5N1c N=1133**	**Placebo N=367**
Day 1, N	N=1116	N=372	N=1133	N=367
Day 1 % HI ≥1:40 (95% CI)	13.0 (10.7, 15.6)	15.0 (11.5, 19.4)	27.8 (24.9, 30.9)	24.5 (20.1, 29.6)
Day 43, N	N=1076	N=349	N=1080	N=351

Day 43 **% HI ≥1:40** **(95% CI)**	 95.0 (93.4, 96.2)	 8.5 (5.9, 12.1)	 85.7 (83.3, 87.9)	 20.8 (16.6, 25.8)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 15 and 14.2.1.2.6.1.
Abbreviations: HI=hemagglutinin inhibition; %HI ≥1:40=percentage of subjects with post-vaccination HI titer of at least 1:40; N=number of subjects in the Per Protocol Set at the specified time point; CI=confidence interval.
*ClinicalTrials.gov identifier: NCT02839330
%HI ≥1:40 and 95% CIs were adjusted for site.
Success criteria for %HI ≥1:40: For subjects 18 to <65 years, the lower bound (LB) of the 95% CI for the % HI ≥40 must be ≥70%; for subjects ≥65 years, the LB of the 95% CI for the % HI ≥40 must be ≥60%.

Reviewer comment: The aH5N1c vaccine met the pre-specified co-primary endpoints required to demonstrate an adequate immune response in subjects ≥18 years as determined by age-specific success criteria. Unadjusted analyses of GMTs, GMT ratios, and %HI ≥1:40 also met immune response criteria (V89_18 CSR Tables 14.2.1.1, 14.2.1.2.6, and 14.2.1.2.6.1). The sponsor chose to use unadjusted estimates for the %HI ≥1:40 in the package insert (PI). Because differences between adjusted and unadjusted results were small and not clinically significant, the statistical reviewer stated that either result would be appropriate to use in the PI. During labeling discussions, the review team felt that the pre-specified endpoints were more appropriate to include in the PI and asked Seqirus to revise the PI accordingly or provide a rationale for using unadjusted secondary endpoint results rather than the pre-specified adjusted %HI ≥1:40 results.

6.1.11.2 Analyses of Secondary Endpoints

Secondary immunogenicity endpoints were based on HI antibody responses elicited by study vaccine to the homologous H5N1 strain, and included GMTs, % HI ≥1:40, and SCRs at various time points, overall and by age group.

Table 12 presents analyses of GMTs at baseline (Day 1) and Day 43 by treatment and age group (Day 22 and Day 183 results not shown). Baseline GMTs were slightly higher in subjects ≥65 years (20.5-20.6) as compared to subjects 18 to <65 years (13.5-13.7). Within age groups, baseline HI GMTs were similar between aH5N1c and placebo groups. After vaccination with aH5N1c, in both age groups, GMTs increased at Day 22 and increased further at Day 43. At Day 43, the increase in GMTs relative to baseline as measured by the geometric mean ratio (GMR, data not shown) was more than twice as high in aH5N1c recipients 18 to <65 years (GMR 12.70) as compared to aH5N1c recipients ≥65 years (GMR 4.90). By Day 183, GMTs returned to baseline in aH5N1c recipients ≥65 years but remained slightly above baseline in aH5N1c recipients 18 to <65 years. GMTs did not increase following vaccinations in placebo recipients. Please see V89_18 CSR Tables 16, 17, 14.2.1.4, and 14.2.1.4.6 for additional information.

Table 12: HI GMTs Pre- and Postvaccination (Day 43) by Age Group – V89_18 (Per Protocol Set)*

Age group	**18 to <65 yrs**	**18 to <65 yrs**	**≥65 years**	**≥65 years**
Treatment	**aH5N1c**	**Placebo**	**aH5N1c**	**Placebo**
Day 1 GMT** (95% CI)	N=1116 13.5 (12.8,14.2)	N=372 13.7 (12.5,15.0)	N=1133 20.5 (19.4,21.8)	N=367 20.6 (18.6,22.7)
Day 43 GMT** (95% CI)	N=1076 170.7 (160.5,181.6)	N=349 11.0 (9.9,12.2)	N=1080 97.9 (92.1,104.1)	N=351 16.7 (15.0,18.5)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 17 and 14.2.1.4.6.

Abbreviations: HI=hemagglutination inhibition; GMT=geometric mean titer; CI=confidence interval; N=number of subjects in the Per Protocol Set at the specified time point.
*ClinicalTrials.gov identifier: NCT02839330
**GMTs and 95% CIs adjusted for treatment, site, and (Day 1) pre-vaccination titer.

Secondary analyses of %HI ≥1:40 (data not shown) indicated that a single vaccination with aH5N1c was insufficient to meet immune response criteria at Day 22 (the LBs of the 95% CIs for subjects 18 to <65 years and ≥65 years were 60.1% and 52.6%, respectively), and that the %HI ≥1:40 at Day 183 was ~30% (the LB of the 95% CIs for subjects 18 to <65 years and ≥65 years were 31.3% and 28.1%, respectively). Placebo recipients did not meet immune response criteria for %HI ≥1:40 at any time point post-injections. Please see V89_18 CSR Tables 19, 20, 14.2.1.2, and 14.2.1.2.6 for additional information.

Reviewer comment: Primary analyses of the %HI ≥1:40 were adjusted for site while secondary analyses of the %HI ≥1:40 were unadjusted and only slightly different (the LB of the 95% CI was 91.4% for subjects 18 to <65 years and 81.2% for subjects ≥65 years). The Applicant proposed using the unadjusted rates (from the secondary analyses) in the PI but, at CBER's request, agreed to replace unadjusted %HI ≥1:40 (secondary analyses) in the draft PI with results from the pre-specified adjusted primary analyses.

Analyses of SCRs showed that aH5N1c recipients in both age groups met the pre-specified criteria for seroconversion after two vaccinations (Day 43, presented in Table 13) but not after a single vaccination (Day 22). By Day 183, neither age group met criteria for seroconversion. SCRs in aH5N1c recipients 18 to <65 years were higher as compared to ≥65 years at all time points. Placebo recipients did not achieve seroconversion. Please see V89_18 CSR Tables 23 and 14.2.1.3.6 for additional information.

Table 13: Seroconversion Rates after Two Vaccinations (Day 43) by Age Group, V89_18 (Per Protocol Set)*

Age Group		**18 to <65 yrs**	**18 to <65 yrs**	**≥65 yrs**	**≥65 yrs**
Treatment		**aH5N1c N=1076**	**Placebo N=349**	**aH5N1c N=1080**	**Placebo N=351**
Day 43 SCR (95% CI)		79.9 (77.4, 82.3)	0.3 (0.0, 1.6)	54.0 (51.0, 57.0)	1.7 (0.6, 3.7)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 23 and 14.2.1.3.6.
Abbreviations: N=number of subject in the Per Protocol Set at Day 43; SCR=seroconversion rate; CI=confidence interval.
*ClinicalTrials.gov identifier: NCT02839330
Seroconversion=either a prevaccination (baseline) HI titer <1:10 and a postvaccination HI titer ≥1:40, or a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer.
Success criteria for seroconversion: For subjects 18 to <65 years, the lower bound (LB) of the 95% CI for the SCR must be ≥40%; for subjects ≥65 years, the LB of the 95% CI for the SCR must be ≥30%.

Reviewer comment: Immune responses as measured by HI GMTs, %HI ≥1:40, and SCRs were inversely related to age, consistent with immunoscenescence. Although subjects were considered immunologically naïve to the H5N1 virus, baseline GMTs were above zero, possibly explaining why %HI ≥1:40 and SCRs were not equal within treatment and age groups, and were higher in subjects ≥65 years than in subjects 18 to <65 years. The larger difference in SCRs as compared to the difference in %HI ≥1:40 between age cohorts may have been due to higher

baseline GMTs in subjects ≥65 years making a 4-fold rise (seroconversion) more difficult to achieve than in the older age group.

Reviewer comment: Because the study population was considered immunologically naïve to influenza A/H5N1 viruses, baseline GMTs higher than zero (13.5-20.6) and baseline %HI ≥1:40 in the range of 13%-27.8% appeared unexpected to the clinical review team. This issue was discussed with the statistical and CMC assay reviewers and DVP who indicated that elevated A/H5N1 HI titers are sometimes seen at baseline especially in older individuals. Although they could not identify a specific cause for the baseline GMT elevations, the CMC reviewers indicated that elevations may be due in part to non-specific properties of the HI assay such as serologic variability due to use of different red blood cell lots (for agglutination inhibition), some uncertainty around measurements of the lower limit of quantitation (LLOQ) (individual titers below the LLOQ were set to half of the lower limit), or to factors related to conduct of the assay in the laboratory. CMC/DVP stated that the difference in baseline titers between young subjects and older adults likely reflects some cross-reactivity of antibodies against seasonal strains rather than being indicative of unrecognized prior exposure to avian influenza A/H5N1 viruses or a problem with the HI assay. DVP indicated that previous studies have observed a phenomenon of positive baseline HI or MN titers against AH5N1 viruses in older adults and have postulated that baseline seropositivity may be due to immunologic cross-reactivity resulting from repeated exposure to seasonal influenza viruses and/or vaccinations. According to the CMC reviewers, the HI assay validation was acceptable, and the baseline GMTs were not significantly elevated and should not negatively impact the ability to interpret immunogenicity results, including the use of the % HI ≥1:40 primary endpoint in determining the effectiveness of the aH5N1c vaccine. The review team also noted that elevated baseline HI titers made it more difficult to achieve a 4-fold postvaccination rise in titer (i.e., seroconversion) and that both age cohorts met the secondary SCR endpoint. Additionally, secondary analyses of SCRs according to baseline HI titer of <1:10 or ≥1:10 (described below this comment) showed that both groups met the SCR endpoint. Consistent immunogenicity results across the Phase 2 and Phase 3 studies also suggested that the data were robust.

Descriptive secondary analyses were also conducted according to whether the baseline HI titer was <1:10 or ≥1:10. For aH5N1c recipients ≥18 years (PPS), results showed that:

- the % HI ≥1:40 at Day 43 was higher in subjects with a baseline HI titer ≥1:10 (91.3%) than in those with a baseline titer <1:10 (82.6%), and
- the SCR at Day 43 was higher in subjects with a baseline HI titer <1:10 (82.6%) than in those with a baseline titer ≥1:10 (58.8%).

The differences between groups were statistically significant (non-overlapping 95% CIs).

Secondary analyses conducted according to whether aH5N1c recipients ≥18 years (PPS) had received a seasonal influenza vaccine in the previous 12 months showed slightly higher GMTs (162.5 vs 108.2), % HI ≥1:40 (91.3% vs 85.7%), and SCRs (74.5% vs 60.4%) at Day 43 in previously unvaccinated subjects as compared to previously vaccinated subjects, respectively. The differences were small but statistically significant (non-overlapping 95% CIs).

Reviewer comment: The influence of baseline HI titer on immune responses have been observed in other studies of influenza vaccines. The effect of previous seasonal influenza vaccination on the immune response is complex, incompletely understood, and is an active area of research.

6.1.11.3 Subpopulation Analyses

Subpopulation analyses of immunogenicity conducted by sex, race and ethnicity were pre-specified secondary descriptive analyses and were not powered for statistical hypothesis testing.

Sex

Males and females comprised 44.5% and 55.5%, respectively, of the overall PPS (n=2988). Post-vaccination immune responses were similar between sexes in each treatment group. Immune responses at Day 43 in male and female aH5N1c recipients, respectively, were as follows: GMTs (129.7 vs 131.0); % HI ≥1:40 (86.9% vs 89.5%); and SCRs (64.7% vs 68.7%).

Race

The majority of subjects in the PPS (n=2988) were white (84.4%) or black/African American (13.2%) while other racial groups each comprised ≤1.2% of the PPS. Small sample sizes precluded meaningful sub-analyses of immune responses to the aH5N1c vaccine at Day 43 other than for white (n=1828) and black/African American race (n=276). For these two subgroups, blacks/African Americans showed numerically higher GMTs (207.0 vs 122.7), %HI ≥1:40 (95.3% vs 87.1%), and SCRs (77.2% vs 65.2%), all with non-overlapping 95% CIs (data not shown), as compared to whites.

Ethnicity

The majority of subjects in the PPS (n=2988) were non-Hispanic (91.7%) while Hispanic/Latino subjects comprised 7.3% of the PPS. At Day 43, Hispanic/Latino subjects showed numerically higher GMTs (200.0 vs 126.5, non-overlapping 95% CIs), SCRs (80.0% vs 65.9%, non-overlapping 95% CIs), and %HI ≥1:40 (91.3% vs 88.1%, overlapping 95% CIs), as compared to non-Hispanic/Latinos.

6.1.11.4 Dropouts and/or Discontinuations

Please see Sections 6.1.9, Statistical Considerations and Statistical Analysis Plan, and 6.1.10.1.3, Subject Disposition. Dropouts were not replaced and missing data were not imputed. Within age groups, discontinuation rates and reasons for discontinuation were similar between treatment groups and were unlikely to introduce bias or impact interpretation of immunogenicity results.

6.1.11.5 Exploratory and Post Hoc Analyses

Additional analyses of immunogenicity according to age subgroups 18-49 years, 50-64 years, 65-69 years, and ≥70 years, and according to study site followed patterns observed in the overall study population. Similar to sub-analyses according to age 18 to <65 years and ≥65 years described in Section 6.1.11.2, post-vaccination GMTs according to additional age subgroups were inversely related to age.

6.1.12 Safety Analyses

6.1.12.1 Methods

The Overall Safety Set (OSS) was used to summarize all safety data. The OSS was comprised of 3191 subjects, including 2395 and 796 who were vaccinated with aH5N1c and placebo, respectively. Most subjects (n=3114, 97.6%) received both vaccinations. Data were analyzed according to actual treatment received.

Following each vaccination, subjects were observed by study staff for vital signs and AEs for at least 30 minutes as described in Section 6.1.2. Solicited AEs in the SSS were actively collected via a diary card from 30 minutes through seven days following each vaccination (Days 1 through 7 and Days 22 through 28). Because rates of solicited AEs following influenza vaccination have been observed to differ between younger adult and elderly populations (e.g., generally lower in the elderly), analyses of Solicited AEs following any vaccination are presented for the SSS by age group. All Solicited AEs were considered related to study product. The OSS was used to summarize unsolicited AEs and SAEs, overall and by age group. All Unsolicited AEs (including SAEs, MAAEs, NOCDs, and AESIs) were passively collected from Day 1 through the end of the study (Day 387). This review will summarize all non-serious Unsolicited AEs reported through 21 days after the second vaccination (Day 1 through Day 43), overall and by age group. All SAEs, MAAEs, NOCDs, and AESIs reported from Day 1 through Day 387 will be presented, overall and by age group.

Table 14 presents an overview of the safety analysis sets.

Table 14: Safety Analysis Sets Overall and by Age Groups (Exposed Set, As Treated) – V89_18*

Age Group	**≥18 yrs**	**≥18 yrs**	**≥18 yrs**	**18 to <65 yrs**	**18 to <65 yrs**	**18 to <65 yrs**	**≥65 yrs**	**≥65 yrs**	**≥65 yrs**
Treatment Group	**aH5N1c N=2395 n (%)**	**Placebo N=796 n (%)**	**Total N=3191 n (%)**	**aH5N1c N=1198 n (%)**	**Placebo N=398 n (%)**	**Total N=1596 n (%)**	**aH5N1c N=1197 n (%)**	**Placebo N=398 n (%)**	**Total N=1595 n (%)**
Exposed Set	2395 (100)	796 (100)	3191 (100)	1198 (100)	398 (100)	1596 (100)	1197 (100)	398 (100)	1595 (100)
ES-1	2395 (100)	796 (100)	3191 (100)	1198 (100)	398 (100)	1596 (100)	1197 (100)	398 (100)	1595 (100)
ES-2	2335 (97.5)	779 (97.9)	3114 (97.6)	1159 (96.7)	385 (96.7)	1544 (96.7)	1176 (98.2)	394 (99.0)	1570 (98.4)
**OSS, USS 1-43, and USS 1-387	2395 (100)	796 (100)	3191 (100)	1198 (100)	398 (100)	1596 (100)	1197 (100)	398 (100)	1595 (100)
Solicited Safety Set – Any	2352 (98.2)	784 (98.5)	3136 (98.3)	1163 (97.1)	387 (97.2)	1550 (97.1)	1189 (99.3)	397 (99.7)	1586 (99.4)
Completed Protocol	2235 (93.3)	746 (93.7)	2981 (93.4)	1082 (90.2)	363 (91.2)	1445 (90.5)	1153 (96.3)	383 96.2)	1536 (96.1)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 30, 31, 14.1.1.1.1, 14.1.1.2.1, and 14.1.1.2.2 and electronic datasets.
Abbreviations: N=total number of subjects; n=number of subjects with values in categories; ES=Exposed Set; ES-1 and ES-2=Exposed Set after 1st and 2nd vaccinations, respectively; SSS=Solicited Safety Set;USS=Unsolicited Safety Set; USS 1-43=USS Days 1-43; USS 1-387=USS Days 1-387.
*ClinicalTrials.gov identifier: NCT02839330
**Because the numbers of subjects in the ES, OSS, and USS (both Days 1-43 and 1-387) were identical, they are not shown as separate rows in the table.
Exposed Set (ES): All subjects in the All Enrolled Set who received a study vaccination.
Solicited Safety Set (SSS): All subjects in the ES who underwent any assessment of local and systemic site reaction and/or assessment of any use of analgesics/antipyretics within seven days post-vaccination (Days 1-7 and/or Days 22-28). In this table, the SSS after any vaccination excludes the 30-minute post-vaccination observation period. During the 30-minute observation period following any vaccination, a total of

n=2395 (100%) and n=796 (100%) of exposed subjects in the pooled aH5N1c and placebo groups, respectively, provided safety data. The SSS for the 30-minute observation periods post-vaccinations were analyzed separately and not shown in the table.
Unsolicited Safety Set (USS): All subjects in the ES who underwent any AE assessment (but did not need to have an AE to be included).
Overall Safety Set (OSS): All subjects in the Solicited Safety Set and/or in the Unsolicited Safety Set.

Reviewer comment: The V89_18 Exposed Set, Overall Safety Set and Unsolicited Safety Set for Days 1-43 and Days 1-387 were identical. Therefore, although the V89_18 CSR labels unsolicited AE tables as based on the Unsolicited Safety Set, they are essentially based on the (identical) ES or OSS.

Reviewer comment: Safety analysis populations were confirmed by evaluation of the electronic datasets. Among subjects enrolled and randomized, n=5 were not treated. Most subjects (93.4%) completed the protocol.

6.1.12.2 Overview of Adverse Events

Table 15 summarizes the occurrence of all solicited and unsolicited AEs by treatment group, overall and by age groups. Rates of unsolicited AEs (through 21 days after any vaccination) and long-term safety events (through study termination) between pooled aH5N1c and placebo groups were generally similar except for the rates of solicited AEs which occurred more frequently in aH5N1c vaccine recipients.

Table 15: Summary of Solicited and Unsolicited Adverse Events by Age and Treatment Groups (Solicited and Overall Safety Sets) – V89_18*

Age Group	**≥18 yrs**	**≥18 yrs**	**18 to <65 yrs**	**18 to <65 yrs**	**≥65 yrs**	**≥65 yrs**
Treatment Group	**aH5N1c N=2395**	**Placebo N=796**	**aH5N1c N=1198**	**Placebo N=398**	**aH5N1c N=1197**	**Placebo N=398**
Solicited Safety Set, N	**N=2352**	**N=784**	**N=1163**	**N=387**	**N=1189**	**N=397**
Overall Safety Set, N	**N=2395**	**N=796**	**N=1198**	**N=398**	**N=1197**	**N=398**
% subjects with AE	**%**	**%**	**%**	**%**	**%**	**%**
Any Solicited AE[1]	59.7	38.0	70.5	45.5	49.0	30.7
Any Solicited local AE[1]	50.2	14.7	64.4	19.9	36.3	9.6
Any Solicited systemic AE[1]	38.2	32.8	44.0	38.5	32.5	27.2
Any Unsolicited AE[2]	23.4	22.2	20.0	21.4	26.8	23.1
Any related Unsolicited AE[2]	7.0	6.2	5.9	5.5	8.1	6.8
Any SAE[3]	6.7	9.3	2.9	3.3	10.5	15.3
Any related SAE[3]	0	0.3	0	0	0	0.5
Any withdrawal due to AE[3]	0.5	0.4	0.3	0.3	0.8	0.5
Any MAAE[3]	46.5	46.0	39.0	37.2	54.1	54.8
Any NOCD[3]	9.5	9.2	7.8	5.0	11.2	13.3
Any AESI[3]	0.3	0.9	0.1	0	0.5	1.8
Any Death[3]	0.5	0.1	0.1	0	0.8	0.3

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 32, 33, 34, 35, 14.3.1.1, 14.3.1.1.1, 14.3.1.13, 14.3.1.13.1, 14.3.1.16, 14.1.3.16.1, 14.3.2.1, 14.3.2.1.1, 14.3.2.2, 14.3.2.2.1, 14.3.2.3, 14.3.2.3.1, 14.3.2.4, 14.3.2.4.1, 14.3.2.6, 14.3.2.6.1, 14.3.2.7, 14.3.2.7.1, 14.3.2.8, and 14.3.2.8.1.
Abbreviations: N=number of subjects in denominator; AE=adverse event; SAE=serious adverse event; MAAE=medically-attended adverse event; NOCD=new onset of chronic disease; AESI=adverse event of special interest.
*ClinicalTrials.gov identifier: NCT02839330
Percentages are based on number of subjects in each group. Denominators are based on the Overall Safety Set (OSS) except for solicited AEs which are based on Solicited Safety Set. The OSS included all subjects in the Solicited Safety Set and Unsolicited Safety Set and was equivalent to both the Exposed Set and Unsolicited Safety Set.
Solicited Safety Set (SSS): All subjects in the Exposed Set who underwent any assessment of local and systemic site reaction and/or assessment of any use of analgesics/antipyretics within seven days post-

vaccination (Days 1-7 and/or Days 22-28). In this table, the SSS after any vaccination (vaccination 1 and vaccination 2) exclude the 30-minute post-vaccination observation period.
1Solicited AEs collected in the seven days after each vaccination.
2Non-serious unsolicited AEs collected in the 21 days after each vaccination.
3Deaths, SAEs, AESIs, NOCDs, MAAEs, and AEs leading to withdrawal collected through 12 months after the second vaccination (Day 387).

Solicited Adverse Events

The SSS after any vaccination was derived from data recorded on the solicited AE diary card and was comprised of n=2352 aH5N1c recipients (18 to <65 years n=1163; ≥65 years, n=1189) and n=784 placebo recipients (18 to <65 years, n=387; ≥65 years, n=397). Overall, 98% and 96.4% of subjects returned diary cards after the first and second vaccinations, respectively, similar between treatment groups. Tables 16 and 17 present the rates of solicited local and systemic AEs by treatment, age, and severity. Among all subjects ≥18 years, injection site pain was the most frequent solicited local AE, occurring in 49.9% and 14.7% of aH5N1c and placebo recipients, respectively. Other local AEs occurred in <1% of subjects in both treatment groups. Among all subjects, solicited systemic AEs were less frequently reported than injection site reactions. The most frequent systemic symptoms among aH5N1c and placebo recipients ≥18 years, respectively, were fatigue (22.2% vs 20.4%), headache (19.9% vs 19.3%), and malaise (19.0% vs 11.9%). Rates of systemic AEs were generally similar between treatment groups except for malaise (aH5N1c 19.0% vs placebo 11.9%). In both aH5N1c and placebo groups, the frequencies of solicited local and systemic AEs were lower after the second vaccination than after the first vaccination.

Solicited Local Adverse Events by Age Group

Table 16 summarizes the frequencies of solicited local AEs reported in the seven days following any vaccination, excluding the 30 minute observation period, by treatment, age group, and maximum severity.

Table 16: Solicited Local Adverse Events Occurring on Day 1 through Day 7 after Any Vaccination (excluding 30 minute post-vaccination observation period) by Age, Treatment and Maximum Severity (Solicited Safety Set) – V89_18*

Age Group	Age Group	18-64yr	18-64yr	≥65yr	≥65yr	≥18yr	≥18yr
Treatment	Treatment	aH5N1c N=1163	PBO N=387	aH5N1c N=1189	PBO N=397	aH5N1c N=2352	PBO N=784
Solicited Local AE	Severity	%	%	%	%	%	%
Any Local AE	Any	64.4	19.9	36.3	9.6	50.2	14.7
Any after Dose 1	Any	57.3	14.8	29.4	5.8	43.2	10.2
Any after Dose 2	Any	44.8	10.6	23.4	4.3	33.9	7.4
Ecchymosis	Any Grade 1-3	0.3	0	0.6	0.3	0.4	0.1
Ecchymosis	Grade 3	0	0	0	0	0	0
Induration	Any Grade 1-3	0.4	0	0.7	0	0.6	0
Induration	Grade 3	0	0	0	0	0	0
Erythema	Any Grade 1-3	0.6	0	0.4	0	0.5	0
Erythema	Grade 3	0.1	0	0	0	0	0
Pain	Any Grade 1-3	64.1	19.9	35.9	9.6	49.9	14.7
Pain	Grade 3	0.3	0.3	0	0	0.2	0.1

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 37, 14.3.1.1, 14.3.1.1.1, 14.3.1.2, and 14.3.1.2.1.
Abbreviations: PBO=placebo; n/a=not applicable.
*ClinicalTrials.gov identifier: NCT02839330
Percentages are based on number of subjects in each group. Denominators are based on the Solicited Safety Set (SSS) which included all subjects in the Exposed Set who underwent any assessment of local and systemic site reaction and/or assessment of any use of analgesics/antipyretics within seven days post-

vaccination (Days 1-7 and/or Days 22-28). In this table, the SSS after any vaccination (vaccination 1 and vaccination 2) exclude the 30-minute post-vaccination observation period.
Scale for measured local AEs: Grade 0: <25mm; Grade 1: 25-50mm; Grade 2: 51-100mm; Grade 3: >100mm.

In both age groups, injection site pain was the most frequently reported solicited local reaction and was reported more frequently by aH5N1c recipients as compared to placebo and by subjects in the younger age group (18 to <65 years 64.1% vs 19.9%; ≥65 years 35.9% vs 9.6%, respectively). Most pain was mild in severity. Severe pain occurred in 0.3% of subjects 18 to <65 years and in no subjects ≥65 years. The mean duration of pain following either vaccination was <2 days across age and treatment groups. In both age groups, other local reactions of any severity grade occurred in <1% of subjects in each treatment group.

Reviewer comment: Evaluation of the electronic datasets indicated that the numbers and percentages of subjects who reported local reactions, overall and by maximum severity, were identical to the Applicant's report.

Solicited Systemic Adverse Events

Table 17 summarizes solicited systemic AEs reported after any vaccination, excluding the 30-minute observation period, by treatment, age group, and maximum severity.

Table 17: Solicited Systemic Adverse Events Occurring on Day 1 through Day 7 after Any Vaccination (excluding 30 minute post-vaccination observation period) by Age Group and Maximum Severity (Solicited Safety Set) – V89_18*

Age Group	Age Group	18-64yr	18-64yr	≥65yr	≥65yr	≥18yr	≥18yr
Treatment	Treatment	aH5N1c N=1163	PBO N=387	aH5N1c N=1189	PBO N=397	aH5N1c N=2352	PBO N=784
Solicited Systemic AE	Severity	%	%	%	%	%	%
Any Systemic AE	Any	44.0	38.5	32.5	27.2	38.2	32.8
Any after Dose 1	Any	36.3	31.9	25.2	20.2	30.7	26.0
Any after Dose 2	Any	24.4	21.0	18.3	16.3	21.3	18.6
Nausea	Any	10.1	10.9	7.4	6.3	8.7	8.5
Nausea	Grade 3	0.3	1.6	0.3	0.3	0.3	0.9
Fatigue	Any	24.8	21.4	19.7	19.4	22.2	20.4
Fatigue	Grade 3	0.9	1.6	0.4	1.0	0.7	1.3
Myalgia	Any	14.4	11.4	9.4	8.3	11.9	9.8
Myalgia	Grade 3	0.4	0.3	0.3	0.5	0.3	0.4
Arthralgia	Any	10.4	9.3	9.9	8.8	10.2	9.1
Arthralgia	Grade 3	0.6	0.5	0.4	0	0.5	0.3
Headache	Any	24.5	22.7	15.5	15.9	19.9	19.3
Headache	Grade 3	1.0	2.3	0.2	0	0.6	1.1
Chills	Any	4.2	4.4	4.4	3.3	4.3	3.8
Chills	Grade 3	0.1	0.5	0.3	0.8	0.2	0.6
Malaise	Any	22.1	12.1	16.1	11.6	19.0	11.9
Malaise	Grade 3	0.5	1.8	0.3	0.8	0.4	1.3
Loss of appetite	Any	8.1	9.3	5.7	5.8	6.9	7.5
Loss of appetite	Grade 3	0.2	0.8	0.1	0	0.1	0.4
Fever	Any	0.6	2.3	0.7	0.3	0.6	1.3
Fever	Grade 1	0.3	1.8	0.4	0.3	0.4	1.0
Fever	Grade 2	0	0.5	0.1	0	0.0	0.3
Fever	Grade 3	0.1	0	0.2	0	0.1	0
Fever	Grade 4	0.2	0	0	0	0.1	0

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 37, 14.3.1.1, 14.3.1.1.1, 14.3.1.2, 14.3.1.2.1, 14.3.1.4, and 14.3.1.4.1.
Abbreviations: PBO=placebo
*ClinicalTrials.gov identifier: NCT02839330
Percentages are based on number of subjects in each group. Denominators are based on the Solicited Safety Set (SSS) which included all subjects in the Exposed Set who underwent any assessment of local and systemic site reaction and/or assessment of any use of analgesics/antipyretics within seven days post-vaccination (Days 1-7 and/or Days 22-28). In this table, the SSS after any vaccination (vaccination 1 and vaccination 2) exclude the 30-minute post-vaccination observation period.
Grading scale for body temperature: The statistical analysis plan specified that body temperature would be analyzed by two methods: 1) as None (<38.0°C, <100.4°F) or Any (≥38.0°C, ≥100.4°F); and 2) in 0.5°C increments. The toxicity grading scale for fever used in this review is as follows: Grade 0: <38.0°C (<100.4°F); Grade 1: 38.0°C -38.4°C (100.4°F-101.1°F); Grade 2: 38.5°C-38.9°C (101.2°F-102.0°F); Grade 3: 39.0°C to ≤40.0°C (102.1°F to ≤104.0°F); Grade 4: >40.0°C (>104.0°F).

Reviewer comment: The V89_18 protocol (Appendix 16.1.1, sub-Appendix C) and the Integrated Summary of Safety (ISS) defined Grade 3 fever as 102.1°F to ≤104°F (39.0°C to ≤40°C), and Grade 4 fever as >104°F (>40°C). However, the protocol, statistical analysis plan (SAP), and CSR indicated that body temperature would be analyzed by two methods: 1) as None (<38.0°C, <100.4°F) or Any (≥38.0°C, ≥100.4°F); and 2) in 0.5°C increments. The 0.5°C increments, as defined in the SAP and reported in Section 14 of the CSR, included the categories of ≥39.0°C to <39.5°C, ≥39.5°C to <40.0°C, and ≥40.0°C, which differs slightly from the toxicity grading scale with respect to 40.0°C. This review will use the toxicity grading scale as pre-defined and categorize temperatures of 40.0°C (104.0°F) as Grade 3. The discrepancy between the toxicity grading scale and the actual categorization of a temperature of 40.0°C (104.0°F) in the safety analyses was not an issue in this study because no subject had a maximum solicited temperature of exactly 40.0°C.

Among subjects 18 to <65 years, the most common (≥10%) solicited systemic AEs reported by either aH5N1c or placebo recipients, respectively, were fatigue (24.8% vs 21.4%), headache (24.5% vs 22.7%), malaise (22.1% vs 12.1%), myalgia (14.4% vs 11.4%), arthralgia (10.4% vs 9.3%), and nausea (10.1% vs 10.9%). Fever was infrequent, occurring in 0.6% and 2.3% of aH5N1c and placebo recipients, respectively. Most systemic symptoms were mild to moderate (Grades 1 or 2) in severity. Severe symptoms occurred in ≤1.0% and ≤2.3% of aH5N1c and placebo recipients, respectively. One aH5N1c recipient (0.1%) 18 to <65 years had a Grade 3 fever (102.1°F to ≤104.0°F as categorized by the protocol toxicity grading scale; 102.1°F to <104.0°F as categorized by the SAP and CSR analyses) and two aH5N1c recipients (0.2%) had fever ≥104.0°F. No placebo recipients had fever Grade 3 or higher in the seven days post-vaccination. Most subjects reported onset of symptoms in the first three days post-vaccinations. The duration of symptoms in both treatment groups was generally <3 days.

Among subjects ≥65 years, the most common (≥10%) solicited systemic AEs reported by either aH5N1 or placebo recipients, respectively, were fatigue (19.7% vs 19.4%), malaise (16.1% vs 11.6%) and headache (15.5% vs 15.9%). Most symptoms were mild to moderate in severity. Severe symptoms occurred in 0.4% and 0.8% of aH5N1c and placebo recipients, respectively. Two aH5N1c recipients (0.2%) and no placebo recipients had Grade 3 fever as categorized by SAP and CSR analyses (102.1°F to <104.0°F). Most subjects reported onset of symptoms in the first three days post-vaccinations. The duration of systemic symptoms in both treatment groups was generally <3 days.

As compared to aH5N1c recipients ≥65 years, aH5N1c recipients 18 to <65 years experienced more injection site pain (64.1% vs 35.9%), headache (24.5% vs 15.5%), fatigue (24.8% vs 19.7%), malaise (22.1% vs 16.1%), myalgia (14.4% vs 9.4%), and to a lesser extent, nausea (10.1% vs 7.4%), and loss of appetite (8.1% vs 5.7%). Placebo recipients 18 to <65 years also reported more injection site pain than placebo recipients ≥65 years (19.9% vs 9.6%) as well as somewhat higher rates of systemic AEs, particularly headache (22.7% vs 15.9%), suggesting that younger subjects were generally more likely to report systemic symptoms.

Antipyretic or analgesic use to treat fever or pain was greater in aH5N1c recipients 18 to <65 years (4.3%) as compared to placebo recipients 18 to <65 years (1.6%), or as compared to aH5N1c and placebo recipients ≥65 years (1.9% and 0.8%, respectively).

Reviewer comment: Evaluation of the electronic datasets indicated that the numbers and percentages of subjects who reported solicited systemic AEs, overall and by maximum severity, were identical to the Applicant's report.

Unsolicited Adverse Events (Day 1 through Day 43)
Only treatment emergent AEs (TEAE), i.e., those that began or were exacerbated after exposure to study treatment, were included in the analyses of unsolicited AEs. Multiple occurrences of the same AE were counted only once per subject. Table 18 presents the percentage of subjects who reported unsolicited AEs with a frequency of at least 1% in any treatment group in the 21 days after any vaccination according to age and treatment group, as categorized by MedDRA PT and SOC, version 20.0.

Table 18: Unsolicited Adverse Events Reported by ≥1% of Subjects in Any Treatment Group in the 21 Days following Any Vaccination (Day 1 through Day 43) by Age and Treatment Group (Unsolicited Safety Set) – V89 18*

Age group	**≥18 yrs**	**≥18 yrs**	**18 to <65 yrs**	**18 to <65 yrs**	**≥65 yrs**	**≥65 yrs**
Treatment	**aH5N1c N=2395**	**Placebo N=796**	**aH5N1c N=1198**	**Placebo N=398**	**aH5N1c N=1197**	**Placebo N=398**
Subjects with any AE, %	23.4	22.2	20.0	21.4	26.8	23.1
Grade 1 (mild), %	16.5	15.2	14.0	14.6	19.0	15.8
Grade 2 (moderate), %	9.5	9.0	8.2	8.0	10.9	10.1
Grade 3 (severe), %	1.5	1.9	1.2	1.8	1.9	2.0
Subjects with any related AE, % [1]	7.0	6.2	5.9	5.5	8.1	6.8
Subjects with Grade 3 AE assessed as related,[1] %	0.3	0.6	0.4	1.0	0.3	0.3
System Organ Class Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Cardiac disorders	-	-	-	-	0.6	1.0
Gastrointestinal disorders	2.6	3.4	2.3	3.5	2.9	3.3
Diarrhoea	-	-	0.6	1.3	1.2	0.5
Nausea	-	-	0.6	1.0	-	-
General disorders and administration site conditions	5.4	5.0	4.1	4.0	6.7	6.0
Fatigue	1.9	1.5	1.6	1.5	2.2	1.5
Injection site bruising	1.6	1.6	1.0	1.5	2.3	1.8
Discomfort	-	-	-	-	1.0	0.5
Infections and infestations	6.0	6.5	4.8	5.3	7.1	7.8
Urinary tract infection	0.9	1.6	0.8	1.5	1.1	1.8
Viral upper respiratory tract infection	1.0	0.4	1.0	0.5	1.0	0.8

Age group	≥18 yrs	≥18 yrs	18 to <65 yrs	18 to <65 yrs	≥65 yrs	≥65 yrs
Treatment	**aH5N1c N=2395**	**Placebo N=796**	**aH5N1c N=1198**	**Placebo N=398**	**aH5N1c N=1197**	**Placebo N=398**
Injury, poisoning and procedural complications	2.6	2.0	2.3	2.5	2.9	1.5
Metabolic and nutrition disorders	1.3	0.9	1.4	1.0	1.2	0.8
Decreased appetite	-	-	0.8	1.0	-	-
Musculoskeletal and connective tissue disorders	4.6	4.1	4.0	5.0	5.2	3.3
Arthralgia	1.6	1.3	1.3	2.3	1.8	0.3
Myalgia	1.1	1.0	1.2	1.3	1.1	0.8
Back pain	0.8	1.3	0.4	1.5	1.1	1.0
Nervous system disorders	3.0	3.8	2.9	3.8	3.1	3.8
Headache	1.9	2.0	2.1	2.5	1.7	1.5
Respiratory, thoracic and mediastinal disorders	2.4	1.8	1.8	1.5	3.0	2.0
Skin and subcutaneous tissue disorders	2.0	0.8	2.0	1.5	2.1	0

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 40, 41, 14.3.1.13, 14.3.1.13.1, 14.3.1.14, 14.3.1.14.1, 14.3.1.17, and 14.3.1.17.1.
Abbreviations: N=numbers of subjects in each treatment group.
*ClinicalTrials.gov identifier: NCT02839330
Percentages are based on denominators of subjects in each treatment group. Within each age group category, percentages are not shown if <1% for both treatment groups. The Unsolicited Safety Set was identical to the Overall Safety Set and Exposed Set.
Bold type indicates MedDRA system organ class (SOC), MedDRA version 20.0
[1]Possibly or probably related as assessed by the investigator.

A total of 738 subjects (23.1%) ≥18 years reported unsolicited AEs in the 21 days following any vaccination (through Day 43), with similar frequencies between treatment groups (aH5N1c 23.4%, placebo 22.2%). Unsolicited AEs were reported by n=240 (20.0%) and n=85 (21.4%) of aH5N1c and placebo recipients 18 to <65 years, respectively, and by n=321 (26.8%) and n=92 (23.1%) of aH5n1c and placebo recipients, respectively, ≥65 years. re

Reviewer comment: Overall, rates of unsolicited AEs were low, mostly mild to moderate in severity, and generally similar between treatment groups. No large imbalances or unusual patterns of specific events were observed. No subjects had missing data regarding the severity of an unsolicited AE. Evaluation of the electronic datasets yielded numbers of AEs nearly identical to the Applicant's report.

Subpopulation Analyses of Solicited and Unsolicited Adverse Events

Sex

Overall, 55.8% and 43.3% of females and males, respectively, reported solicited local AEs in the seven days following any vaccination with aH5N1c, and 25.5% and 20.9%, respectively, reported unsolicited AEs in the 21 days following any vaccination with aH5N1c. The frequencies of specific solicited and unsolicited events followed the pattern of the overall study population but were generally higher in females as compared to males.

Race

Sample sizes were too small to make meaningful comparisons between racial subgroups other than between whites and blacks/African Americans. Overall, whites reported only slightly more solicited local and systemic AEs (50.2% and 37.8%,

respectively) as compared to blacks/African Americans (48.9% and 40.8%, respectively). Rates of specific solicited events were generally similar. More whites than blacks/African Americans reported unsolicited AEs in the 21 days following any vaccination, 24.7% and 15.5% white and black/African American aH5N1c recipients, respectively.

Ethnicity
A total of 172 (7.3%) of aH5N1c recipients (n=2352) in the Solicited Safety Set were Hispanic/Latino. Both solicited local and systemic AEs occurred more frequently among Hispanic/Latino recipients of aH5N1c as compared to non-Hispanic/non-Latinos in the seven days following any vaccination with aH5N1c. Overall, 58.7% and 49.4% of Hispanic/Latino and non-Hispanic/non-Latino aH5N1c recipients, respectively, reported solicited local AEs, and 44.2% and 37.6%, respectively, reported solicited systemic AEs. Analyses of unsolicited AEs according to ethnicity showed patterns similar to the overall study population with 53.1% of both Hispanic/Latino and non-Hispanic/non-Latino aH5N1c recipients reporting any unsolicited AE in the 21 days following any vaccination.

Reviewer comment: Interpretation of solicited AE analyses by race and ethnicity were limited by relatively small sample sizes and the descriptive nature of the analyses.

Reviewer comment: Small sample sizes and infrequent events limited subpopulation analyses of long-term unsolicited adverse events reported in the individual studies submitted to the BLA (e.g., Sections 6.1.12.3 – 6.1.12.7, Deaths, SAEs, AESIs, NOCDs, and MAAEs). Therefore, subpopulation analyses of long-term safety will be reviewed in Section 8, the Integrated Overview of Safety.

6.1.12.3 Deaths

A total of 12 (0.4%) subjects, 11 (0.5%) aH5N1c and 1 (0.1%) placebo recipient, died during the study. Eleven of 12 (91.7%) deaths occurred in subjects ≥65 years and 11 (91.7%) occurred after Day 43. Six (50%) of 12 deaths were due to cardiac disorders. None of the deaths were assessed by the investigator as related to study product. Table 19 summarizes all adverse events that resulted in death through the end of the study.

Table 19: Summary of Deaths following Vaccination Day 1 through Day 387 (Unsolicited Safety Set) – V89 18*

System Organ Class Preferred Term	Group	Subject	Age/ Sex[1]	Onset[1]	Death[1]	Related[2]
Cardiac disorders	-	(b) (6)	-	-	(b) (6)	-
Cardio-respiratory arrest	aH5N1c		85F	163		Not related
Cardio-respiratory arrest	aH5N1c		67M	243		Not related
Hypertensive heart disease	aH5N1c		56M	282		Not related
Hypertensive heart disease (and myocardial infarction)	aH5N1c		72M	53		Not related
Myocardial infarction	aH5N1c		73M	232		Not related
Cardiogenic shock	Placebo		83M	226		Not related
General disorders and administrative site conditions	-		-	-		-
Death[3]	aH5N1c		70F	393		Not related
Infections and infestations	-		-	-		-
Pneumonia	aH5N1c		94M	343		Not related
Sepsis	aH5N1c		94M	343		Not related
Septic shock	aH5N1c		70F	34		Not related
Injury, poisoning and procedural complications	-		-	-		-

System Organ Class Preferred Term	Group	Subject	Age/ Sex[1]	Onset[1]	Death[1]	Related[2]
Subdural hematoma	aH5N1c	(b) (6)	90M	276	(b) (6)	Not related
Nervous system disorders	-	-	-	-	-	-
Cerebral infarction	aH5N1c	(b) (6)	79M	125	(b) (6)	Not related
Renal and urinary disorders	-	-	-	-	-	-
Renal failure	aH5N1c	(b) (6)	85F	163	(b) (6)	Not related
Respiratory, thoracic and mediastinal disorders	-	-	-	-	-	-
Respiratory failure	aH5N1c	(b) (6)	71F	362	(b) (6)	Not related

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR, Tables 43, 44, 14.3.2.1, 14.3.2.12, Narratives in Appendix 14.3.3.1, and electronic datasets.
*ClinicalTrials.gov identifier: NCT02839330
The Unsolicited Safety Set was identical to the Overall Safety Set and Exposed Set.
[1]Age is age at time of first vaccination. For Onset and Death, number represents the analysis study day (number of days post-vaccination plus one).
[2]Relationship as assessed by the investigator.
[3]Reported term: Death (unknown).

The Applicant's case narratives, tables, listings, and electronic datasets for subjects who died during the study were reviewed. Summaries are provided for two cases where death occurred close to vaccination and subjects were relatively young:

- Subject ID (b) (6) – Septic shock. The subject was a 71-year-old female with a medical history including intermittent diarrhea (since 1975) and diverticulitis. Medication included ciprofloxacin. She received the first (and only) vaccination of aH5N1c on (b) (6), 8 days post-vaccination, she was hospitalized for worsening abdominal pain and constipation. CT scan revealed a small bowel obstruction (SBO) with circumferential thickening of the distal and terminal ileum, consistent with infection and/or an inflammatory or neoplastic process. No abscess or free air were seen. A colonoscopy on (b) (6) revealed diffuse, congested, nodular and ulcerated mucosa in the distal ileum. Histopathology revealed active ileitis with ulceration, granulation tissue, and edema. The subject was thought to have inflammatory bowel disease (IBD), possibly Crohn's disease, and she was treated with levofloxacin, metronidazole, prednisone, and omeprazole. Following discharge on an unspecified date, she was re-admitted on (b) (6) for recurrent abdominal pain. She required dialysis and intubation, and on (b) (6) underwent a laparotomy that revealed adenocarcinoma of the colon with a large cecal mass and invasion into the psoas muscle (explaining the prior bowel obstruction) and colitis also seen at colonoscopy. IBD was felt to be a separate process. The mass was resected but the subject developed post-operative septic shock and multiorgan system failure and died on (b) (6). The death was attributed to septic shock and adenocarcinoma of the colon with IBD as a possible contributing factor. The investigator assessed the events as not related to study vaccine.

Reviewer comment: Subject (b) (6) had septic shock as a complication of laparotomy and resection of invasive colon cancer as a direct cause of death. The proximity of vaccination to the initial hospitalization for an SBO raises the possibility of a systemic inflammatory response to vaccination as exacerbating a pre-existing ileitis and colitis, perhaps contributing to local bowel inflammation and obstruction, but the aH5N1 vaccine was not directly related to the underlying conditions (adenocarcinoma and IBD) that ultimately caused this subject's

demise. Rather, the subject had symptoms, endoscopic, and histopathologic evidence of pre-existing conditions (IBD and invasive colon cancer) that directly caused her death.

- Subject ID (b) (6) – Hypertensive cardiovascular disease. The subject was a 72-year-old male with a history of hypertension not on any medications at enrollment. He received aH5N1c vaccine on (b) (6) . On (b) (6) , he had a myocardial infarction while driving a motor vehicle and died. No autopsy was performed. The investigator considered progression of underlying hypertensive cardiovascular disease as contributing to the subject's death and assessed study vaccine as not related.

Reviewer comment: Although the rates of death were low, there was a small imbalance between treatment groups (aH5N1c 0.5% vs placebo 0.1%). However, this reviewer agrees with the Applicant's assessment that the deaths were not related to study vaccine due to the lack of a close temporal relationship, existence of a more plausible alternative etiology, and/or a lack of biological plausibility.

6.1.12.4 Nonfatal Serious Adverse Events

Table 20 summarizes the frequencies of SAEs reported from the time of the first vaccination through the end of the study (~Day 387) by treatment, age group, and overall, as categorized by MedDRA SOC. Overall, the occurrence of SAEs was slightly lower in aH5N1c than placebo recipients ≥18 years (6.7% vs 9.3%, respectively), and was lower in aH5N1c and placebo recipients 18 to <65 years (2.9% and 3.3%, respectively) as compared to subjects ≥65 years (10.5% and 15.3%, respectively). Overall, the MedDRA SOC categories with the highest frequencies of SAEs in both aH5N1c and placebo treatment groups, respectively, in subjects ≥18 years were: cardiac disorders (1.3% vs 2.8%), musculoskeletal and connective tissue disorders (1.3% vs 1.0%), infections and infestations (1.0% vs 1.1%), and neoplasms benign, malignant and unspecified, including cysts and polyps (0.9% vs 1.3%). No aH5N1c recipients had SAEs considered related to study vaccine while two (0.3%) placebo recipients had SAEs considered possibly related (polymyalgia rheumatica [PMR] and immune thrombocytopenic purpura [ITP]).

Reviewer comment: The SAEs of PMR and ITP in the placebo group illustrate the importance of a placebo group because these events were clearly unrelated, despite the investigator's blinded assessment, due to a lack of biological plausibility.

Table 20: Subjects with Serious Adverse Events following Any Vaccination through Study Termination (~Day 387) by System Organ Class, Overall and by Age Group (Unsolicited Safety Set) – V89_18*

Age Group	**≥18 yrs**	**≥18 yrs**	**18-64 yrs**	**18-64 yrs**	**≥65 yrs**	**≥65 yrs**
System Organ Class	**aH1N1c N=2395 n (%)**	**PBO N=796 n (%)**	**aH1N1c N=1198 n (%)**	**PBO N=398 n (%)**	**aH1N1c N=1197 n (%)**	**PBO N=398 n (%)**
Subjects with any SAE	161 (6.7)	74 (9.3)	35 (2.9)	13 (3.3)	126 (10.5)	61 (15.3)
Blood and lymphatic system disorders	3 (0.1)	1 (0.1)	0	0	3 (0.3)	1 (0.3)
Cardiac disorders	31 (1.3)	22 (2.8)	9 (0.8)	2 (0.5)	22 (1.8)	20 (5.0)
Ear and labyrinth disorders	1 (0.0)	1 (0.1)	0	0	1 (0.1)	1 (0.3)
Gastrointestinal disorders	17 (0.7)	9 (1.1)	4 (0.3)	1 (0.3)	13 (1.1)	8 (2.0)

Age Group	≥18 yrs	≥18 yrs	18-64 yrs	18-64 yrs	≥65 yrs	≥65 yrs
System Organ Class	**aH1N1c N=2395 n (%)**	**PBO N=796 n (%)**	**aH1N1c N=1198 n (%)**	**PBO N=398 n (%)**	**aH1N1c N=1197 n (%)**	**PBO N=398 n (%)**
General disorders and administration site conditions	4 (0.2)	1 (0.1)	3 (0.3)	0	1 (0.1)	1 (0.3)
Hepatobiliary disorders	4 (0.2)	3 (0.4)	2 (0.2)	0	2 (0.2)	3 (0.8)
Immune system disorders	2 (0.1)	0	0	0	2 (0.2)	0
Infections and infestations	23 (1.0)	9 (1.1)	7 (0.6)	2 (0.5)	16 (1.3)	7 (1.8)
Injury, poisoning and procedural complications	14 (0.6)	1 (0.1)	3 (0.3)	0	11 (0.9)	1 (0.3)
Metabolism and nutrition disorders	4 (0.2)	2 (0.3)	0	0	4 (0.3)	2 (0.5)
Musculoskeletal and connective tissue disorders	31 (1.3)	8 (1.0)	2 (0.2)	1 (0.3)	29 (2.4)	7 (1.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	22 (0.9)	10 (1.3)	5 (0.4)	2 (0.5)	17 (1.4)	8 (2.0)
Nervous system disorders	17 (0.7)	7 (0.9)	2 (0.2)	1 (0.3)	15 (1.3)	6 (1.5)
Pregnancy, puerperium and prenatal conditions	1 (0.0)	2 (0.3)	1 (0.1)	2 (0.5)	0	0
Psychiatric disorders	1 (0.0)	3 (0.4)	1 (0.1)	3 (0.8)	0	0
Renal and urinary disorders	6 (0.3)	1 (0.1)	2 (0.2)	0	4 (0.3)	1 (0.3)
Reproductive system and breast disorders	1 (0.0)	1 (0.1)	0	0	1 (0.1)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	11 (0.5)	6 (0.8)	5 (0.4)	1 (0.3)	6 (0.5)	5 (1.3)
Skin and subcutaneous tissue disorders	1 (0.0)	0	0	0	1 (0.1)	0
Surgical and medical procedures	1 (0.0)	0	0	0	1 (0.1)	0
Vascular disorders	6 (0.3)	4 (0.5)	0	1 (0.3)	6 (0.5)	3 (0.8)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR Tables 46, 47, 14.3.2.2, 14.3.2.2.1, and electronic datasets.
*ClinicalTrials.gov identifier: NCT02839330
Abbreviations: SAE=serious adverse event; PBO=placebo; N=denominator or number of subjects in respective age and treatment group; n=number of subjects with SAE in respective group.
The Unsolicited Safety Set was identical to the Overall Safety Set and Exposed Set.

Table 21 summarizes the frequencies of SAEs reported from the time of the first vaccination through 21 days after the second vaccination (Day 43) by treatment and age subgroup, as categorized by MedDRA SOC and PT. Overall, a total of 14 (0.6%) aH5N1c and 9 (1.1%) placebo recipients had SAEs during this time period with most SAEs occurring in subjects ≥65 years (aH5N1c n=10 [0.8%] and placebo n=9 [2.3%]). The SOCs with the highest number of SAEs were infections and infestations (total n=7) and cardiac disorders (total n=5). Placebo recipients ≥65 years had more cardiac SAEs overall as compared to aH5N1c recipients ≥65 years (0.8% vs 0.1%). No other large imbalances were observed at the level of SOCs or individual PTs. All 28 SAEs were assessed by the investigator as not related to study product.

Table 21: Subjects with Serious Adverse Events through 21 Days following the Second Vaccination (Day 43) by Age Group and Preferred Term (Unsolicited Safety Set) – V89_18*

Age Group	18-64 yrs	18-64 yrs	≥65 yrs	≥65 yrs
System Organ Class **Preferred Term (Subject ID)**	**aH1N1c N=1198 n(%)**	**PBO N=398 n (%)**	**aH1N1c N=1197 n (%)**	**PBO N=398 n(%)**
Subjects with any SAE	4 (0.3)	0	10 (0.8)	9 (2.3)
Blood and lymphatic system disorders	-	-	1 (0.1)	0
Anaemia (b) (6)	-	-	1 (0.1)	0
Cardiac disorders	1 (0.1)	0	1 (0.1)	3 (0.8)
Acute myocardial infarction (b) (6)	1 (0.1)	0	-	-
Atrial fibrillation (b) (6)	-	-	0	1 (0.3)
Atrial flutter (b) (6)	-	-	1 (0.1)	0
Atrioventricular block (b) (6))	-	-	1 (0.1)	0
Cardiac failure congestive (b) (6)	-	-	0	1 (0.3)
Cardiac perforation (b) (6))	-	-	0	1 (0.3)
Cardiac tamponade (b) (6)	-	-	0	1 (0.3)

Age Group	18-64 yrs	18-64 yrs	≥65 yrs	≥65 yrs
System Organ Class **Preferred Term (Subject ID)**	**aH1N1c** **N=1198** **n(%)**	**PBO** **N=398** **n (%)**	**aH1N1c** **N=1197** **n (%)**	**PBO** **N=398** **n(%)**
Gastrointestinal disorders	-	-	0	3 (0.8)
Colitis ulcerative ((b) (6)	-	-	0	1 (0.3)
Pancreatitis (b) (6)	-	-	0	1 (0.3)
Rectal haemorrhage ((b) (6)	-	-	0	1 (0.3)
General disorders and administration site conditions	1 (0.1)	0	-	-
Non-cardiac chest pain (b) (6))	1 (0.1)	0	-	-
Infections and infestations	1 (0.1)	0	4 (0.3)	2 (0.5)
Appendicitis ((b) (6)	-	-	1 (0.1)	1 (0.3)
Diverticulitis ((b) (6)	1 (0.1)	0	0	1 (0.3)
External ear cellulitis (b) (6)	-	-	1 (0.1)	0
Septic shock (b) (6)	-	-	1 (0.1)	0
Shigella infection (b) (6)	-	-	1 (0.1)	0
Metabolism and nutrition disorders	-	-	1 (0.1)	0
Hyponatremia ((b) (6)	-	-	1 (0.1)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.1)	0	1 (0.1)	1 (0.3)
Breast cancer ((b) (6)	1 (0.1)	0	1 (0.1)	0
Prostate cancer (b) (6)	-	-	0	1 (0.3)
Nervous system disorders	-	-	2 (0.2)	0
Cerebral haematoma (b) (6)	-	-	1 (0.1)	0
Presyncope ((b) (6)	-	-	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	-	-	1 (0.1)	0
Asthma (b) (6)	-	-	1 (0.1)	0
Surgical and medical procedures	-	-	1 (0.1)	0
Hospitalisation ((b) (6)	-	-	1 (0.1)	0
Vascular disorders	-	-	0	1 (0.3)
Deep vein thrombosis ((b) (6)	-	-	0	1 (0.3)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR Tables 47, 14.3.2.2.1, and electronic datasets.
*ClinicalTrials.gov identifier: NCT02839330
Abbreviations: SAE=serious adverse event; PBO=placebo; N=denominator or number of subjects in respective age and treatment group; n=number of subjects with SAE in respective group.
The Unsolicited Safety Set was identical to the Overall Safety Set and Exposed Set.

Reviewer comment: Overall, no large imbalances in SAEs were observed between treatment groups during the 21-day follow-up period or through the end of the study. The numbers of subjects who reported each type of SAE through Day 387 found in the electronic datasets were identical to the Applicant's report.

Case narratives of all non-fatal SAEs were reviewed. Selected narratives are summarized below and include only those SAEs with a strong temporal relationship to vaccination and/or events with potential biologic plausibility for relatedness to vaccination with aH5N1c. Please see Section 6.1.12.3 for a review of deaths, all of which were considered SAEs. Additionally, while some adverse events of special interest (AESIs), including potential immune-mediated events, were also assessed as serious and are reviewed with other non-fatal SAEs in this section of the review, non-serious AESIs are reviewed in Section 6.1.12.5.

<u>SAEs among aH5N1c Recipients – Onset Day 1 through Day 43</u>

- Subject (b) (6) – Acute myocardial infarction. This 60-year-old female had a medical history of sinus headaches, tinea pedis, and muscle strain. Medications included aspirin, topical triamcinolone, clotrimazole, betamethasone, and acetaminophen. She received aH5N1c on (b) (6) , 14 hours after the second vaccination (study Day 23), she was hospitalized for symptoms of dizziness, lightheadedness, and diaphoresis, and an EKG consistent with non-ST segment elevation myocardial infarction (STEMI). CXR showed no active disease. Transthoracic echocardiogram showed normal chamber sizes, anterior and antero-septal hypokinesis, and mildly depressed left ventricular function (EF 45-50%). Coronary angiography showed 99% stenosis of the proximal LAD, mild hypokinesis of the left anterior wall, and EF ~60%. Cardiac stents were placed in the LAD and the subject was discharged on (b) (6) on a regimen of cardiac medications. The investigator assessed the MI as moderate in severity, serious, and not related to study vaccine. The investigator did not identify contributory factors or medications that may have contributed to the event.

Reviewer comment: This subject had an underlying 99% stenosis of the proximal LAD as the direct cause of her acute non-STEMI. This reviewer cannot exclude the possibility that cytokines related to a systemic inflammatory response to vaccination may have exacerbated inflammation associated with atherosclerotic plaque in the LAD, perhaps leading to plaque rupture and thrombosis. However, many elderly patients with underlying CAD tolerate influenza vaccination without an increased risk of acute MI, and previous experience with other MF59-adjuvanted vaccines has not identified an increased risk of cardiac AEs associated with MF59. Vaccination in this subject may have been non-contributory and the close temporal relationship coincidental. Although this subject was the only person to have an acute MI in study V89_18, the placebo group had a higher incidence of cardiac SAEs than aH5N1c recipients overall (2.8% vs 1.3% of subjects ≥18 years). Although we cannot be completely certain, a causal relationship between the acute MI and vaccination appears unlikely to this reviewer given the severe predisposing coronary artery stenosis, and the occurrence of this SAE does not change the risk/benefit assessment for the aH5N1c vaccine.

- Subject (b) (6) – Cerebral haematoma. The subject was a 75-year-old female with a medical history including hypothyroidism, osteoarthritis, and hypertension. She received her first dose of aH5N1c vaccine on (b) (6) , and on the following day, fell at home and was hospitalized with a head injury and parafalcine subdural hematoma revealed on CT of the head. She also had a non-serious AE of facial bones fracture due to the fall. She was discharged on (b) (6) and recovered. She did not receive the second vaccination. The investigator assessed the subdural hematoma as due to a fall and not related to vaccination.

Reviewer comment: Although the investigator assessed this SAE as not related, the close temporal relationship between vaccination and the subject's fall raises the possibility that systemic reactogenicity to vaccination may have been contributory. However, review of the electronic datasets, individual subject solicited AE listings, CRF (requested from the Applicant), and response to a request for additional information, indicated that the subject brought her diary

card to the hospital but documented no local or systemic AEs, including fever, that may have contributed to the fall.

<u>SAEs among aH5N1c Recipients – Onset Day 44 through ~Day 387</u>

All SAEs that occurred in aH5N1c recipients from Day 44 through the end of the study were reviewed and were assessed by the investigator as being unrelated to study vaccine. The following narrative summaries include only those SAEs where the reviewer cannot completely exclude relatedness to aH5N1c vaccination or where the SAE is related to pregnancy.

- Subject (b) (6) – Abortion Spontaneous. The subject is a 31-year old female who received aH5N1c vaccine on (b) (6) . Medical and obstetrical history were remarkable for three live full-term births and two elective abortions without congenital anomalies. At enrollment she was using a contraceptive implant but she removed it on an unspecified date, then used foam and condoms as contraception. She had a positive pregnancy test on March 17, 2017 (last menstrual period February 18, 2017, estimated date of conception March 4, 2017, estimated date of delivery November 25, 2017). Prenatal testing revealed no congenital anomalies. On (b) (6) she presented to the ER with pain, syncope, anemia (hematocrit 27.2%, normal 36%-46%), and an incomplete spontaneous abortion. She underwent dilation and curettage, recovered, and was discharged without hospital admission. The investigator assessed the SAE as not related to study vaccine.

Reviewer comment: In the opinion of this reviewer, relatedness between the spontaneous abortion and vaccination is unlikely due to the prolonged interval, approximately seven months, between the last vaccination and conception.

- Subject (b) (6) – Worsening of sarcoidosis. This SAE was also categorized as an AESI. The subject was a 78-year old female whose medical history included hypertension, hypothyroidism, sarcoidosis since 1983, depression, asthma, anxiety, insomnia, seasonal allergies, urinary retention, and neck pain. She took multiple medications but none for sarcoidosis. She received aH5N1c vaccine on (b) (6) (study Day 99) she was hospitalized with respiratory symptoms that began 3 weeks prior to admission and a CXR that showed worsening sarcoidosis. She was treated with corticosteroids, bronchodilators, and azithromycin. She was discharged on (b) (6) and was assessed as recovered by December 17, 2016. The investigator assessed the SAE as progression of pre-existing sarcoidosis and unrelated to study vaccine.

Reviewer comment: Sarcoidosis is a multisystem disease of unknown etiology characterized by non-caseating granuloma formation in involved tissues, particularly the lung and hilar lymph nodes but also other lymph nodes, eyes, skin, and joints. Granulomas are comprised of central macrophages, epithelioid cells, multinucleated giant cells, and CD4 Th1 lymphocytes. The central area is surrounded by CD4 and CD8 T-cells, B lymphocytes, monocytes, mast cells, and fibroblasts. Over time, the granuloma is surrounded by collagen and fibrous tissue. Granuloma formation is felt to be initiated by presentation of an unspecified foreign antigen to macrophages or dendritic cells which then present

the antigen to and activate CD4 T-cells. Although the onset of symptoms in Subject (b) (6) ***appears to have begun ~Day 78 or ~57 days after the second vaccination, this reviewer cannot completely exclude the possibility that the H5N1 antigen and/or immunostimulatory properties of MF59 contributed to worsening of pre-existing sarcoidosis.***

- Subject (b) (6) – Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). This SAE was also categorized as an AESI. The subject is a 79-year old female whose medical history included hypersomnolence, acute respiratory failure, chest pain, and surgery for a hip fracture in 2016. She received aH5N1c vaccination on (b) (6) , she was hospitalized for shortness of breath which had been present since April 2016. CXR showed basilar volume loss and atelectasis but no active disease; heart size and pulmonary vasculature were normal. Arterial blood gas showed hypercapnia, hypoxia, and a respiratory acidosis (pH 7.54, pO2 76.9 mmHg, pCO2 70.5mm Hg, 02 saturation 86.4%). CT of the head showed small vessel disease but no acute abnormality. Diaphragmatic fluoroscopy showed hypomotility of the diaphragm and a suggestion of paralysis of the right diaphragm, with ventilation accomplished primarily through accessory muscle use. She was treated for presumed chronic demyelinating polyneuropathy with human immune globulin and bilevel positive airway pressure. A lumbar puncture revealed no CSF abnormalities. She was transferred to a rehabilitation unit and was recovering at the end of the study. The investigator assessed the event as not related to study vaccine because symptoms began prior to study vaccination.

Reviewer comment: CIDP is an acquired disorder of peripheral nerves and nerve roots characterized by demyelination and a chronic progressive or relapsing-remitting course. Pathogenesis is thought to be immune-mediated, with both humoral and cellular arms of the immune system involved in the destruction of myelin. Specific triggers, e.g., infection, vaccination, surgery, are identified in <30% of cases. Prevalence is ~0.8 to 8.9 per 100,000. It may affect persons of any age but is more common in older males. Symptoms commonly progress over a two-month period and include symmetric or asymmetric muscle weakness (proximal greater than distal), areflexia, cranial or bulbar nerve involvement (in 10%-20%), and sensory symptoms (vibration and position more than temperature and pain, distal greater than proximal). Diagnosis is supported by electromyography and nerve conduction tests consistent with demyelination, CSF showing elevated protein without a pleocytosis, MRI showing abnormal nerve roots or plexuses, and nerve biopsy. Treatment includes corticosteroids, immune globulin and plasma exchange. Subject (b) (6) ***had chronic progressive respiratory symptoms and evidence of diaphragmatic hypomotility compatible with CIDP and an apparent response to immune globulin, but no other evidence confirming the diagnosis is provided. Because the subject's symptoms began prior to vaccination and progression appeared to accelerate >2 months after vaccination, this reviewer is inclined to agree with the investigator's assessment (not related) but cannot entirely exclude a possible causal relationship.***

- Subject (b) (6) – Polymyalgia Rheumatica (PMR). This SAE was also categorized as an AESI. The subject was a 69-year old male who received aH5N1c vaccine on (b) (6) . Medical history included neck pain (since February 2017), GERD and polyarthritis. Medications

included probiotics, omeprazole, diazepam, acetaminophen and multivitamins. On (b) (6) (study day 395), he was diagnosed with PMR after presenting with a polyarthritis six months in duration, including neck pain and stiffness, symmetric bilateral pain of the shoulders and hips, headache, and weight loss. Examination revealed Heberden and Bouchard nodes (characteristic of osteoarthritis) and tenderness of the cervical and lumbar spine. CRP was markedly elevated (not specified). X-rays of the cervical spine showed degenerative changes. Treatment included prednisone, aspirin, baclofen, and gabapentin. The SAE was ongoing at the end of the study. The investigator assessed the SAE as idiopathic and not related to study vaccine.

Reviewer comment: The onset of this subject's symptoms of polyarthritis and neck pain appeared to have started ~6-7 months after the second vaccination. PMR is more common in females than males but occurs in both sexes with a peak incidence between 70-80 years. Incidence varies geographically, is highest in Scandinavian and northern European countries (e.g., 113 per 100,000 per year), and is associated with HLA-DR4 alleles. Immunologic abnormalities include increased circulating CD4+ T-cells (Th17) and proinflammatory cytokines, e.g., IL-6. Studies of viruses as potential triggers have been inconclusive. This reviewer cannot completely exclude the possibility that study vaccine serve as an immunologic trigger for the onset of PMR in this subject versus vaccine being unrelated in causality.

Reviewer comment: Overall, no large imbalance or unusual patterns of SAEs were observed between treatment groups. For the majority of SAEs, this reviewer agrees with the investigators' assessments of relatedness to the aH5N1c vaccine due to lack of a biological plausibility and/or a close temporal relationship between vaccination and the event and/or presence of a more likely pathogenic mechanism. However, for the SAEs of acute non-STEMI and fall/cerebral hematoma, a close temporal association between vaccination and onset of the event make it difficult to completely exclude causality. Regarding potential immune-mediated SAEs (e.g., worsening sarcoidosis, CIDP and PMR), a theoretical concern for the potential for adjuvants to trigger immune-mediated conditions make it difficult to completely exclude a causal relationship between vaccination and such SAEs. Conversely, there was no close temporal relationship or clear immunopathological mechanism to support causality between the described SAEs and the aH5N1c vaccine and, in this reviewer's opinion, relatedness is unlikely. Notably, close temporal relationships were observed between receipt of placebo and SAEs/AESIs, but in these cases causality could be excluded due to the lack of biological plausibility.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESIs), including those assessed as SAEs, were reported in 7 (0.3%) and 7 (0.9%) of aH5N1c and placebo recipients, respectively. No AESIs reported among aH5N1c recipients were assessed as related to study product by the investigator. Table 22 summarizes all AESIs by MedDRA SOC and PT, treatment, and day of onset relative to the first vaccination.

Table 22: Subjects ≥18 Years with Adverse Events of Special Interest (AESI) following Any Vaccination Day 1 through Study Termination (~Day 387) by System Organ Class and Preferred Term and Treatment (Unsolicited Safety Set) – V89_18*

Age Group	≥18 yrs	≥18 yrs
System Organ Class **Preferred Term (Subject ID, Onset[1])**	**aH1N1c N=2395 n (%)**	**PBO N=796 n (%)**
Subjects with Any AESI	7 (0.3)	7 (0.9)
Musculoskeletal and connective tissue disorders	2 (0.1)	3 (0.4)
Polymyalgia rheumatica ((b) (6) , D395; (b) (6) , D56; (b) (6) , D305)	1 (0.0)	2 (0.3)
Ankylosing spondylitis (b) (6) , D304)	1 (0.0)	0
Rheumatoid arthritis ((b) (6) , D114)	0	1 (0.1)
Endocrine disorders	1 (0.0)	0
Basedow's disease ((b) (6) , D54)	1 (0.0)	0
Eye disorders	1 (0.0)	0
Uveitis ((b) (6) , D255)	1 (0.0)	0
Immune system disorders	1 (0.0)	0
Sarcoidosis ((b) (6) , D99)	1 (0.0)	0
Nervous system disorders	1 (0.0)	0
Chronic inflammatory demyelinating polyradiculoneuropathy (b) (6) , D310)	1 (0.0)	0
Skin and subcutaneous tissue disorders	1 (0.0)	0
Systemic lupus erythematosus rash ((b) (6) D205)	1 (0.0)	0
Gastrointestinal disorders	0	2 (0.3)
Coeliac disease ((b) (6) , D78)	0	1 (0.1)
Colitis ulcerative ((b) (6) , D42)	0	1 (0.1)
Blood and lymphatic system disorders	0	1 (0.1)
Immune thrombocytopenic purpura (b) (6) , D75)	0	1 (0.1)
Hepatobiliary disorders	0	1 (0.1)
Biliary cirrhosis primary (b) (6) D318)	0	1 (0.1)

Source: Adapted from STN 125692/0, Module 5, V89_18 CSR Tables 4, 14.3.2.8, and electronic datasets.
*ClinicalTrials.gov identifier: NCT02839330
Abbreviations: AESI=adverse event of special interest; PBO=placebo; N=denominator or number of subjects in respective age and treatment group; n=number of subjects with AESI in respective group.
[1]Study Day of onset of AESI relative to first vaccination (Day 1, D1).
The Unsolicited Safety Set was identical to the Overall Safety Set and Exposed Set.

All but one AESI, Basedow's Disease in a aH5N1c recipient, occurred in subjects ≥65 years. One subject had onset of an AESI within 43 days of the first vaccination, colitis ulcerative onset Day 42. The other 13 AESIs were diagnosed during the follow-up period, on or after Day 54. Nine AESIs were also considered serious (reviewed in Section 6.1.12.4). The remaining five AESIs were assessed as non-serious. Among aH5N1c recipients, one non-serious AESI could not be completely excluded as unrelated by this reviewer and is summarized below:

- Subject (b) (6) – Basedow's Disease (Graves' Disease). The subject was a 59-year old female, with no reported medical history or concomitant medication, who received aH5N1c vaccine on (b) (6) (Study Day 54), hyperthyroidism was diagnosed by her primary care physician and was confirmed by an endocrinologist. Laboratory results were not reported. She was treated with metoprolol and thiamazole. The investigator considered the event unrelated to study vaccine.

Reviewer comment: Graves' (Basedow's) disease is caused by thyrotropin receptor antibodies and is treated with beta-blockers and thionamides. The relatively rapid onset of symptoms following vaccination make a causal

relationship less likely in the opinion of this reviewer. However, the lack of information regarding duration of symptoms and laboratory tests makes the assessment of causality uncertain.

Reviewer comment: AESIs, serious and non-serious, were infrequent and occurred in more placebo than aH5N1c recipients (0.9% vs 0.3%, respectively). Most appeared unrelated to study vaccine because of lack of clear biologic plausibility and/or temporal relationship, and/or pre-existing and potentially predisposing conditions. Evaluation of the electronic datasets was consistent with the Applicant's report.

Medically-Attended Adverse Events (MAAEs)
The proportions of subjects who reported MAAEs from Day 1 through Day 387 in the overall study population were similar between aH5N1c and placebo recipients (46.5% and 46.0%, respectively), with a <3% difference in frequencies between treatment groups for any individual SOC.

Reviewer comment: Review of MAAEs by preferred term (V89_18 CSR Tables 14.3.2.7 and 14.3.2.7.1) did not identify large imbalances between treatment groups or new safety concerns. Evaluation of the electronic datasets was consistent with the Applicant's report.

New Onset of Chronic Disease (NOCD)
The proportions of subjects who reported any unsolicited AE leading to NOCD from Day 1 through study termination in the overall study population were similar between aH5N1c and placebo recipients (9.5% and 9.2%, respectively). The most frequently reported SOC for NOCDs was musculoskeletal and connective tissue disorders (2.0% vs 1.8%). Lower proportions of subjects 18 through 64 years reported NOCDs (aH5N1c 7.8% vs placebo 5.0%) as compared to subjects ≥65 years (11.2% vs 13.3%, respectively). Overall frequencies of NOCDs by SOC were low, with no large imbalances observed between treatment groups. Three of 419 (0.72%) NOCDs were considered possibly related to aH5N1c vaccine (hypothyroidism [n=2], neither identified as Hashimoto's thyroiditis) or placebo (PMR), but lack biological plausibility in the opinion of this reviewer.

Reviewer comment: Review of NOCDs by SOC and PT (V89_18 CSR Tables 14.3.2.6 and 14.3.2.6.1) did not identify any new safety concerns. Evaluation of the electronic datasets was consistent with the Applicant's report.

6.1.12.6 Clinical Test Results

Clinical safety laboratories were not collected systematically in this study. Any laboratory or vital sign abnormalities obtained in the evaluation of serious or otherwise significant AEs are described in Sections 6.1.12.2 – 6.1.12.4. Evaluation of electronic datasets revealed no episodes of hypotension or anaphylaxis in the 30 minutes post-vaccination and no apparent vaccine-related laboratory abnormalities.

6.1.12.7 Dropouts and/or Discontinuations

A total of 16 subjects, 13 (0.5%) and 3 (0.4%) aH5N1c and placebo recipients, respectively, were discontinued from the study due to AEs. Twelve of these subjects also died and are reviewed in Section 6.1.12.3 of this review. Three subjects, all 18 to

<65 years, who were discontinued due to AEs had AEs considered possibly related to study treatment, including two aH5N1c recipients:

- Subject (b) (6) (aH5N1c) withdrew due to constipation on Study Day 6.
- Subject (b) (6) (aH5N1c) withdrew due to a rash on the chest on Study Day 4, described as non-serious, moderate in severity, and resolved with a non-prescription medication. The AE was not medically-attended.

Reviewer comment: In the opinion of this reviewer, the non-fatal discontinuation due to constipation did not appear clearly related to study product due to lack of biological plausibility. Causality in the subject discontinued due to a rash cannot be excluded given the temporal relationship.

6.1.13 Study Summary and Conclusions

Immunogenicity Conclusions

Vaccination with the aH5N1c vaccine elicited immune responses that met the pre-specified co-primary endpoints of lot-to-lot consistency and %HI ≥1:40 in subjects ≥18 years. Secondary immunogenicity analyses showed that subjects 18 to <65 years and ≥65 years also met criteria for anti-HI antibody seroconversion at Day 43. Subjects in neither age group met SCR criteria after a single vaccination (Day 22). GMTs, %HI ≥1:40, and SCRs all decreased toward baseline by Day 183. Placebo recipients did not meet immune response criteria.

Subgroup analyses of aH5N1c recipients showed that post-vaccination GMTs, %HI ≥1:40, and SCRs were similar between sexes. Subanalyses by race showed a statistically significant trend toward higher (non-overlapping 95% CIs) GMTs, %HI ≥1:40, and SCRs in blacks/African Americans as compared to whites. Very small sample sizes precluded meaningful analyses of other racial groups. Subanalyses by ethnicity showed a trend towards statistically significantly higher responses in Hispanic/Latino subjects as compared to non-Hispanic/Latinos. Determining the clinical significance of the subpopulation analyses is limited by relatively small sample sizes and the descriptive nature of the analyses. Subgroup analyses by sex, race and ethnicity generally followed the patterns observed in the overall study population.

Safety Conclusions

The safety of the aH5N1c vaccine appeared acceptable in adults ≥18 years.

Overall rates of any solicited local AE were higher in aH5N1c recipients than placebo (50.2% vs 14.7%), and among aH5N1c recipients, were higher in subjects 18-64 years (64.4%) than subjects ≥65 years (36.3%). Injection site pain was the most frequently reported local AE following any vaccination among aH5N1c recipients in both the 18-64 years and ≥65 years age groups (64.1% and 35.9%, respectively). In both age groups, other local reactions occurred in <1% of subjects in each treatment group. The majority of solicited local AEs were mild in severity and <2 days in duration across age and treatment groups. The overall rates of any solicited systemic AE in subjects ≥18 years were similar between aH5N1c and placebo groups (38.2% and 32.8%, respectively). The most frequent solicited systemic AEs among aH5N1c recipients 18-64 years and ≥65 years, respectively, were fatigue (24.8% and 19.7%), headache (24.5% and 15.5%), and malaise (22.2% and 16.1%). Rates of fatigue and headache among placebo recipients were similar to aH5N1c recipients, but placebo recipients 18-64 years and ≥65 years had lower rates of malaise (12.1% and 11.6%, respectively). Most solicited

systemic AEs were mild to moderate in severity and were <3 days in duration. Solicited local and systemic AEs occurred less frequently following the second vaccination.

Rates of unsolicited AEs in subjects ≥18 years, reported in the 21 days following any vaccination (through Day 43), were similar between treatment groups (aH5N1c 23.4%, placebo 22.2%). AEs occurred slightly more frequently in subjects ≥65 years and were mostly mild to moderate in severity. No large imbalances or unusual patterns were observed.

A total of 11 (0.5%) and 1 (0.1%) deaths were reported in the 12 months following receipt of aH5N1c or placebo, respectively. None were assessed as related to study treatment. A total of 16 subjects, 13 (0.5%) and 3 (0.4%) aH5N1c and placebo recipients, respectively, were discontinued from the study due to AEs, including twelve who died. The remaining three AEs leading to discontinuation were considered possibly related to study treatment, including two AEs in aH5N1c recipients: constipation (Day 6) and a non-medically attended moderately severe rash on the chest (Day 4).

SAEs occurred slightly less frequently in aH5N1c than placebo recipients ≥18 years (6.7% vs 9.3%, respectively), and were more frequent in aH5N1c and placebo recipients ≥65 years (10.5% and 15.3%, respectively) as compared to subjects 18 to <65 years (2.9% and 3.3%, respectively). No aH5N1c recipients had SAES assessed by the investigator as related to study vaccine.

Adverse events of special interest (AESIs), including those assessed as SAEs, were reported in 7 (0.3%) and 7 (0.9%) of aH5N1c and placebo recipients, respectively. AESIs in aH5N1c recipients included polymyalgia rheumatica, ankylosing spondylitis, Basedow's disease, uveitis, worsening of sarcoidosis, chronic inflammatory demyelinating polyradiculopathy, and systemic lupus erythematosus rash. Relatedness between aH5N1c and AESIs appeared unlikely but could not be definitively excluded by this reviewer in all cases. AESIs also occurred in placebo recipients without biological plausibility.

MAAEs and NOCDs occurred with similar frequencies between treatment groups. No large imbalances or unusual patterns of events were observed.

A total of six aH5N1c and five placebo recipients became pregnant during the study. Three pregnancies (aH5N1c n=1, placebo n=2) resulted in spontaneous abortions.

6.2 Trial #2

"A Phase 2 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".

Protocol ID: V89_04
ClinicalTrials.gov ID: NCT01776541
Date First Subject Enrolled: January 31, 2013
Date Last Subject Completed: May 20, 2014
Date of Final Study Report: December 16, 2014

6.2.1 Objectives

Primary Immunogenicity Objective: To select low (half) or high (full) dose aH5N1c to test in Phase 3 based on CBER criteria 3 weeks after the second vaccination.

Primary Safety Objective: To evaluate the safety and tolerability of low and high dose aH5N1c vaccine in subjects 18-64 years.

Secondary Immunogenicity Objectives:

- For each dose level, to evaluate achievement of CBER and CHMP criteria 3 weeks after the first and second vaccinations as measured by HI assay.
- To evaluate the immunogenicity of low and high dose vaccines 12 months after the primary 2-dose course.

Exploratory objectives included evaluation of antibody responses to heterologous influenza strains as measured by HI and microneutralization (MN) assays.

6.2.2 Design Overview

V89_04 was a Phase 2, randomized, observer-blind, multicenter study to evaluate the safety and immunogenicity of low (i.e., half dose, 3.75 mcg HA/0.125 mL MF59) and high dose (i.e., full dose 7.5 mcg HA/0.25 mL MF59) aH5N1c vaccine in healthy adults 18 through 64 years. A total of 979 subjects were enrolled and randomized 1:1 to receive two doses of either low or high dose aH5N1c vaccine administered IM into the deltoid muscle on Days 1 and 22. Diary cards were used to collect solicited and unsolicited AEs that occurred from Days 1-7 and Days 22-28, inclusive, as well as ongoing solicited and any other unsolicited AEs that occurred from Days 8-21 and 29-43, inclusive. SAEs, MAAEs, NOCDs, AESIs, and concomitant medications and vaccines were collected from Day 1-387, inclusive, via the diary card, interviews, and review of medical records. Serologies were collected prior to vaccinations on Days 1 and 22, and on Days 43 and 387.

6.2.3 Population

V89_04 enrolled healthy adults 16 through 64 years who met all eligibility criteria which were similar to study V89_18 (please see Section 6.1.3 of this review). Exclusion criteria included volunteers with a history of autoimmune disease except for Hashimoto's thyroiditis that had been clinically stable for ≥5 years, immunosuppressive conditions or therapies, progressive or severe neurologic disorders, recent GBS, females who were pregnant or breastfeeding, and females of childbearing potential who did not use an acceptable method of contraception for at least 2 months prior to study entry through 21 days after the second vaccination (Day 43).

6.2.4 Study Treatments or Agents Mandated by the Protocol

Please see Section 6.1.4 for a description of the aH5N1c vaccine. The vaccine virus strain used in V89_04 was A/turkey/Turkey/1/2005 (H5N1) NIBRG-23.

- High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL.
- Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL.

Study vaccines were supplied in prefilled syringes, Lot number: C53D29N1.

6.2.5 Directions for Use

Not applicable.

6.2.6 Sites and Centers

The study was conducted at four centers in the U.S., three in Australia, and one in Thailand, presented in Table 23.

Table 23: Study Sites, Investigators, and Subjects Enrolled - V89_04* (All Enrolled Set)

Site	Investigator	Location	#Subjects
01	Eric A. Sheldon, MD	Miami Research Associates, South Miami, FL, USA	259
02	Timothy R. Smith, MD	Mercy Health Research, St. Louis, MO, USA	95
03	Sharon Frey, MD	St. Louis University School of Medicine, St. Louis, MO, USA	63
04	Laurance Chu, MD	Benchmark Medical Research, Austin TX, USA	171
46	Sepehr Shakib, Bachelor of Medicine, Bachelor of Surgery (MBBS), Clinical Pharmacology, PhD	CMAX, Adelaide, SA, Australia	70
47	Janakan Krishnarajah, MBBS, Clinical Pharmacology.	Linear Clinical Research, Nedlands, Western Australia	80
48	Marc A Russo, MBBS, Diploma of Anaesthesia, Fellow in Pain Medicine	Hunter Clinical Research, Broadmeadow, NSW, Australia	69
80	Pornthep Chanhavanich, MD, Pediatric Infectious Diseases	Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand	172
Total	--	--	979

Source: Adapted from STN 125692/0, Module 5, V89_04 CSR, Appendix 16, Description of Investigators and Sites, and SDTM datasets SUPPDM.
*ClinicalTrials.gov identifier: NCT01776541

6.2.7 Surveillance/Monitoring

The schedule of study procedures and safety monitoring in V89_04 were nearly identical to study V89_18 (Section 6.1.7, Table 5) except that diary reminder calls occurred on Days 3, 7, 24, and 28 instead of on Days 3, 5, 24, and 26, and safety follow up calls (Visits 8-12) occurred on Days 213, 244, 274, 305, and 335 instead of on Days 217, 251, 285, 319, and 353.

Definitions and Criteria for the Assessment of Severity and Causality of AEs

Definitions of AEs, SAEs, and SUSARs, and reporting requirements were consistent with those in 21 CFR 312.32. AEs were followed to resolution or stabilization. Solicited AEs and severity grading scales for both solicited and unsolicited AEs were the same as those used in study V89_18 (please see Section 6.1.7 of this review and V89_04 CSR Appendix 16.1.1, V89_04 protocol v.7.0, Appendices B and C).

Reviewer comment: Solicited AEs and severity grading scales were consistent other influenza vaccine studies conducted by the Applicant.

Definitions of MAAEs and NOCD were identical to study V89_18. As in V89_18, AESIs represented potential immune-mediated diseases and were prospectively defined in the protocol according to a list provided by FDA prior to study initiation. The list of AESIs (found in V89_04 CSR, Appendix 16.1.1, protocol version 7.0, Appendix A) grew larger as clinical development proceeded, but was generally similar across studies.

Assessment of Causality
Solicited AEs were not assessed for relatedness. The relationship of all other AEs to study treatment was determined by the investigator based on the same criteria as for study V89_18 (Section 6.1.7 of this review).

6.2.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints
Co-primary immunogenicity endpoints as measured by the HI assay against the H5N1 homologous vaccine virus strain at Day 43 were the: 1) SCR and 2) %HI ≥1:40.

Success criteria for the SCR and %HI ≥1:40 were the same as for subjects 18 to <65 years in study V89_18 (see Section 6.1.8).

Secondary Immunogenicity Endpoints
Secondary immunogenicity endpoints included the following:

- GMTs at Days 1, 22, 43, and 387
- SCRs at Days 22, 43, and 387
- % HI ≥1:40 at Days 22, 43, and 387

CHMP endpoints will not be described in this review. Exploratory endpoints included responses to heterologous strains.

Safety Endpoints
Safety endpoints included the following:

- Percentages of subjects with solicited local, systemic and other unsolicited AEs occurring in the 7 days following each vaccination and any vaccination, calculated for 4 time intervals: 30 minute observation period, Day 1 through Day 7 (without 30 minutes), Day 1 through Day 3 (without 30 minutes), and Day 4 through Day 7 (without 30 minutes).
- Percentages of subjects with unsolicited AEs through 21 days after each and any vaccination.
- Percentages of subjects reporting SAEs, MAAEs, NOCDs, AESIs, AEs leading to withdrawal, and concomitant medications associated with these events, collected from Day 1 to Day 387.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Statistical hypotheses for the primary immunogenicity endpoints were:

- For SCR: $H_0: \pi_i - \pi_0 \leq 0$ vs $H_1: H_1: \pi_i - \pi_0 > 0$
- For %HI≥1:40: $H_0: \tau_i - \tau_0 \leq 0$ vs $H_1: H_1: \tau_i - \tau_0 > 0$

Where π_i represents an unknown SCR and π_0 represents the threshold for seroconversion (0.4), and τ_i represents an unknown %HI ≥1:40 and τ_0 represents the threshold for %HI ≥1:40 (0.7).

Because, for each of the two dose groups, both null hypotheses were to be rejected simultaneously, an alpha adjustment was not required. However, an adjustment for multiple (two) dose groups was made by testing the hypotheses in each dose group at one half the full alpha level, i.e., at 2.5% instead of 5%. If the low dose group rejected both null hypotheses at an alpha of 2.5% (2-sided 97.5% CIs), then the high dose group

could be tested using an alpha of 5.0% (2-sided 95% CIs) for each hypothesis. If unsuccessful, the high dose group would also be tested with a two-sided 97.5% CI.

For an adjusted two-sided alpha level of 0.025, assuming that the true %HI ≥1:40 and SCR were identical and at least 77% in the low dose group (based on observed rates in study V89P1), a sample size of n=437 was calculated as providing > 85% power to demonstrate the %HI ≥1:40 endpoint criterion and >99% power to demonstrate the SCR criterion. The overall power was ~85%. A sample size of n=486 accounted for a dropout rate of 10%.

Primary immunogenicity analyses were adjusted for vaccine group, baseline HI titers, and center. Secondary analyses were performed with covariate adjustments for gender, race and center. Secondary analyses of GMTs and proportions of subjects with % HI ≥1:40 and seroconversion were presented with 95% CIs.

Safety data were analyzed using descriptive statistics. MedDRA version 17.0 was used to code unsolicited AEs.

Protocol Deviations

Major protocol deviations were defined in a manner similar to study V89_18.

Missing Data

Missing immunogenicity data were not imputed. The primary and secondary immunogenicity analyses were conducted in the Full Analysis Set and were also conducted in the Per Protocol Set as sensitivity analyses (with similar results).

Safety data were analyzed according to different time intervals post-vaccination (e.g., for solicited AEs, 30 minutes, Days 1-3, Days 4-7, Days 1-7; for unsolicited AEs, Days 1-22, Days 23-44, Days 44-387). For each of the analysis intervals, if <20% of subjects were missing any of data for a specific analysis, then only the safety set pertaining to the interval would be analyzed. If ≥20% of subjects were missing any solicited or unsolicited AE data for a specific time interval, but the percentage of missing subjects did not differ significantly between treatment groups (p>0.05), then the data were considered “missing completely at random” and were not imputed (i.e., analyzed without the missing values). If ≥20% of subjects were missing any solicited or unsolicited AE data for a specific time interval, and the percentage of missing subjects differed significantly between treatment groups (p ≤0.05), then missing data were considered conditional on the treatment group and multiple imputation methods would be employed. The sponsor reported that no safety analysis sets had missing data ≥20% so that no imputation of missing data was necessary.

Changes in the Planned Analyses

Changes in the protocol and planned analyses following the first versions of the protocol and SAP, and prior to enrollment of the first subject, included:

- Elimination of a booster dose at Day 387 with 6-month follow-up.
- Removal of subanalyses by age groups 65 to <75 years and ≥75 years.
- At CBER’s request, addition of immunogenicity subanalyses according to seasonal influenza vaccination in the previous year.
- Exploratory analyses of MN titers.
- Revised time intervals for unsolicited safety sets.

- At CBER's request, updates to the list of AESIs.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Predefined analysis populations for study V89_04 were essentially the same as for study V89_18 except for the third (final) immunogenicity analysis sets: The Full Analysis Set (FAS) Day 387 and Per Protocol Set (PPS) Day 387 included subjects in the All Enrolled Set who provided immunogenicity data at Day 1 and Day 387 (instead of at Day 1 and Day 183 as defined in V89_18) and fulfilled the other criteria for inclusion in the FAS or PPS. Please see Section 6.1.10.1 for definitions of the analysis populations.

6.2.10.1.1 Demographics

Table 24 presents demographic and baseline characteristics of the All Enrolled Set according to treatment group. Distribution of characteristics between treatment groups was balanced. Countries of enrollment included Australia (22%), Thailand (18%), and the U.S. (60%). Females, whites, and non-Hispanic/Latinos comprised the majority of subjects in the overall study population (56%, 59%, and 79%, respectively). The mean age of all subjects was 38.7 (SD 14.0) years. Overall, 24% of subject reported ever having received an influenza vaccination, 20% within the previous 12 months, with nearly identical proportions between treatment groups.

Table 24: Demographic and Baseline Characteristics – V89_04 (All Enrolled Set)*

Treatment	**Low dose N=491**	**High dose N=488**	**Total N=979**
Mean Age (years) (SD)	38.4 (14.2)	39.0 (13.7)	38.7 (14.0)
Sex – Male, %	47	42	44
Sex – Female, %	53	58	56
Race, %	-	-	-
American Indian or Alaskan Native	0.2	0.4	0.3
Asian	20	19	19
Black or African American	20	20	20
Native Hawaiian or Pacific Islander	0.2	0	0.1
White	59	60	59
Other	0.8	1	0.9
Ethnicity, %	-	-	-
Hispanic/Latino	20	22	21
Non-Hispanic/Latino	80	78	79
Country of Enrollment, %	-	-	-
Australia, %	23	22	22
Thailand, %	18	18	18
United States of America, %	60	60	60
Body Mass Index (kg/m2), Mean (SD)	25.7 (4.3)	26.2 (4.3)	26.0 (4.3)
Previous seasonal influenza vaccination, %	24	24	24
Seasonal influenza vaccination in the previous 12 months, %	19	20	20

Source: Adapted from STN 125692/0, Module 5, V89_04 CSR, Tables 11.2-1 and 14.1.1.3.
Abbreviations: SD=standard deviation
*ClinicalTrials.gov identifier: NCT01776541
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Percentages are based on the number of subjects in each treatment group.

Reviewer comment: Differences between treatment groups in demographic and baseline characteristics were small and unlikely to impact interpretation of study results. The proportion of whites in this study (59%) were underrepresented relative to the U.S. population (76.5%) while Asians and blacks/African Americans (19% and 20%, respectively) were overrepresented relative to the U.S. population (5.9% and 13.4%, respectively). Non-Hispanics/Latinos (79%) approximated the U.S. population (82.4%). Because consistent correlations between sex, race and ethnicity and the safety and immunogenicity of influenza vaccines have not been established, the study population was deemed sufficiently representative of the U.S. population for whom the vaccine is intended. [41]

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Baseline medical history was similar between treatment groups.

6.2.10.1.3 Subject Disposition
Table 25 presents the disposition of subjects and selected analysis populations for immunogenicity and safety, overall and by treatment group. Analysis populations are defined in Section 6.2.10.1.

Table 25: Disposition of Subjects and Analysis Populations for Immunogenicity and Safety by Treatment Group – V89_04, (Enrolled Set)*

Treatment Group	Low Dose N=491 n (%)	High Dose N=488 n (%)	Total N=979 n (%)
Enrolled	491 (100)	488 (100)	979 (100)
Exposed (as randomized)	490 (100)	485 (99)	975 (100)
Completed	416 (85)	432 (89)	848 (87)
Withdrew	75 (15)	56 (11)	131 (13)
Death	0	4 (<1)	4 (<1)
Withdrew consent	20 (4)	12 (2)	32 (3)
Lost to follow-up	48 (10)	27 (6)	75 (8)
Administrative	2 (<1)	6 (1)	8 (<1)
Protocol violation	1 (<1)	2 (<1)	3 (<1)
Other	4 (<1)	5 (1)	9 (<1)
Immunogenicity Populations (as randomized)	-	-	-
FAS Day 1	483 (98)	478 (98)	961 (98)
FAS Day 43	440 (90)	451 (92)	891 (91)
PPS Day 43	399 (81)	412 (84)	811 (83)
Safety Populations (as treated)	-	-	-
Overall Safety Set	490 (100)	485 (100)	975 (100)
Solicited Safety Set Overall (6 hr-Day7)	471 (96)	473 (98)	944 (97)
Unsolicited Safety Set[1]	475 (97)	476 (98)	951 (98)

Source: Adapted from STN 125692/0, Module 5, V89_04 CSR, Tables 10.1-1, 11.1-1, 12.1-1, 14.1.1.1, 14.1.1.2, 14.1.1.1.1, and electronic datasets.
Abbreviations: FAS=Full Analysis Set; PPS=Per Protocol Set
*ClinicalTrials.gov identifier: NCT01776541
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Percentages of subjects in the Exposed, Subject Disposition,and Immunogenicity Populations are based on denominators using the numbers of subjects in the All Enrolled Set, as randomized, in each treatment group. Percentages in the Safety Populations are based on denominators using the numbers of subjects in the Exposed Set, according to actual treatment.
[1]The Unsolicited Safety Sets for Days 1-43 and Days 1-387 were identical.

Of a total of n=979 enrolled subjects, n=491 and n=488 were randomized to receive low and high dose vaccine, respectively. One subject in the low dose group and three

subjects in the high dose group were not vaccinated, and were excluded from the FAS, PPS, and Safety Populations. No subjects received the wrong treatment.

A total of 848 (86.6%) of enrolled subjects completed the protocol while 13.4% withdrew early. The primary reasons for subject discontinuation were lost to follow-up (7.7%) and withdrawal of consent (3.3%). Premature discontinuations due to death occurred in four (0.4%) high dose recipients and no low dose recipients. No other AEs leading to premature withdrawal were reported.

Major protocol deviations, resulting in exclusion from the PPS for immunogenicity, occurred in a total of 260 (26.6%) enrolled subjects, and were generally balanced between treatment groups (28.1% vs 25.0% of low vs high dose recipients). The most frequent major deviations were no blood draw or missing serologies at visits 1, 2, or 3 (9.3%) or not receiving the second vaccination (6.1%).

Reviewer comment: Evaluation of listings and the electronic datasets confirmed the Applicant's report of subject disposition and protocol deviations. While a relatively high percentage (13.4%) of subjects withdrew early in this phase 2 dose-finding study, most were due to lost-to-follow-up and a small percentage (0.4%) were due to AEs (all non-vaccine related, fatal). Discontinuation rates and analysis set exclusions due to deviations were balanced between treatment groups and were unlikely to have significantly impacted the interpretation of immunogenicity or safety results.

Reviewer comment: In response to our May 24, 2019 IR (STN 125692/0/14) regarding analysis sets used for the analyses of unsolicited AEs, the sponsor clarified that the Unsolicited Safety Set (Day 1-Day 43) was used for the analyses of all unsolicited AEs occurring from Day 1-Day 43 and the (identical) Unsolicited Safety Set (Day 1-Day 387) was used for the analyses of unsolicited AEs occurring over the entire study period, including all deaths, SAEs, AESIs, MAAEs and NOCDs. In response to our request for a rationale for not basing the analyses of unsolicited AEs on the Overall Safety Set (or equivalently the Exposed Set), the sponsor explained that this statistical approach was pre-specified in the SAP and was deemed appropriate because subjects who did not contribute any valid data (i.e., those missing all unsolicited AE data) were excluded from the analysis sets. The approach was deemed more conservative than using the OSS/ES because percentages of AEs were higher due to the smaller denominators. The sponsor also noted that the difference between the OSS/ES (total n=975, 100%) and the USS (Day 1-43 and Day 1-387) (total n=951, 98%) was small and use of the USS did not affect interpretation of the data. The clinical review team accepted the sponsor's response as reasonable and noted that the previous review team had found the SAP acceptable.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity objective was to select low or high dose aH5N1c to test in Phase 3 based on meeting co-primary endpoints of SCR and % HI ≥1:40 at 21 days after the second vaccination (Day 43). The FAS Day 43 was the primary analysis population. A total of 94% and 91% of subjects in the FAS received the first and second

vaccinations, respectively. Table 26 presents GMTs, %HI ≥1:40, and SCR at Day 1 (baseline), Day 22, and Day 43 for subjects in each dose group.

Table 26: Geometric Mean Titers, Seroconversion Rates, and Percentages of Subjects with HI ≥1:40 at Baseline and Post-Vaccination (by HI Assay) – V89_04* (Full Analysis Set)

Treatment Group	Low dose N=483	High dose N=478
GMT Day 1 (95% CI)	5.95 (5.63,6.29) N=483	6.11 (5.78,6.46) N=478
GMT Day 22 (95% CI)	15 (13,17) N=461	33 (28,39) N=464
GMT Day 43 (95% CI)	64 (53,77) N=440	250 (208,302) N=451
SCR Day 22 (97.5% CI)	27% (22,32) N=461	48% (43,54) N=464
SCR Day 43 (97.5% CI)	61% (56,66) N=440	83% (78,87) N=451
%HI ≥1:40 Day 1 (97.5% CI)	4% (2,6) N=483	4% (2,7) N=478
%HI ≥1:40 Day 22 (97.5% CI)	30% (26,35) N=461	52% (46,57) N=464
%HI ≥1:40 Day 43 (97.5% CI)	63% (58,68) N=440	85% (81,88) N=451

Source: Adapted from STN 125692/0, Module 5, V89_04 CSR, Tables 11.4.1-1, 11.4.1-2, 11.4.1-3, 14.2.1.1, 14.2.1.2, and 14.2.1.3.
Abbreviations: HI=hemagglutinin inhibition; GMT=geometric mean titer; SCR=seroconversion rate; %HI ≥1:40=percentage of subjects with an anti-hemagglutination inhibition antibody titer of at least 1:40; CI=confidence interval; LB=lower bound; N=number of subjects in the denominator.
*ClinicalTrials.gov identifier: NCT01776541
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
SCR defined as percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a 4-fold increase in post-vaccination HI titer.
SCR endpoint criteria: the LB of the 2-sided 97.5% CI for the SCR must be ≥40%.
%HI ≥1:40 endpoint criteria: the LB of the 2-sided 97.5% CI for the %HI ≥1:40 must be ≥70%.

The high dose group met success criteria for the SCR (LB of the 2-sided 97.5% CI for the SCR must be ≥40%) and for the %HI ≥1:40 (LB of the 2-sided 97.5% CI for the %HI ≥1:40 must be ≥70%) at Day 43. Low dose vaccine met the SCR but not the %HI ≥1:40 endpoint. Therefore, high dose (7.5 mcg HA + 0.25 mL MF59) was selected to test in Phase 3 clinical development.

6.2.11.2 Analyses of Secondary Endpoints

Table 26 also shows that at 21 days after the first vaccination (Day 22), the high dose but not the low dose group met the SCR and neither dose group met the %HI ≥1:40. Twelve months after the second vaccination (Day 387, data not shown), GMTs declined almost back to baseline titers (particularly in the low dose group), and neither group met the immunogenicity endpoints.

6.2.11.3 Subpopulation Analyses

Subanalyses of the %HI ≥1:40 (95% CIs) at Day 43 among high dose aH5N1c recipients by sex, race and ethnicity showed the following: females 84% (79,88), males 86% (80,90); Asians 82% (73,90), blacks/African Americans 84% (75,91), and Whites 85% (80,89); Hispanic/Latinos 85% (77,92) and non-Hispanic/non-Latinos 85% (80,88). SCRs showed patterns very similar to the %HI ≥1:40. GMTs were similar (and 95% CIs

were overlapping) between sexes, among Asians, blacks/African Americans, and Whites, and between Hispanic/Latinos and non-Hispanic/non-Latinos. The numbers of subjects belonging to other racial subgroups were too small for meaningful analyses.

Reviewer comment: Subanalyses of immunogenicity by sex, race and ethnicity followed patterns observed in the overall study population. Results are limited by the relatively small sample sizes and descriptive nature of the analyses.

6.2.11.4 Dropouts and/or Discontinuations

Please see Section 6.2.9. Missing data were not imputed. Sensitivity analyses showed that %HI ≥1:40, SCRs, and GMTs between the FAS and PPS were nearly identical.

6.2.11.5 Exploratory and Post Hoc Analyses

Exploratory analyses, performed in the high dose group at Day 43, showed some cross-reactive immune responses to heterologous influenza A/H5 strains, with the highest responses observed for A/Egypt/2010, A/Hubei/2010, and A/Vietnam/1203/2004.

Analyses of SCR, %HI ≥1:40, and GMTs using the MN assay showed higher responses but patterns similar to HI assay results.

Analyses of immunogenicity were performed according to baseline HI titers < and ≥ 1:10 or < and ≥ 1:40, and by seasonal influenza vaccination in the previous 12 months. At the Day 43 time point, subjects in the high dose, but not the low dose, group met all SCR and %HI ≥1:40 endpoints in these analyses.

6.2.12 Safety Analyses

6.2.12.1 Methods

The OSS was used to summarize all safety data, was identical to the Exposed Set (ES), and included all subjects who received any study vaccination and provided any safety data. The OSS was comprised of 975 subjects of whom 490 and 485 received low and high dose vaccine, respectively. The Solicited Safety Set (SSS) and Unsolicited Safety Set (USS) were used for the analyses of solicited and unsolicited AEs, respectively. Most subjects (92%) received both vaccinations. Data were analyzed according to actual treatment received. Safety data were collected and analyzed by methods similar to study V89_18 (Section 6.1.12.1). Please refer to Table 25 (Section 6.2.10.1.3, Subject Disposition) for a summary of and comment on safety analyses populations.

6.2.12.2 Overview of Adverse Events

<u>Solicited Adverse Events</u>

The SSS after any vaccination (including the 30-minute post-vaccination observation period) was comprised of n=471 low dose and n=473 high dose aH5N1c recipients. Overall, 96% and 91% of all enrolled subjects returned solicited AE diary cards after the first and second vaccinations, respectively, similar proportions between treatment groups. Excluding the 30-minute post-vaccination observation period, a total of 50% and 68% of subjects in the low and high dose groups, respectively, reported any solicited local AE, and 44% and 47%, respectively, reported any solicited systemic AE following any vaccination. The most frequently reported solicited local AE in either group was pain (low dose 50%, high dose 68%). Injection site erythema, induration, or ecchymosis occurred in ≤3% of subjects in either group. Solicited systemic AEs were reported by

the following percentages of low and high dose aH5N1c recipients, respectively: headache (24% vs 27%), fatigue (23% vs 27%), malaise (21% vs 25%), myalgia (17% vs 23%), arthralgia (11% vs 15%), nausea (10% vs 11%), loss of appetite (8% vs 11%), and any fever ≥100.4°F/38.0°C (1.9% vs 2.3%). Overall, rates of systemic symptoms were generally similar between low and high dose groups. In both groups, rates of solicited local and systemic AEs were lower following the second vaccination as compared to the first.

Most local reactions were mild or moderate in severity and resolved within three days. Severe local reactions occurred in ≤1% of subjects in each group. Most solicited systemic events were mild to moderate and resolved within two days. Severe systemic symptoms occurred in ≤2% of subjects in either group. Grade 3 or 4 fever (≥102.1°F / ≥39.0°C) occurred in 2 (0.4%) high dose recipients and in no low dose recipients. A total of 7% and 8% of low and high dose recipients, respectively, used analgesics or antipyretics to treat pain or fever in the seven days following any vaccination.

Reviewer comment: As in V89_18, the V89_04 protocol defined Grade 3 fever as 102.1°F to ≤104°F (39.0°C to ≤40°C), and Grade 4 fever as >104°F (>40°C). However, the protocol, statistical analysis plan (SAP), and CSR indicated that body temperature would be analyzed by two methods: 1) as None (<38.0°C, <100.4°F) or Any (≥38.0°C, ≥100.4°F); and 2) in 0.5°C increments. The 0.5°C increments, as defined in the SAP and reported in Section 14 of the CSR, included the categories of ≥39.0°C to <39.5°C, ≥39.5°C to <40.0°C, and ≥40.0°C, which differs slightly from the toxicity grading scale with respect to 40.0°C. This review will use the toxicity grading scale as pre-defined and categorize temperatures of 40.0°C (104.0°F) as Grade 3. The discrepancy between the toxicity grading scale and actual categorization of body temperature in the analyses for 40.0°C (104.0°F) affected one subject in the dataset, ID (b) (6) ***high/full dose recipient, who had a maximum temperature of 40.0°C on Day 2 following the first vaccination. However, the discrepancy between methods of categorization of a temperature of 40.0°C (104.0°F) had no meaningful clinical impact on the interpretation of study results.***

Unsolicited Adverse Events (Day 1 through Day 43)
Treatment emergent AEs were collected and categorized in a manner similar to V89_18, using MedDRA version 17.0. A total of 267 (28%) subjects in the USS reported unsolicited AEs in the 21 days following any vaccination (through Day 43), with similar overall rates of AEs between treatment groups (low dose 28%, high dose 29%). No larges imbalances in the rates of individual events as categorized by MedDRA PT or by SOC were observed between treatment groups. The most frequent AEs as categorized by SOC (≥2%) among low and high dose recipients, respectively, were: infections and infestations (8% vs 11%), general disorders and administration site conditions (7% vs 6%), musculoskeletal and connective tissue disorder (4% vs 6%), gastrointestinal disorders (5% vs 4%), nervous system disorders (4% in both groups), respiratory, thoracic and mediastinal disorders (4% vs 3%), injury, poisoning and procedural complications (3% in both groups), skin and subcutaneous tissue disorders (2% vs 1%), and psychiatric disorders (<1% vs 2%). The most frequent AEs as categorized by PT (≥2%) among low and high dose recipients, respectively, were: fatigue (2% vs 1%), injection site bruising (3% vs 1%), upper respiratory tract infection (5% in both groups), arthralgia (1% vs 2%), myalgia (1% vs 2%), headache (2% vs 3%), and oropharyngeal pain (3% vs 1%). Most unsolicited AEs were mild to moderate in severity (20% and

6.6% of subjects, respectively) and unrelated to study vaccine. A total of 1% of subjects in either treatment group reported severe (Grade 3) unsolicited AEs. A total of 9% and 11% of low and high dose recipients, respectively, reported unsolicited AEs assessed as related by the investigator, with <1% of these events assessed as Grade 3 in severity.

Reviewer comment: Overall, rates of unsolicited AEs were low, mostly mild to moderate in severity, and generally similar between treatment groups. No large imbalances or unusual patterns of specific events were observed.

Subpopulation Analyses of Solicited and Unsolicited AEs

Reviewer comment: Subpopulation analyses were descriptive and limited by small sample sizes but, in general, fewer solicited and unsolicited AEs were reported by males as compared to females, blacks/African Americans as compared to whites and Asians, and Hispanics/Latinos as compared to non-Hispanics/non-Latinos. Please see the summary of solicited and unsolicited AEs in Section 8, ISS, which included subjects from V89_04.

6.2.12.3 Deaths

Four deaths occurred during the study, all in high dose recipients and assessed by the investigator as unrelated to study vaccine. The primary causes of death (and study day) were myocardial infarction (Day (b) (6)), acute respiratory failure (Day (b) (6)), sepsis (Day (b) (6)), and cerebral hemorrhage (Day (b) (6)). Case narratives and CRFs were reviewed. This reviewer agreed with the investigators' assessments that the four deaths were unrelated to study vaccine due to a lack of temporal relationship and biological plausibility.

6.2.12.4 Nonfatal Serious Adverse Events

A total of twenty-eight subjects, 20 high dose and 8 low dose recipients, experienced SAEs from Day 1 through Day 387. One SAE, spontaneous abortion, was considered possibly related to study vaccine, the remainder were assessed as unrelated. Three SAEs had onset in the Day 1-43 post-vaccination period, the remainder occurred during the Day 44-387 period. Four SAEs were fatal (Section 6.2.12.3), the remainder were non-fatal. Table 27 summarizes the frequencies of SAEs according to study period, MedDRA PT and SOC, and treatment group. Table 28 lists each SAE by dose group, subject ID, study day of onset, outcome and assessment of relatedness.

Table 27: Subjects with Serious Adverse Events through 366 days following the Second Vaccination (Day 387) by Study Period, Body System, Preferred Term and Treatment Group (Unsolicited Safety Set) – V89_04*

Study Period	Treatment Group	Low Dose N=475	High Dose N=476	Total N=951
D1-387	**Subjects with any SAE, n (%)**	8 (2)	20 (4)	28 (3)
D1-43	**Subjects with any SAE, n (%)**	0	3 (1)	3 (<1)
D44-387	**Subjects with any SAE, n (%)**	8 (2)	17 (4)	25 (3)
D1-43	**System Organ Class, n (%)** **Preferred Term, n (%)**	-	-	-
D1-43	**Infections and infestations** Appendicitis Pyelonephritis	0	2 (<1) 1 (<1) 1 (<1)	2 (<1) 1 (<1) 1 (<1)
D1-43	**Nervous system disorders** Nerve compression	0	1 (<1) 1 (<1)	1 (<1) 1 (<1)

Study Period	Treatment Group	Low Dose N=475	High Dose N=476	Total N=951
D44-387	**System Organ Class, n (%)** **Preferred Term, n (%)**	-	-	-
D44-387	**Cardiac disorders** Myocardial infarction	0	1 (<1) 1 (<1)	1 (<1) 1 (<1)
D44-387	**Gastrointestinal disorders** Pancreatitis	0	1 (<1) 1 (<1)	1 (<1) 1 (<1)
D44-387	**General disorders and administration site conditions** Non-cardiac chest pain	1 (<1) 1 (<1)	0	1 (<1) 1 (<1)
D44-387	**Hepatobiliary disorders** Cholecystitis Cholelithiasis Jaundice	1 (<1) 0 1 (<1) 1 (<1)	2 (<1) 1 (<1) 1 (<1) 0	3 (<1) 1 (<1) 2 (<1) 1 (<1)
D44-387	**Infections and infestations** Gastroenteritis viral Influenza Pneumonia Sepsis	0	5 (<1) 1 (<1) 1 (<1) 2 (<1) 2 (<1)	5 (<1) 1 (<1) 1 (<1) 2 (<1) 2 (<1)
D44-387	**Injury, poisoning and procedural complications** Brain contusion Contusion Limb crushing injury Post-laminectomy syndrome Postoperative adhesion Road traffic accident	3 (<1) 0 (<1) 1 (<1) 1 (<1) 1 (<1) 0 0	3 (<1) 1 (<1) 0 0 0 1 (<1) 1 (<1)	6 (1) 1 (<1) 1 (<1) 1 (<1) 1 (<1) 1 (<1) 1 (<1)
D44-387	**Neoplasms benign, malignant and unspecified (including cysts and polyps)** Laryngeal squamous cell carcinoma	1 (<1) 1 (<1)	0	1 (<1) 1 (<1)
D44-387	**Nervous system disorders** Cerebral haemorrhage Subarachnoid haemorrhage	0	2 (<1) 1 (<1) 1 (<1)	2 (<1) 1 (<1) 1 (<1)
D44-387	**Pregnancy, puerperium and perinatal disorders** Abortion missed Abortion spontaneous	2 (<1) 1 (<1) 1 (<1)	1 (<1) 0 1 (<1)	3 (<1) 1 (<1) 2 (<1)
D44-387	**Renal disorders** Nephrolithiasis	0	2 (<1) 2 (<1)	2 (<1) 2 (<1)
D44-387	**Respiratory, thoracic and mediastinal disorders** Acute respiratory failure	0	1 (<1) 1 (<1)	1 (<1) 1 (<1)
D44-387	**Vascular disorders** Raynaud's phenomenon	0	1 (<1) 1 (<1)	1 (<1) 1 (<1)

Source: Adapted from STN 125692/0, Module 5, V89_04 CSR Tables 12.3.1.2-1, 14.3.2.2.2, 14.3.2.2.3, and 14.3.2.2.3.5, and evaluation of the ISS ADAE datasets.
*ClinicalTrials.gov identifier: NCT01776541
Abbreviations: SAE=serious adverse event; N=denominator or number of subjects in respective treatment group; n=number of subjects with SAE in respective group.
Denominators for Study Days 1-43 and 1-387: Low Dose N=475, High Dose N=476, Total N=951.
Denominators for Study Days 44-387: Low Dose N=433, High Dose N=452, Total N=885.
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

Table 28: Summary of SAEs by with Onset from Day 1 through Day 387 after the First Vaccination by Treatment, Day of Onset, Outcome, and Relatedness (Unsolicited Safety Set) – V89_04*

Subject	Group[1]	Preferred Term	Onset[2]	Outcome[3]	Relatedness[3]
(b) (6)	Low	Non-cardiac chest pain	324	Rec/Res	None
	Low	Abortion spontaneous	(b) (6)	Rec/Res	None
	Low	Post-laminectomy syndrome	169	Rec/Res	None
	Low	Cholelithiasis	216	Rec/Res	None
	Low	Jaundice	221	Rec/Res	None
	Low	Contusion	98	Rec/Res	None
	Low	Laryngeal squamous cell carcinoma	209	Rec/Res	None

Subject	Group[1]	Preferred Term	Onset[2]	Outcome[3]	Relatedness[3]
(b) (6)	Low	Limb crushing injury	48	Seq	None
	Low	Abortion missed	(b) (6)	Rec/Res	None
	High	Myocardial infarction	(b) (6)	Fatal	None
	High	Acute respiratory failure	(b) (6)	Fatal	None
	High	Sepsis	(b) (6)	Not Rec	None
	High	Pneumonia	337	Rec/Res	None
	High	Nephrolithiasis	239	Rec/Res	None
	High	Pyelonephritis	21	Rec/Res	None
	High	Road traffic accident	250	Rec/Res	None
	High	Nerve compression	35	Not Rec	None
	High	Pneumonia	240	Unknown	None
	High	Sepsis	(b) (6)	Fatal	None
	High	Nephrolithiasis	340	Rec/Res	None
	High	Raynaud's phenomenon	281	Not Rec	None
	High	Contusion	98	Rec/Res	None
	High	Gastroenteritis viral	282	Rec/Res	None
	High	Subarachnoid haemorrhage	235	Rec/Res	None
	High	Influenza	258	Rec/Res	None
	High	Cerebral haemorrhage	(b) (6)	Fatal	None
	High	Abortion spontaneous	(b) (6)	Rec/Res	Possibly
	High	Postoperative adhesion	120	Rec/Res	None
	High	Appendicitis	6	Rec/Res	None
	High	Cholelithiasis	227	Rec/Res	None
	High	Pancreatitis	227	Rec/Res	None
	High	Cholecystitis	258	Rec/Res	None
	High	Brain contusion	374	Res/Res	None

Source: Adapted from STN 125692/0, Module 5, V89_04 CSR Tables 12.3.1.2-1 and 14.3.2.12.1, and evaluation of the electronic ISS ADAE datasets.
*ClinicalTrials.gov identifier: NCT01776541
Abbreviations: SAE=serious adverse event.
[1]High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
[1]Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
[2]Onset is study day relative to the first vaccination on Day 1.
[3]Outcome: Rec/Res=recovered/resolved; Not Rec=not recovered.
[4]Relatedness as assessed by the investigator.

Case narratives of all SAEs were reviewed. Selected narratives are summarized below and include one SAE of spontaneous abortion assessed by the investigator as at least possibly related to study vaccine and two other spontaneous abortions assessed as not related. This reviewer agreed with the investigators' assessments that the remaining SAEs were unrelated to study vaccine due to the lack of biologic plausibility for relatedness and existence of more likely explanations for the events. Please see Section 6.1.12.3 for the list of four deaths, all considered SAEs and unrelated to study vaccine.

- Subject ID (b) (6) – Abortion spontaneous. The subject was a 30-year old female with a history of spontaneous abortion in April 2001, cholelithiasis and cholecystectomy, using ethinylestradiol for contraception and desvenlafaxine for social anxiety. Her last menstrual period (LMP) was on February 1, 2013. She was vaccinated with aH5N1c 7.5 mcg + MF59 0.25 mL on (b) (6) and (b) (6) (Study Day (b) (6), she presented to the hospital with a spontaneous abortion secondary to a molar pregnancy. Ultrasound revealed absent fetal heartbeat and an estimated gestational age of 11 weeks one day. She underwent a dilation and curettage. Analysis of fetal tissue suggested an XXX triploid chromosome (triple X syndrome or trisomy X) which

occurs in ~1 in 1000 births and is commonly associated with a partial hydatidiform mole. The patient recovered and was discharged. The investigator assessed the event as medically significant, and therefore serious, and possibly related to study vaccine.

Reviewer comment: Molar pregnancies are non-viable and occur in ~1 in 1000 pregnancies. Risk factors include age ≥35 years and previous molar pregnancy. There is no known association between molar pregnancy and influenza disease or vaccination. The subject also had a history of prior spontaneous abortion which occurs with frequencies ranging 8-20%. Risk factors include previous spontaneous abortion. There is no established causal relationship between spontaneous abortion and influenza vaccination. Previous non-clinical and clinical experience with the MF59 adjuvant have not identified risks associated with pregnancy.

- Subject ID (b) (6) – Abortion spontaneous. The subject was an 18-year old female with a history of hypermetropia in 2003, on no medications other than a spermicide used with condoms for contraception. Her LMP was on March 15, 2013. She was vaccinated with aH5N1c 3.75 mcg + MF59 0.125 mL on (b) (6) and, on the day of the planned second vaccination, had a positive pregnancy test and was discontinued from the second dose. She received counseling and did not return for follow-up despite calls and certified letters. On July 26, 2013, she was contacted and informed the site that she had a complete spontaneous abortion on (b) (6) (Study Day (b) (6), gestational age estimated at 11 weeks 6 days. No congenital abnormalities were reported. The investigator assessed the event as serious and not related to study vaccine because exposure occurred 8 weeks before the event.
- Subject ID (b) (6) – Abortion missed. The subject was a 25-year old female gravida 4 para 3, without other significant medical history who was using cyproterone acetate with ethinylestradiol for contraception. She was vaccinated with aH5N1 3.75 mcg + MF59 0.125 mL on (b) (6). Her LMP was August 9, 2013. In October 2013 (unspecified date) she had a positive pregnancy test. She did not receive prenatal care. On October 29, 2013 (Study Day 241), she began having vaginal bleeding but did not see an obstetrician as advised. On (b) (6), she had increased bleeding and presented to the hospital. Ultrasound revealed absent fetal heartbeat and an estimated gestational age of 6 weeks. An aspiration was performed for the diagnosis of missed abortion. The patient recovered without complications. The investigator assessed the event as serious and not related to study vaccine.

Reviewer comment: Overall, more SAEs occurred in the high dose group as compared to the low dose group (4% vs 2%), however, none appeared clearly related to study vaccine and no unusual patterns or large imbalances in individual types of events were observed. Evaluation of the electronic datasets (ISS ADAE) were consistent with the CSR tables and listings.

<u>Subpopulation Analyses of SAEs</u>

The Applicant provided subpopulation analyses of SAEs with onset from Day 1 through Day 387. Review of subpopulation analyses identified no large differences in the rates of SAEs between sexes, among racial subgroups or by ethnicity.

Reviewer comment: Analyses were limited by small sample sizes and low rates of events. Please see Section 8, Integrated Overview of Safety for additional information.

6.2.12.5 Adverse Events of Special Interest (AESI)

One Adverse Event of Special Interest (AESI), Raynaud's phenomenon, occurred during the study and is summarized below. The event occurred in a 24-year old female recipient who received high dose vaccine and was also reported as an SAE.

- Subject ID (b) (6) – Raynaud's phenomenon. The subject was a 24-year old female who received aH5N1c 7.5 mcg + MF59 0.25 mL on (b) (6) . Medical history included seasonal and dander allergies and anxiety for which she received cetirizine hydrochloride, pseudoephedrine, and buspirone. She had a history of cold hands and feet while growing up and a grandfather with Raynaud's syndrome. On (b) (6) (Study Day 281), during extreme cold weather, she was diagnosed with Raynaud's phenomenon of moderate severity and was treated with nifedipine from January 13, 2014 to January 16, 2014. The investigator assessed the condition as medically significant, and therefore serious, and unrelated to study vaccine, noting the pre-existing symptoms and family history.

Reviewer comment: Primary Raynaud's phenomenon is an exaggerated vasoconstriction response to cold exposure. Prevalence in females is 3-20% and the condition occurs more commonly in young women with onset between 15 and 30 years. In this reviewer's opinion, the assessment of unrelatedness is reasonable given the prolonged temporal relationship between vaccination and onset, lack of biological plausibility, pre-existing symptoms, and family history.

New Onset of Chronic Diseases (NOCDs), collected from Day 1 through Day 387, were reviewed. A total of 25 (2.6%) subjects, 14 (2.9%) low dose and 11 (2.3%) high dose recipients, reported NOCDs, all assessed by the investigator as unrelated to study vaccine. This reviewer agrees with the investigators' assessments based on a lack of temporal relationship and/or biological plausibility.

Medically-attended adverse events (MAAEs) were reviewed. A total of 324 (34%) of all subjects reported MAAEs with onset from Day 1 through Day 387, with 8% (n=78) of subjects experiencing MAAEs in the 21 days after either vaccination (Days1-43). Types of events, as categorized by MedDRA SOC and PT, showed patterns similar to all unsolicited AEs with no unusual patterns or additional AEs of interest not already reported as SAEs or AESIs.

6.2.12.6 Clinical Test Results

Clinical safety laboratories were not systematically collected during the study.

6.2.12.7 Dropouts and/or Discontinuations

Four subjects discontinued prematurely due to AEs during the study, all received high dose vaccine and had AEs that lead to death (described in Section 6.2.12.3).

6.2.13 Study Summary and Conclusions

Immunogenicity Conclusions

The primary immunogenicity objective of the study was to select low (half) dose (3.75 mcg HA + 0.125 mL MF59) or high (full) dose (7.5 mcg HA + 0.25 mL MF59) vaccine to carry forward in Phase 3 development. At 21 days following the second vaccination (Day 43), subjects 18 through 64 years in the high dose vaccine group achieved the primary endpoint for the %HI ≥1:40 with a LB of the 2-sided 95% CI ≥70% in 81% of subjects, and the secondary endpoint for the SCR with a LB of the 2-sided 95% CI ≥40% in 78% of subjects. The low dose group did not meet the %HI ≥1:40 endpoint (LB of the 2-sided 95% CI = 58%). The high dose formulation was selected for Phase 3 development.

Immune responses declined towards baseline at 12 months post-vaccination.

Some cross-reactive anti-HI antibody responses to heterologous influenza H5N1 strains were observed at Day 43.

Safety Conclusions

In both low and high dose vaccine groups, most solicited local and systemic AEs were mild to moderate in severity, and most resolved within 2-3 days. Severe solicited local and systemic AEs occurred in ≤1% and ≤2% of all subjects, respectively. Overall, the most common solicited AEs were injection site pain, headache, fatigue, malaise and myalgia. Trends towards higher rates of solicited AEs were observed in high dose as compared to low dose recipients, and after the first vaccination as compared to the second.

The frequencies and types of unsolicited AEs occurring in the 21 days after any vaccination were similar between treatment groups. Overall, 28%-29% of subjects in each group reported unsolicited AEs, with 1% assessed as severe in intensity and 10% assessed as at least possibly related to study vaccine. No unusual patterns of AEs were observed.

A total of twenty-eight (3%) subjects, 20 (4%) high dose and 8 (2%) low dose recipients, experienced SAEs from Day 1 through Day 387. Three (<1%) SAEs had onset in the Day 1-43 post-vaccination period, the remainder during the Day 44-387 period. Four (0.4%) of subjects had SAEs that lead to death and premature withdrawal from the study. The four deaths occurred in high dose recipients, ≥3 months after vaccinations, and were assessed as unrelated to study vaccine by the investigator. One SAE, a spontaneous abortion, was considered by the investigator as possibly related to study vaccine, all other SAEs were assessed as unrelated including two other spontaneous abortions. In the opinion of this reviewer, all SAEs appeared unrelated to study vaccine due to a lack of biological plausibility and/or temporal relationship.

One AESI, Raynaud's phenomenon, was reported during the study and appeared unrelated to study vaccine. Analysis of NOCDs and MAAEs did not reveal unusual patterns or identify safety concerns.

Overall, aH5N1c vaccine, 7.5 mcg HA + 0.25 mL MF59, administered to persons 18-64 years as two IM doses 21 days apart was immunogenic with an acceptable safety profile.

6.3 Trial #3

"A Phase 2, Randomized, Observer-Blind, Multi-Center, Study to evaluate Safety, Tolerability and Immunogenicity of an Adjuvant Cell Culture-Derived H5N1 Subunit Influenza Virus Vaccine at Two Different Formulations in Healthy Elderly Subjects".

Protocol ID: V89_13
ClinicalTrials.gov ID: NCT1766921
Date First Subject Enrolled: January 14, 2013
Date Last Subject Completed: June 30, 2014
Date of Final Study Report: March 4, 2015

6.3.1 Objectives

Primary Immunogenicity Objective
To select the vaccine (low dose or high dose aH5N1c) to be tested in Phase 3 based on achievement of CBER criteria 3 weeks after the second vaccination as measured by strain-specific HI assays.

Primary Safety Objective
To evaluate the safety and tolerability of low dose and high dose aH5N1 vaccine in subjects ≥65 years.

Secondary Immunogenicity Objectives

- For each aH5N1c vaccine (low or high dose), to evaluate achievement of all CHMP criteria 3 weeks after the second vaccination.
- For each aH5N1c vaccine, to evaluate achievement of CBER and CHMP criteria 3 weeks after the first vaccination.
- To evaluate the immunogenicity of each aH5N1 vaccine 12 months after the primary 2-dose course with respect to CBER and CHMP criteria.

Exploratory Objectives
To evaluate antibody responses against 1) heterologous strains as measured by the HI assay and 2) homologous and heterologous strains as measured by the MN assay.

6.3.2 Design Overview

V89_13 was a Phase 2, randomized, observer-blind, multicenter study to evaluate the safety and immunogenicity of low (3.75 mcg HA/0.125 mL MF59) and high dose (7.5 mcg HA/0.25 mL MF59) aH5N1c vaccine in a healthy elderly population ≥ 65 years. A total of 1393 subjects were enrolled and randomized 1:1 to receive two doses of either low or high dose aH5N1c vaccine administered IM into the deltoid muscle on Days 1 and 22. Diary cards were used to collect solicited and unsolicited AEs that occurred from Days 1-7 and Days 22-28, inclusive, as well as ongoing solicited and any other unsolicited AEs that occurred from Days 8-21 and 29-43, inclusive. SAEs, MAAEs, NOCDs, AESIs, and concomitant medications and vaccines were collected from Day 1-387, inclusive, on the diary card, by interviews, and review of medical records. Blood for HI and MN responses were collected prior to vaccinations on Days 1 and 22, and on Days 43 and 387.

6.3.3 Population

Selected Inclusion Criteria

- Males and females ≥65 years in good health as determined by medical history, physical exam, and clinical judgment of the investigator.

Selected Exclusion Criteria

- Any history or illness that could, in the opinion of the investigator, pose an additional risk to the subject due to participation in the study.
- Any serious chronic or progressive disease including but not limited to: advanced cardiopulmonary disease; autoimmune disease except for Hashimoto's thyroiditis that had been stable for ≥5 years; type 1 diabetes or poorly controlled type 2 diabetes; acute or progressive renal or hepatic disease; severe neurologic or psychiatric disorder; cancer (except for benign or localized skin cancer, cancer in remission for ≥10 years, or localized prostate cancer clinically stable for >2 years without treatment).
- Conditions or therapies leading to impaired immune function or alterations of immune function (e.g., immunostimulants, intravenous immunoglobulin or plasma products).
- Progressive or severe neurologic disorder, recent history of Guillain Barre syndrome.
- Allergy to latex or vaccine components.
- Prior H5N1 vaccination, any other influenza vaccination within 60 days prior to enrollment.
- BMI ≥35 kg/m^2

6.3.4 Study Treatments or Agents Mandated by the Protocol

Please see Section 6.1.4 for a complete description of the aH5N1c vaccine. The monovalent vaccine virus strain used in V89_04 was A/turkey/Turkey/1/2005 (H5N1) NIBRG-23.

- High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL.
- Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL.

Study vaccines were supplied in prefilled syringes marked with a ring to indicate the volume for administration of the low dose. Lot numbers: C53D28N1 and C53D30N1A.

6.3.5 Directions for Use

Not applicable.

6.3.6 Sites and Centers

The study was conducted at 23 sites, four centers in Thailand (n=474), five in Australia (n=179), two in New Zealand (n=160), and twelve in the U.S. (n=580). Study sites are presented in Table 29.

Table 29: Study Sites, Investigators, and Number of Subjects* - V89_13 (All Enrolled Set)**

Site	Investigator	Location	#Subjects*
01	Peter Levins, MD	Phoenix, AZ, USA	29
02	Timothy Smith, MD	St. Louis, MO, USA	92
03	Sharon Frey, MD	St. Louis, MO, USA	39
04	Laurence Chu, MD	Austin, TX, USA	27
05	David Seiden, MD	Hollywood, FL, USA	37
06	Suchet Patel, MBBS	Endwell, NY, USA	88
07	Richard Egelhof, MD	Wichita, KS, USA	68

Site	Investigator	Location	#Subjects*
08	James Peterson, MD	Salt Lake City, UT, USA	51
09	Thomas Klein, MD	Wichita, KS, USA	39
10	Shane Christensen, MD	Salt Lake City, UT, USA	42
11	Katie Julien, MD	South Jordan, UT, USA	43
12	Gregg Lucksinger, MD	Austin, TX, USA	25
40	Sepehr Shakib, MBBS	Adelaide, SA, AUS	74
41	Janakan Krishnarajah, MBBS	Nedlands, WA, AUS	13
42	Mark Russo, MBBS	Broadmeadow, NSW, AUS	28
44	Julie Todhunter, MBBS	Auchenflower, AUS	37
45	Peter Richmond, MBBS	Perth, AUS	27
50	Simon Carson, MBBS	Christchurch, NZ	86
51	Jason Pryke, MBBS	Christchurch, NZ	74
71	Sirakarn Tejavanija, MD	Bangkok, Thailand	150
72	Terapong Tantawichien, MD	Bangkok, Thailand	150
73	Yupin Suputtamongkol, MD	Bangkoknoi, Thailand	100
74	Khuanchai Supparatpinyo, MD	Sripoom Maung, Thailand	74
Total	--	--	1393

Source: Adapted from STN 125692/0, Module 5, V89_13 CSR, Appendix 16.1.4, Description of Investigators and Sites and Table 14.1.1.3.2.
*Number of subjects enrolled.
**ClinicalTrials.gov identifier: NCT1766921

6.3.7 Surveillance/Monitoring

Like V89_04, the schedule of study procedures and safety monitoring in V89_13 were nearly identical to study V89_18 (Section 6.1.7, Table 5) except that diary reminder calls occurred on Days 3, 7, 24, and 28 instead of on Days 3, 5, 24, and 26. Safety follow up calls (Visits 8-12) occurred on Days 213, 244, 274, 305, and 335 instead of on Days 217, 251, 285, 319, and 353. Pregnancy tests were not performed.

Definitions and Criteria for the Assessment of Severity and Causality of AEs

Definitions of AEs and SAEs and reporting requirements were consistent with 21 CFR 312.32. AEs were followed to resolution or stabilization. Solicited AEs and severity grading scales for both solicited and unsolicited AEs were the same as for study V89_18 (please see Section 6.1.7 of this review and V89_13 CSR Appendix 16.1.1, V89_13 protocol v.7.0, Appendices B and C).

The definitions of MAAEs and NOCD were identical to study V89_18. AESIs were pre-defined in the protocol according to a list provided by FDA. The list of AESIs grew as clinical development proceeded but was similar across studies. The list of AESIs for V89_13 is found in CSR Appendix 16.1.1, protocol version 7.0, Appendix A.

Assessment of Causality

Solicited AEs were not assessed for relatedness. The relationship of all other AEs to study treatment was determined by the investigator based on the same criteria as for study V89_18 (please see Section 6.1.7 of this review).

6.3.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints

Co-primary immunogenicity endpoints as measured by the HI assay against the H5N1 homologous vaccine virus strain at Day 43 were the: 1) SCR and 2) %HI ≥1:40.

Success criteria for the SCR and %HI ≥1:40 were the same as for subjects ≥65 years in study V89_18 (please see Section 6.1.8).

Secondary Immunogenicity Endpoints
Secondary immunogenicity endpoints included the following:

- GMTs at Days 1, 22, 43, and 387
- SCRs at Days 22, 43, and 387
- % HI ≥1:40 at Days 22, 43, and 387

Exploratory endpoints included responses to heterologous strains.

Safety Endpoints
Safety endpoints included the same solicited and unsolicited AE parameters, monitored over the same time intervals as described for V89_04 (Section 6.2.8 of this review).

6.3.9 Statistical Considerations & Statistical Analysis Plan

Statistical hypotheses for the primary immunogenicity endpoints were:

- For SCR: H_0: $\pi_i - \pi_0 \leq 0$ vs H_1: H_1: $\pi_i - \pi_0 > 0$
- For %HI≥1:40: H_0: $\tau_i - \tau_0 \leq 0$ vs H_1: H_1: $\tau_i - \tau_0 > 0$

Where π_i represents an unknown SCR and π_0 represents the threshold for seroconversion (0.3), and τ_i represents an unknown %HI ≥1:40 and τ_0 represents the threshold for %HI ≥1:40 (0.6).

The multiplicity adjustment strategy for the primary analysis required that both the %HI ≥1:40 and SCR hypotheses be rejected using a two-sided 97.5% CI in the low dose group, and if successful, the high dose group could be tested using a two-sided 95% CI for each hypothesis. If unsuccessful, the high dose group would also be tested with a two-sided 97.5% CI.

Assuming a dropout rate of 10% and a true SCR of 50%, the sponsor calculated that a sample size of n=694 per treatment group would provide 80% power to demonstrate the %HI ≥1:40 endpoint (with a two-sided alpha level of 2.5%), 99% power to demonstrate the SCR endpoint, and an overall power of 80% to demonstrate both endpoints.

Primary immunogenicity analyses were adjusted for vaccine group, baseline HI titers, and center. Secondary analyses were performed with covariate adjustments for gender, race and center. Secondary analyses of GMTs, proportions of subjects with HI ≥1:40, and seroconversion were to be calculated with 2-sided 95% CIs.

Safety data were analyzed using descriptive statistics. MedDRA version 17.0 was used to code unsolicited AEs.

Protocol Deviations
Protocol deviations were defined similar to V89_18 and V89_04. Deviations leading to exclusions from analysis sets were defined in the SAP prior to unblinding.

Missing Data
Missing immunogenicity data were not imputed. The primary and secondary immunogenicity analyses were conducted in the Full Analysis Set and were also conducted in the Per Protocol Set as sensitivity analyses.

Missing safety data were handled in a manner similar to the approach outlined for V89_04 (please see Section 6.2.9 of this review, SAP Section 8.2.1, and the statistical review).

Changes in the Planned Analyses

Changes in the protocol and planned analyses following the first versions of the protocol and SAP, and prior to enrollment of the first subject, included:

- Elimination of a booster dose at Day 387 and subsequent related analyses.
- Addition of subanalyses by age groups 65 to <75 years and ≥75 years.
- At CBER's request, addition of immunogenicity subanalyses according to seasonal influenza vaccination in the previous year.
- At CBER's request, updates to the list of AESIs.
- Clarification that persons with a diagnosis on the AESI list as a chronic disease would be excluded.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

Analysis populations for V89_13 were identical to V89_04 and nearly identical to V89_18 except for the third (final) immunogenicity analysis sets: The Full Analysis Set (FAS) Day 387 and Per Protocol Set (PPS) Day 387 included subjects in the All Enrolled Set who provided immunogenicity data at Day 1 and Day 387 (instead of at Day 1 and Day 183 as defined in V89_18) and fulfilled the other criteria for inclusion in the FAS or PPS. Please see Section 6.1.10.1 for definitions of the analysis populations.

6.3.10.1.1 Demographics

Table 30 presents demographic and baseline characteristics of the All Enrolled Set (AES) according to treatment group. Distribution of characteristics between treatment groups was balanced. Countries of enrollment included Australia (13%), New Zealand (11%), Thailand (34%), and the U.S. (42%). Females, whites, and non-Hispanic/Latinos comprised the majority of subjects in the overall study population (59%, 64%, and 98%, respectively). The mean age of all subjects was 71.0 (SD 4.9) years. Overall, 61% of subject reported ever having received an influenza vaccination, 20% within the previous 12 months, with nearly identical proportions between treatment groups.

Table 30: Demographic and Baseline Characteristics – V89_13 (All Enrolled Set)*

Treatment	**Low dose N=693**	**High dose N=700**	**Total N=1393**
Mean Age (years) (SD)	70.7 (4.7)	71.2 (5.1)	71.0 (4.9)
65 through 84 years, %	99	98	98
≥85 years, %	1	2	2
Sex – Male, %	40	42	41
Sex – Female, %	60	58	59
Race, %	-	-	-
American Indian or Alaskan Native	0	<1	<1
Asian	34	34	34
Black or African American	1	1	1
White	64	64	64

Treatment	Low dose N=693	High dose N=700	Total N=1393
Other	<1	<1	<1
Ethnicity, %	-	-	-
Hispanic/Latino	2	2	2
Non-Hispanic/Latino	98	98	98
Country of Enrollment, %	-	-	-
Australia, %	13	13	13
New Zealand, %	11	12	11
Thailand, %	34	34	34
United States of America, %	42	41	42
Body Mass Index (kg/m2), Mean (SD)	26.5 (4.2)	26.1 (4.0)	26.3 (4.1)
Previous seasonal influenza vaccination, %	60	61	61
Seasonal influenza vaccination in the previous 12 months, %	20	21	20

Source: Adapted from STN 125692/0, Module 5, V89_13 CSR, Tables 11.2-1 and 14.1.1.3.
Abbreviations: SD=standard deviation
*ClinicalTrials.gov identifier: NCT1766921
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Percentages are based on the number of subjects in each treatment group.

Reviewer comment: Differences between treatment groups in demographic and baseline characteristics were small and unlikely to impact interpretation of study results. The proportion of whites and blacks/African Americans in the study (64% and 1%, respectively) were underrepresented relative to the total U.S. population (76.5% and 13.4%, respectively). The proportion of Asians and non-Hispanics/Latinos in the study (34% and 98%, respectively) were overrepresented relative to the U.S. population (5.9% and 82.4%). Because consistent correlations between sex, race and ethnicity and the safety and immunogenicity of influenza vaccines have not been established, the study population was deemed sufficiently representative of the U.S. population. [41]

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Baseline medical history as categorized by MedDRA SOC and PT was balanced between treatment groups and was characterized by conditions commonly seen in an elderly population.

6.3.10.1.3 Subject Disposition
Table 31 presents the disposition of subjects and selected analysis populations for immunogenicity and safety, overall and by treatment group.

Table 31: Disposition of Subjects and Analysis Populations for Immunogenicity and Safety by Treatment Group – V89_13, (Enrolled Set)*

Treatment Group	Low Dose N=693 n (%)	High Dose N=700 n (%)	Total N=1393 n (%)
Enrolled (as randomized)	693 (100)	700 (100)	1393 (100)
Exposed (as randomized)	690 (100)	698 (100)	1388 (100)
Completed	676 (98)	676 (97)	1352 (97)
Withdrew	17 (2)	24 (3)	41 (3)
Death	1 (0.1)	1 (0.1)	2 (0.1)
Withdrew consent	5 (0.7)	14 (2)	19 (1.4)
Lost to follow-up	3 (0.4)	1 (0.1)	4 (0.3)
Administrative	5 (0.7)	5 (0.7)	10 (0.7)

Treatment Group	Low Dose N=693 n (%)	High Dose N=700 n (%)	Total N=1393 n (%)
Protocol violation	1 (0.1)	1 (0.1)	2 (0.1)
Other	2 (0.3)	2 (0.3)	4 (0.3)
Immunogenicity Populations (as randomized)	-	-	-
FAS Day 1	683 (99)	693 (99)	1376 (99)
FAS Day 43	664 (96)	673 (96)	1337 (96)
PPS Day 43	569 (82)	594 (85)	1163 (83)
Safety Populations (as treated)	-	-	-
Exposed (as treated)	689 (100)	699 (100)	1388 (100)
Overall Safety Set	689 (100)	699 (100)	1388 (100)
Solicited Safety Set Overall (6 hr-Day7)	683 (99)	693 (99)	1376 (99)
Unsolicited Safety Set[1]	686 (100)	694 (99)	1380 (99)

Source: Adapted from STN 125692/0, Module 5, V89_13 CSR, Tables 10.1-1, 11.1-1, 14.1.1.1, 14.1.1.1.2, and 14.1.1.2.
Abbreviations: FAS=Full Analysis Set; PPS=Per Protocol Set; AE=adverse event.
*ClinicalTrials.gov identifier: NCT1766921High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Percentages of subjects in the Subject Disposition and Immunogenicity Populations are based on denominators using the numbers of subjects in the All Enrolled Set, with exposure/treatment as randomized.
Percentages in the Safety Populations are based on denominators using the numbers of subjects in the Exposed Set (as treated), according to actual treatment.
[1]Unsolicited Safety Set for Days 1-43 and Days 1-387 were identical.

Of a total of n=1393 enrolled subjects, n=693 and n=700 were randomized to receive low and high dose vaccine, respectively. Three subjects in the low dose group and two subjects in the high dose group were not vaccinated and were excluded from the Exposed Set (as randomized). Two subjects randomized to receive low dose actually received high dose vaccine, and one subject randomized to high dose actually received low dose vaccine. A total of 1352 (97%) of enrolled subjects completed the protocol while 3% withdrew early. The primary reason for subject discontinuation was withdrawal of consent (1.4%). Premature discontinuations due to death occurred in one (0.1%) subject in each treatment group. No other AEs leading to premature withdrawal were reported during the study.

Protocol deviations were similar between treatment groups and were primarily due to having a study visit outside the specified window. A total of 4% of subjects in each treatment group were excluded from the Full Analysis Set at Day 43 (primary immunogenicity analysis), including 3% in each group for not having serologies drawn at the Day 43 time point. Twelve (0.9%) subjects were excluded from the overall Solicited Safety Set (6 hours-7 days following any vaccination) and n=8 subjects (0.6%) were excluded from the Unsolicited Safety Set for providing no safety data for the relevant analyses. However, all n=1388 exposed subjects provided some solicited or unsolicited AE safety data and were included in the Overall Safety Set.

Reviewer comment: Most subjects (97%) completed the study. Discontinuation rates and analysis set exclusions due to deviations were balanced between treatment groups and were unlikely to have significantly impacted the interpretation of immunogenicity or safety results.

Reviewer comment: In response to our May 24, 2019 IR (STN 125692/0/14) regarding analysis sets used for the analyses of unsolicited AEs, the sponsor

clarified that the USS (Day 1-Day 43) was used for the analyses of all unsolicited AEs occurring from Day 1-Day 43 and the (identical) USS (Day 1-Day 387) was used for the analyses of unsolicited AEs occurring over the entire study period, including all deaths, SAEs, AESIs, MAAEs and NOCDs. In response to our request for a rationale for not basing the analyses of unsolicited AEs on the Overall Safety Set (or equivalently the Exposed Set), the sponsor explained that this statistical approach was pre-specified in the SAP and was deemed appropriate because subjects who did not contribute valid data (i.e., those missing all unsolicited AE data) were excluded from the analysis sets. The approach was deemed more conservative than using the OSS/ES because percentages of AEs were higher due to the smaller denominators. The sponsor also noted that the difference between the OSS/ES (total n=1388, 100%) and the USS (Day 1-43 and Day 1-387) (total n=1380, 99%) was very small and use of the USS did not affect interpretation of the data. The clinical review team accepted the sponsor's response as reasonable and noted that the previous review team had found the SAP acceptable.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity objective was to select low or high dose aH5N1c to test in Phase 3 based on meeting co-primary endpoints of SCR and % HI ≥1:40 at 21 days after the second vaccination in the FAS (Day 43). Table 32 presents GMTs, %HI ≥1:40, and SCR at Day 1 (baseline), Day 22, and Day 43 for subjects in each dose group.

Table 32: Geometric Mean Titers, Seroconversion Rates, and Percentages of Subjects with HI ≥1:40 at Baseline and Post-Vaccination (by HI Assay) – V89_13* (Full Analysis Set)

Treatment Group	**Low dose N=683**	**High dose N=693**
GMT Day 1 (97.5% CI)	7.67 (7,8.4) N=683	8.29 (7.57,9.08) N=693
GMT Day 22 (97.5% CI)	16 (14,18) N=673	26 (23,30) N=681
GMT Day 43 (97.5% CI)	45 (38,53) N=644	129 (110,152) N=673
SCR Day 22 (97.5% CI)	21% (18,25) N=673	36% (32,40) N=681
SCR Day 43 (97.5% CI)	52% (48,56) N=664	74% (70,77) N=673
%HI ≥1:40 Day 1 (97.5% CI)	10% (8,13) N=683	12% (10,15) N=693
%HI ≥1:40 Day 22 (97.5% CI)	32% (28,36) N=673	49% (44,53) N=681
%HI ≥1:40 Day 43 (97.5% CI)	63% (58,67) N=664	81% (77,84) N=673

Source: Adapted from STN 125692/0, Module 5, V89_13 CSR, Tables 11.4.1-1, 11.4.1-2, 11.4.1-3, 14.2.1.1, 14.2.1.2, and 14.2.1.3.
Abbreviations: HI=hemagglutinin inhibition; GMT=geometric mean titer; SCR=seroconversion rate; %HI ≥1:40=percentage of subjects with an anti-hemagglutination inhibition antibody titer of at least 1:40; CI=confidence interval; LB=lower bound; N=number of subjects in the denominator.
*ClinicalTrials.gov identifier: NCT1766921
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

SCR defined as percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a 4-fold increase in post-vaccination HI titer.
SCR endpoint criteria: the LB of the 2-sided 97.5% CI for the SCR must be ≥30%.
%HI ≥1:40 endpoint criteria: the LB of the 2-sided 97.5% CI for the %HI ≥1:40 must be ≥60%.

At Day 43, the high dose group met success criteria for the SCR (LB of the 2-sided 97.5% CI for the SCR must be ≥30%) and for the %HI ≥1:40 (LB of the 2-sided 97.5% CI for the %HI ≥1:40 must be ≥60%). The low dose group met the SCR endpoint but just missed the %HI ≥1:40 endpoint (LB of the 95% CI = 58%). High dose vaccine (7.5 mcg HA + 0.25 mL MF59) was selected to test in Phase 3 development.

6.3.11.2 Analyses of Secondary Endpoints

Table 32 shows that, at 21 days after the first vaccination (Day 22), only the high dose met criteria for the SCR endpoint and neither dose group met criteria for the %HI ≥1:40. Twelve months after the second vaccination (Day 387, data not shown), GMTs in the low dose group declined almost back to baseline titers, GMTs in the high dose group declined but remained ~2 times the baseline level, and neither group still met immunogenicity endpoints.

6.3.11.3 Subpopulation Analyses

Analyses of SCRs and %HI ≥1:40 at Day 43 were also performed according to age subgroups of 65 to <75 and ≥75 years. Subjects 65 through 74 years in both low and high dose groups met criteria for both endpoints. Subjects ≥75 years in both dose groups met the SCR endpoint but only the high dose group met the %HI ≥1:40 endpoint. The LB of the 2-sided 97.5% CI for %HI ≥1:40 for subjects ≥75 years in the low dose group was 47%.

Subanalyses of the %HI ≥1:40 (95% CIs) at Day 43 among high dose aH5N1c recipients by sex, race and ethnicity showed the following: females 81% (77,85), males 80% (75,85); Asians 80% (74,85), blacks/African Americans 100% (54,100), and whites 81% (77,85); Hispanic/Latinos 81% (54,96) and non-Hispanic/non-Latinos 81% (78,84). SCRs were somewhat lower but showed patterns similar to the %HI ≥1:40. GMTs were similar (and 95% CIs were overlapping) between sexes, between Asians and whites, and between Hispanic/Latinos and non-Hispanic/non-Latinos. The GMT at Day 43 in blacks/African Americans was higher than in Asians or whites but the sample size was notably small (n=6) and 95% CIs wide [GMT 455 (95% CI: 63, 3282)].

Reviewer comment: Subpopulation analyses of immunogenicity by sex, race and ethnicity followed patterns observed in the overall study population. Results are limited by the relatively small sample sizes and descriptive nature of the analyses.

6.3.11.4 Dropouts and/or Discontinuations

Please see Section 6.3.9. Missing data were not imputed. Sensitivity analyses showed that %HI ≥1:40, SCRs, and GMTs between the FAS and PPS were nearly identical.

6.3.11.5 Exploratory and Post Hoc Analyses

Exploratory analyses performed in the high dose group showed some cross-reactive HI antibody responses to heterologous influenza A/H5 strains. Analyses of SCR, %HI ≥1:40, and GMTs using the MN assay showed patterns similar to HI assay results.

Analyses of immunogenicity performed according to baseline HI titers (< and ≥ 1:10 or 1:40) and by seasonal influenza vaccination in the previous 12 months showed that subjects in the high dose, but not the low dose, group met SCR and %HI ≥1:40 endpoints (at Day 43).

6.3.12 Safety Analyses

6.3.12.1 Methods

The OSS was used to summarize all safety data, was identical to the Exposed Set (ES), and included all subjects who received any study vaccination and provided any safety data. The OSS was comprised of 1388 subjects of whom 689 and 699 received low and high dose vaccine, respectively. The Solicited Safety Sets and Unsolicited Safety Sets were used for the analyses of solicited and unsolicited AEs, respectively. Most subjects (96%) received both vaccinations. Data were analyzed according to actual treatment received. Safety data were collected and analyzed by methods similar to studies V89_18 and V89_04 (Sections 6.1.12.1 and 6.2.12.1).

6.3.12.2 Overview of Adverse Events

Solicited Adverse Events

The SSS after any vaccination (including the 30-minute post-vaccination observation period) was comprised of n=689 low dose and n=699 high dose aH5N1c recipients. Overall, 99% and 96% of all enrolled subjects returned solicited AE diary cards after the first and second vaccinations, respectively, similar proportions between treatment groups. Excluding the 30-minute post-vaccination observation period, a total of 31% and 45% of subjects in the low and high dose groups, respectively, reported any solicited local AE, and 33% and 36%, respectively, reported any solicited systemic AE following any vaccination. The most frequently reported solicited local AE in either group was pain (low dose 30%, high dose 45%). Injection site erythema, induration, or ecchymosis occurred in ≤3% of subjects in either group. The proportions of low and high dose aH5N1c recipients, respectively, who reported solicited systemic AEs after any vaccination were: malaise (17% in both groups), fatigue (16% vs 17%), headache (13% in both groups), myalgia (12% vs 13%), arthralgia (10% vs 9%), nausea (6% vs 7%), loss of appetite (6% in both groups), and any fever ≥100.4°F/38.0°C (1% vs 2%). Overall, rates of systemic symptoms were generally similar between low and high dose groups. In both groups, rates of solicited local and systemic AEs were lower following the second vaccination as compared to the first.

Most local reactions were mild or moderate in severity and resolved within three days. Severe local reactions occurred in ≤0.1% of subjects in each group. Most solicited systemic events were mild to moderate and resolved within two days. Severe systemic symptoms occurred in ≤1% of subjects in either group. Grade 3 fever (39.0°C to ≤40.0°C [102.1°F to ≤104.0°F]) occurred in 4 (0.6%) high dose recipients and in no low dose recipients. A total of 7% and 8% of low and high dose recipients, respectively, used analgesics or antipyretics to treat pain or fever in the seven days following any vaccination.

Unsolicited Adverse Events (Day 1 through Day 43)

Treatment emergent AEs were collected and categorized by methods similar to V89_18 and V89_04, using MedDRA version 17.0.

A total of 440 (32%) subjects reported unsolicited AEs in the 21 days following any vaccination (through Day 43), with similar overall rates of AEs between treatment groups (low dose 34%, high dose 30%). No larges imbalances in the rates of individual events as categorized by MedDRA PT or by SOC were observed between treatment groups.

Reviewer comment: Overall, rates of unsolicited AEs were low, mostly mild to moderate in severity, and generally similar between treatment groups. No large imbalances or unusual patterns of specific events were observed.

Subpopulation Analyses of Solicited and Unsolicited AEs

Reviewer comment: Subpopulation analyses were descriptive and limited by small sample sizes. In general, males as compared to females, and blacks/African Americans as compared to whites and Asians, reported fewer solicited local and systemic AEs. Overall rates of unsolicited AEs were similar between sexes and higher in whites as compared to other racial groups. The significance of these differences is unknown due to the descriptive nature of the analyses.

Reviewer comment: The Applicant did not perform subpopulation analyses of solicited or unsolicited AEs for the Hispanic/Latino subgroup in study V89_13 because the small sample size (n=32 [2.3%] of 1393 enrolled subjects) precluded meaningful analyses. However, Hispanic/Latino subjects from this study were included in the subpopulation analyses of ethnicity in the Integrated Overview of Safety. Please see Section 8 for additional information.

6.3.12.3 Deaths

One subject in each treatment group died during the study. The primary causes of death were acute myocardial infarction (high dose group, Day 162) and lung adenocarcinoma and pneumonia (low dose group, Day 155). Both deaths were assessed by the investigator as unrelated to study vaccine.

Reviewer comment: Case narratives were reviewed. This reviewer agrees that the two deaths were unrelated to study vaccine due to a lack of temporal relationship, lack of biological plausibility, and presence of a more plausible alternative explanation for the deaths.

6.3.12.4 Nonfatal Serious Adverse Events

A total of ninety-six subjects, 53 low dose and 43 high dose recipients, experienced SAEs from Day 1 through Day 387. All SAEs were considered unrelated to study vaccine by the investigator. Ten subjects (low dose n=6, high dose n=4) had SAEs with onset in the Day 1-43 post-vaccination period, and 89 subjects (low dose n=49, high dose n=40) had SAEs with onset during the Day 44-387 period. Two subjects had SAEs leading to death (please see Section 6.3.12.3), and the remaining SAEs were non-fatal. SAEs represented conditions commonly seen in elderly populations. Most SAEs, as categorized by MedDRA PT, occurred at rates of 0.1%. The most frequently reported SAE was osteoarthritis (n=4, 0.4%). Table 33 summarizes the frequencies of all SAEs according to study period, MedDRA SOC, and treatment group. Evaluation of the electronic datasets (ISS ADAE) was consistent with the sponsor's report.

Table 33: Subjects with Serious Adverse Events through 366 days following the Second Vaccination (Day 387) by Study Period, Body System, and Treatment Group (Unsolicited Safety Set) – V89_13*

Study Period	Treatment Group	Low Dose N=686	High Dose N=694	Total N=1380
D1-387	**Subjects with any SAE, n (%)**	53 (8)	43 (6)	96 (7)
D1-43	**Subjects with any SAE, n (%)**	6 (1)	4 (1)	10 (1)
D44-387	**Subjects with any SAE, n (%)**	49 (7)	40 (6)	89 (6)
D1-43	**System Organ Class, n (%)**	-	-	-
D1-43	**Cardiac disorders**	0	1 (0.1)	1 (0.1)
D1-43	**Ear and labyrinth disorders**	1 (0.1)	0	1 (0.1)
D1-43	**Gastrointestinal disorders**	2 (0.3)	0	2 (0.1)
D1-43	**Hepatobiliary disorders**	0	1 (0.1)	1 (0.1)
D1-43	**Infections and infestations**	0	1 (0.1)	1 (0.1)
D1-43	**Injury, poisoning and procedural complications**	1 (0.1)	0	1 (0.1)
D1-43	**Neoplasms benign, malignant and unspecified (including cysts and polyps)**	1 (0.1)	0	1 (0.1)
D1-43	**Nervous system disorders**	2 (0.3)	0	2 (0.1)
D1-43	**Renal and urinary disorders**	0	1 (0.1)	1 (0.1)
D44-387	**System Organ Class, n (%)**	-	-	-
D44-387	**Cardiac disorders**	9 (1)	7 (1)	16 (1)
D44-387	**Eye disorders**	1 (0.1)	0	1 (0.1)
D44-387	**Gastrointestinal disorders**	6 (1)	4 (1)	10 (1)
D44-387	**General disorders and administration site conditions**	5 (1)	1 (0.1)	6 (0.4)
D44-387	**Hepatobiliary disorders**	0	1 (0.1)	1 (0.1)
D44-387	**Immune system disorders**	0	1 (0.1)	1 (0.1)
D44-387	**Infections and infestations**	5 (1)	1 (0.1)	6 (0.4)
D44-387	**Injury, poisoning and procedural complications**	6 (1)	2 (0.3)	8 (1)
D44-387	**Metabolism and nutrition disorders**	0	1 (0.1)	1 (0.1)
D44-387	**Musculoskeletal and connective tissue disorders**	5 (1)	4 (1)	9 (1)
D44-387	**Neoplasms benign, malignant and unspecified (including cysts and polyps)**	6 (1)	6 (1)	12 (1)
D44-387	**Nervous system disorders**	8 (1)	7 (1)	15 (1)
D44-387	**Psychiatric disorders**	0	1 (0.1)	1 (0.1)
D44-387	**Renal and urinary disorders**	1 (0.1)	1 (0.1)	2 (0.3)
D44-387	**Reproductive system and breast disorders**	1 (0.1)	0	1 (0.1)
D44-387	**Respiratory, thoracic and mediastinal disorders**	3 (0.4)	2 (0.3)	5 (0.4)
D44-387	**Skin and subcutaneous tissue disorders**	0	2 (0.3)	2 (0.1)
D44-387	**Surgical and medical procedures**	0	1 (0.1)	1 (0.1)
D44-387	**Vascular disorders**	2 (0.3)	1 (0.1)	3 (0.2)

Source: Adapted from STN 125692/0, Module 5, V89_13 CSR Tables 14.3.2.1, 14.3.2.2.2, 14.3.2.2.3, 14.3.2.2.4, and evaluation of the ISS ADAE electronic datasets.
*ClinicalTrials.gov identifier: NCT1766921
**Indicates an SAE leading to death. Subject (b) (6) had an acute myocardial infarction. Subject (b) (6) had lung adenocarcinoma and pneumonia.
Abbreviations: SAE=serious adverse event; N=denominator or number of subjects in respective treatment group; n=number of subjects with SAE in respective group.
Denominators for Study Days 1-43 and 1-387: Low Dose N=686, High Dose N=694, Total N=1380.
Denominators for Study Days 44-387: Low Dose N=684, High Dose N=687, Total N=1371.
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

Case narratives of all SAEs were reviewed. Two narratives, selected because of a strong temporal relationship or other characteristics raising the possibility of relatedness, are summarized below.

- Subject ID (b) (6): Transient Ischemic Attack (TIA). The subject was a 65 year-old male with a history including hypertension (treated with hydrochlorothiazide and telmisartan), hyperlipidemia, vertigo, erectile dysfunction (treated with sildenafil citrate), asthma, and multiple allergies, maintained on multiple medications. He received aH5N1c 3.75 mcg + MF59 0.125 mL on (b) (6). On (b) (6) (Study Day 6), he was hospitalized for dizziness and disorientation, initially attributed to a vasovagal episode and later diagnosed as a TIA, treated with clopidogrel, and discharged. The investigator assessed the event as unrelated to study vaccine.

Reviewer comment: Although this subject had risk factors for a TIA (e.g., probable atherosclerotic cardiovascular disease and medications which may have precipitated dehydration and/or vasodilation leading to hypotension), in the opinion of this reviewer, the relatively close temporal relationship to vaccination makes it difficult to exclude a causal relationship with certainty.

- Subject ID (b) (6): VIIth Nerve Paralysis. The subject was a 71-year old female with a history of breast cancer, macular degeneration, osteoarthritis, and allergic sinusitis. Medications included glucosamine sulfate and Macu-Vision. She received aH5N1c 7.5 mcg + MF59 0.25 mL on February (b) (6) Study Day 61), 39 days after the second vaccination, she developed a left Bell's palsy, was treated with prednisone, acupuncture and herbal medications, and completely recovered by May 26, 2013. The investigator assessed the event as not related to study vaccine but suspected a causal relationship between the VIIth nerve palsy and Fluvax influenza vaccine which she had also received on (b) (6).

Reviewer comment: The subject appears to have had an acute peripheral facial nerve palsy which in most cases is thought to be caused by reactivation of latent herpes simplex virus (HSV) infection with immune-mediated inflammation of the VIIth nerve as the underlying pathogenetic mechanism. Other herpes viral infections (e.g., VZV, CMV, EBV) and influenza virus have also been associated with the syndrome. In the 2000-2001 influenza season, an inactivated intranasal influenza vaccine marketed only in Switzerland, Nasalflu, Berna Biotech, was strongly associated with an increased risk (OR 84 [95% CI 20.1, 351.9] as compared to parenteral IIVs) of Bell's palsy (VIIth nerve palsy). The peak occurrence of Bell's palsy was between 31-60 days post-vaccination. This vaccine was adjuvanted with E. coli LT endotoxin and was subsequently withdrawn from the market. An increased risk of VIIth nerve palsy has not been established for other IIVs but inflammatory immune-mediated neurologic complications of influenza vaccination remain theoretical concerns. In the case of Subject ID (b) (6), the onset of VIIth nerve palsy 39 days after administration of both Fluvax and aH5N1c raises the possibility that activation of the immune system following vaccination(s) may have contributed to an inflammatory process involving the VIIth nerve resulting in a nerve palsy. [31]

Reviewer comment: SAEs reported in V89_13 consisted of events typical of an elderly population and did not reveal large imbalances, unusual patterns or safety concerns. Except for the SAEs of TIA and VIIth nerve paralysis, for which causality cannot be definitively excluded, this reviewer agrees with the investigators' assessments that the SAEs, were unrelated to study vaccine due to a lack of

biologic plausibility, existence of more likely alternative causal factors, and/or the absence of a close temporal relationship to vaccination. Regarding the TIA and VIIth nerve paralysis, these SAEs will not be described in the PI because of insufficient evidence to support causality with reasonable certainty.

Subpopulation Analyses of SAEs
The Applicant provided subpopulation analyses of SAEs according to dose group, sex, race, and ethnicity.

Reviewer comment: No clear differences in the rates of SAEs were observed between sexes. Subpopulation analyses of racial groups and Hispanics/Latinos were limited by small sample sizes and low rates of events. Please see Section 8, Integrated Overview of Safety for subpopulation analyses in adults across studies.

6.3.12.5 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest
Two Adverse Events of Special Interest (AESIs) were reported during the study, both in high dose recipients: VII^{h} nerve paralysis (onset Study Day 61) and psoriasis (diagnosed on Study Day 227). Both events were assessed as unrelated to study vaccine by the investigators. Please see Section 6.3.12.4, Non-Fatal SAEs, for additional information.

Reviewer comment: A third AESI was reported in the ISS report body and ISS ADAE dataset: high (full) dose recipient (b) (6) ***had an exacerbation of pre-existing psoriasis on Study Day 75. Given that the list of AESIs evolved over time, "exacerbation" of psoriasis may not have been considered an AESI at the time the V89_13 analyses were performed but was identified as such when AESIs were identified for the ISS using CBER's most recent list.***

New Onset of Chronic Diseases
New Onset of Chronic Diseases (NOCDs), collected from Day 1 through Day 387, were reviewed. A total of 200 (14%) subjects, 92 low dose and 108 high dose recipients, reported NOCDs during the study, with 24 (2%) subjects having onset of new conditions between Days 1-43, and the remainder between Days 44-387. Events as categorized by MedDRA SOC and PT followed patterns similar to all unsolicited AEs with no unusual patterns. Five subjects had NOCDs assessed by the investigators as possibly related to study vaccine: hypertension, osteoarthritis, gastroesophageal reflux disease, hypothyroidism, and cellulitis/dermatitis/plantar fasciitis. For additional information, please see V89_13 CSR Tables 14.3.2.7.2, 14.3.2.7.4, and 14.3.2.12.6.

Reviewer comment: In this reviewer's opinion, new onset of hypertension, cellulitis/dermatitis/plantar fasciitis of the foot and GERD are unlikely to have been caused by the study vaccine due to a lack of biologic plausibility. The relatedness of hypothyroidism and an inflammatory osteoarthritis are also uncertain. No subject was specifically identified as having a new onset of an autoimmune hypothyroidism (Hashimoto's thyroiditis), hyperthyroidism (Grave's disease) or rheumatoid arthritis. Additionally, the rates of primary hypothyroidism (n=1, 0.1%, possibly Hashimoto's) and all cases of hypothyroidism (n=5, 0.4%) in the study did not appear to exceed the prevalence in the U.S. (~4.6% of persons 12 years

and older). Because most cases of thyroid disorders are subclinical rather than overt, it is difficult to determine relatedness to vaccination since they may actually have existed prior to vaccination. The rates of NOCDs are also difficult to interpret in the absence of a placebo group. Please see the ISS for further analyses of NOCDs. [33]

Medically-Attended Adverse Events

Medically-attended adverse events (MAAEs) were reviewed. A total of 756 (55%) of all subjects reported MAAEs with onset from Day 1 through Day 387, with 11% (n=148) of subjects experiencing MAAEs in the 21 days after either vaccination (Days1-43). Rates of MAAEs overall and by body system were balanced between treatment groups. The most frequent (≥5%) MAAEs by SOC occurring in either treatment group were: infections and infestations (22%); musculoskeletal and connective tissue disorders (13%); injury, poisoning and procedural complications (11%); gastrointestinal disorders (8%); skin and subcutaneous tissue disorders (6%); eye disorders (5%); metabolism and nutritional disorders (5%); nervous system disorders (5%); and neoplasms benign, malignant and unspecified, including cysts and polyps (5%). The most frequent (≥3%) events as categorized by PT in either treatment group were: upper respiratory tract infection (4%) and urinary tract infection (3%).

Reviewer comment: Although interpretation of results is limited by the absence of a placebo group, review of the data suggested that the majority of MAAEs were events that occur commonly in an elderly population, and that causal relationships to study vaccine were unlikely, including for many events assessed as possibly related by investigators (due to lack of biological plausibility and/or close temporal relationship). This reviewer agrees with the assessment of possible relatedness in one subject (ID (b) (6)***) who reported a rash "on body" on Study Day 2 and who was withdrawn from the second vaccination. Case narratives were requested for two other subjects who had MAAEs assessed as at least possibly related to study vaccine:***

- Subject ID (b) (6): Osteoarthritis (verbatim term: erosive inflammatory arthritis right wrist). The subject was a 65-year-old female who received low dose vaccine (3.75 mcg H5N1 HA + 0.125 mL MF59) on (b) (6) and (b) (6). She had onset of pain in the right wrist at an unspecified date in February 2013. On (b) (6) (37 days after the second vaccination) she consulted her primary care provider because of aching pain in the right medial wrist and thumb, one month in duration, and was referred to a rheumatologist. Blood tests, including CRP and cyclic citrullinated peptide (CCP), were normal. An x-ray showed minor degenerative changes of the first carpal metacarpal joint, and she was diagnosed with "arthritis right medial wrist". At an unspecified date between June and August 2013, an MRI showed inflammatory changes above the ulnar aspect of the right wrist, enhancing carpal erosions and enhancing synovitis in the distal radio-ulnar joint without significant tenosynovitis, and a small ganglion at the radial aspect of the wrist. She was diagnosed as having an erosive inflammatory arthritis of the right wrist and was treated with methotrexate, prednisone, and a cortisol injection. The AE was reported as resolved on February 9, 2014 (355 days after the second vaccination). The investigator assessed the arthritis as possibly related to vaccination due to the temporal relationship and no other precipitating factor. Although she had no prior history of arthritis, she later reported that she had had

a prior surgery due to an arthritic condition (not specified), however, the investigator did not change the assessment of relatedness. The investigator did modify his original assessment of the AE from serious (due to medical significance) to non-serious because the event was not included in the list of AESIs.

- Subject ID (b) (6) Arthralgia (verbatim term: acute arthralgia right first carpometacarpal joint). Subject ID (b) (6) was a 74-year-old female with a history of low back pain and bilateral knee arthralgia, who received low dose vaccine (3.75 mcg H5N1 HA + 0.125 mL MF59) on (b) (6) On February 6, 2013 (Study Day 3), she was withdrawn from the study due to acute onset of arthralgia involving the right first carpometacarpal joint, moderate in severity, nausea and diarrhea. The arthralgia was treated with celecoxib and paracetamol for 5-6 weeks and was reported as recovered on March 4, 2013. The investigator assessed the arthralgia as probably related to study vaccine and not serious. The subject was discontinued from both the second vaccination and the study due to the AE.

Reviewer comment: The possibility of relatedness cannot be completely excluded for either of these two MAAEs. However, for Subject (b) (6) ***the history of prior surgery for an arthritic condition raises the possibility of a pre-existing condition.***

Reviewer comment: Overall, MAAEs, as categorized by MedDRA SOC and PT, followed patterns similar to all unsolicited AEs with no unusual patterns or additional AEs of interest not already reported as SAEs or AESIs. Please see the ISS for additional information.

6.3.12.6 Clinical Test Results

Safety laboratories were not collected in this study.

6.3.12.7 Dropouts and/or Discontinuations

A total of 41 (3%) subjects withdrew early from the study, 2% of low dose and 3% of high dose recipients. Reasons for withdrawal were balanced between groups. One subject in each treatment group was discontinued from the study due to AEs that lead to death, unrelated to study vaccine: Subject (b) (6) (acute myocardial infarction) and Subject (b) (6) (lung adenocarcinoma). Discontinuations from the second vaccination (regardless of whether due to AEs) were balanced between treatment groups (4% in each group). Two subjects were withdrawn from the study early due to non-fatal AEs assessed as at least possibly related to vaccination: Subject (b) (6) (low dose, decreased appetite, dizziness, fatigue, malaise, and vomiting, onset on Study Day 1) and Subject (b) (6) (high dose, “rash on body”, onset Study Day 2).

6.3.13 Study Summary and Conclusions

Immunogenicity Conclusions

The primary immunogenicity objective of the study was to select low dose (aH5N1c 3.75 mcg + MF59 0.125 mL) or high dose (aH5N1c 7.5 mcg + MF59 0.25 mL) vaccine to carry forward in Phase 3 development. At 21 days following the second vaccination (Day 43), subjects ≥65 years in the high dose vaccine group achieved both co-primary endpoints of the %HI ≥1:40 (LB of the 2-sided 97.5% CI = 77%) and the SCR (LB of the 2-sided 97.5% CI = 70%). The low dose group did not meet the %HI ≥1:40 endpoint (LB

of the 2-sided 97.5% CI = 58%). The high dose formulation was selected for Phase 3 development.

Immune responses following a single vaccination (Day 22) did not achieve both co-primary endpoints in either dose group, i.e., two doses were required for an adequate response. Immune responses declined towards baseline at 12 months post-vaccination.

Subjects 65 through 74 years had higher immune responses than subjects ≥75 years.

Some cross-reactive immune responses to heterologous influenza H5N1 strains were observed at Day 43.

Safety Conclusions

In both low and high dose vaccine groups, most solicited local and systemic AEs were mild to moderate in severity, and most resolved within 2-3 days. Severe solicited local and systemic AEs occurred in ≤0.1% and ≤1% of all subjects, respectively. Overall, the most common solicited AEs were injection site pain, malaise and fatigue. Trends towards higher rates of solicited AEs were observed in high dose as compared to low dose recipients, and after the first as compared to the second vaccination.

The frequencies and types of unsolicited AEs occurring in the 21 days following any vaccination (through Day 43) were similar between treatment groups. Overall, 30%-34% of subjects in each group reported unsolicited AEs, with 1% assessed as severe and 12% assessed as at least possibly related to study vaccine. AEs were typical of an elderly population without unusual patterns.

A total of ninety-six (7%) subjects, 53 (8%) low dose and 43 (6%) high dose recipients, experienced SAEs from Day 1 through Day 387. Ten (1%) subjects (low dose n=6 [1%], high dose n=4 [1%]) had SAEs with onset in the Day 1-43 post-vaccination period. Two subjects had SAEs leading to death and premature withdrawal from the study, the remaining SAEs were non-fatal. SAEs consisted of events typical of an elderly population and did not reveal unusual patterns or clear safety concerns. All were considered unrelated to study vaccine by the investigator. In this reviewer's opinion, two SAEs, a TIA and VIIth nerve paralysis, were most likely unrelated to aH5N1c vaccination but causality could not be excluded with certainty. Therefore, they are described in this review but will not be included in the PI because evidence for causality is insufficient.

Two AESIs were reported during the study, VIIth nerve paralysis and psoriasis. Both appeared probably unrelated to study vaccine. Analysis of NOCDs and MAAEs did not reveal unusual patterns or safety concerns.

Overall, aH5N1c 7.5 mcg + MF59 0.25 mL vaccine administered to persons ≥65 years as two IM doses 21 days apart was immunogenic and had an acceptable safety profile.

6.4 Trial #4

"A Phase 2, Randomized, Observer-Blind, Multi-Center, Study to Evaluate Safety, Tolerability and Immunogenicity of an Adjuvant Cell Culture-Derived H5N1 Subunit Influenza Virus Vaccine at Two Different Formulations in Healthy Pediatric Subjects".

Protocol ID: V89_11

ClinicalTrials.gov ID: NCT01776554
Date First Subject Enrolled: January 31, 2013
Date Last Subject Completed: June 16, 2014
Date of Final Study Report: February 26, 2015
Date of Erratum to Final Study Report: August 31, 2015

6.4.1 Objectives

Primary immunogenicity Objective
To select the vaccine (low dose or high dose aH5N1c) to be tested in Phase 3 based on achievement of CBER criteria 3 weeks after the second vaccine administration as measured by strain-specific hemagglutination inhibition (HI) assays.

Primary Safety Objective
To evaluate the safety and tolerability of low dose and high dose aH5N1c vaccine in subjects 6 months through 17 years of age.

6.4.2 Design Overview

Study V89_11 was a Phase 2, randomized, controlled, observer-blind, multicenter study to evaluate the safety and immunogenicity of two IM doses of either low dose (3.75 mcg HA + 0.125 mL MF59) or high dose (7.5 mcg HA + 0.25 mL MF59) aH5N1c vaccine in healthy subjects 6 months through 17 years, conducted at ten sites in the U.S. and two sites in Thailand. Planned enrollment was ~666 subjects, stratified by site and age cohort (6 through 35 months, 3 through 8 years, and 9 through 17 years) and randomized 1:1 to receive either low or high dose aH5N1c vaccine administered IM three weeks apart. After obtaining informed consent, and assent where applicable, subjects were vaccinated on Study Day 1 and Day 22 and monitored for adverse events for 30 minutes after each vaccination. Diary cards were used to collect solicited AEs, unsolicited AEs, and medications/vaccinations received from Day 1 to Day 7 and Day 22 to Day 28, inclusive. From Day 8 to Day 21 and Day 29 to Day 42, inclusive, unsolicited AEs, ongoing solicited AEs, medications and other vaccinations were collected in the diaries which were returned to the clinic on Days 22 and 43. Parents or guardians completed diary cards for subjects <14 years but, after receiving instructions, subjects ≥14 years could complete the diary card at the discretion of parents or guardians and the investigator. From Day 1 through Day 387, SAEs, AESIs, NOCDs, MAAES, AEs leading to vaccine or study withdrawal, and medications used to treat SAEs, and vaccinations were collected via the diary card, interview of parents or guardians, and/or review of medical records. HI and MN antibody responses were measured before each vaccination on Days 1 and 22, and on Days 43 and 387.

6.4.3 Population

Selected Inclusion Criteria
- Males and females 6 months through 17 years.
- Written informed consent obtained from parents or legal guardians and, where applicable to local regulations, informed assent obtained for subjects above the specified age.
- Good health as determined by medical history, physical assessment and investigator judgment.

Selected Exclusion Criteria (please see Section 9.3.2 of the V89_11 CSR for the full list)
- Inability of parent or guardian to comprehend or follow study procedures.

- History or illness that, in the opinion of the investigator, may pose an additional risk to individuals participating in the study.
- Any serious chronic or progressive disease including: severe cardiac, pulmonary, hepatic, renal, or neurologic disease; type 1 or poorly-controlled type 2 diabetes; autoimmune disease (except for Hashimoto's thyroiditis clinically stable for ≥5 years); and history of underlying medical condition such as major congenital abnormalities requiring surgery, chronic treatment, or associated with developmental delay.
- Disorders of growth or failure to thrive.
- Medically significant cancer.
- Known or suspected impairment/alteration of immune function.
- Allergy to latex or vaccine components.
- Receipt of another investigational product within 30 days prior to the first study visit or before completion of the safety follow-up period.
- Prior receipt of an H5N1 vaccine.
- Receipt of any other type of influenza vaccination within 60 days of enrollment (influenza vaccination allowed after Day 43).
- Receipt of any other inactivated vaccine within 2 weeks or a live vaccine within 4 weeks of enrollment or planning to receive any vaccine within 4 weeks of study vaccines.
- Temperature ≥38.0°C (≥100.4°F) and/or acute illness within three days of intended study vaccination.
- Pregnant or breastfeeding.
- Females of childbearing potential who refused to use an acceptable method of birth control from Day 1 to Day 43, and, if sexually active, who did not use a reliable method of birth control for at least two months prior to study entry.
- BMI ≥35 kg/m2.
- Drug or alcohol abuse.
- Behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, could interfere with the subject's ability to participate.

Subjects must meet eligibility criteria for each vaccination. Additionally, subjects were discontinued from the second vaccination if they:

- Experienced any severe AE or SAE, including hypersensitivity reactions, assessed as at least possibly related to study vaccine or non-study vaccines;
- Developed any new condition which, in the opinion of the investigator, could pose an additional risk to subject participation.

Subjects who withdrew consent early were encouraged to continue participation and asked if they wished to withdraw completely or remain in the study for safety follow-up or a subset of other procedures.

6.4.4 Study Treatments or Agents Mandated by the Protocol

Please see Section 6.1.4 for a description of the aH5N1c vaccine. The monovalent vaccine virus strain used in V89_04 was A/turkey/Turkey/1/2005 (H5N1) NIBRG-23.

- High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL.
- Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL.

Study vaccines were supplied in prefilled syringes. Lot number: C53D30N1.

6.4.5 Directions for Use

Not applicable.

6.4.6 Sites and Centers

The study was conducted at 12 sites, ten in the U.S. (n=182) and two in Thailand (n=480). Study sites are presented in Table 34.

Table 34: Study Sites, Investigators, and Number of Subjects* - V89_11 (All Enrolled Set)**

Site	Investigator	Location	#Subjects*
01	Edwin Anderson, MD	St. Louis, MO, USA	15
02	Stephen Luber, MD	Spokane, WA, USA	5
03	James Cervantes, MD	Bellevue, NE, USA	18
04	Shane Christensen, MD	Salt Lake City, UT, UA	36
05	Richard Egelhof, MD	Wichita, KS, USA	22
06	Brandon Essink, MD	Omaha, NE, USA	15
07	Robyn Hartvickson, MD	Newton, KS, USA	19
08	James Peterson, MD	Salt Lake City, UT, USA	22
09	Thomas Klein, MD	Wichita, KS, USA	17
10	Greg Lucksinger, MD	Austin, TX, USA	13
11/75	Phirangkul Kerdpanich, MD	Bangkok, Thailand	238
12/76	Pornthep Chanthavanich, MD	Bangkok, Thailand	242
Total	--	--	662

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR, Appendix 16.1.4, Description of Investigators and Sites and Table 14.1.1.3.2.
*Number of subjects enrolled.
**ClinicalTrials.gov identifier: NCT01776554

Reviewer comment: The study investigators appeared to have adequate clinical and clinical trial experience, including the Thai investigators who had expertise in pediatrics. Approximately 72.5% of subjects were from Thailand.

6.4.7 Surveillance/Monitoring

Like V89_04 and V89_13, the schedule of study procedures and safety monitoring in V89_11 were nearly identical to study V89_18 (Section 6.1.7, Table 5) except that diary reminder calls occurred on Days 3, 7, 24, and 28 instead of on Days 3, 5, 24, and 26, and safety follow up calls (Visits 8-12) occurred on Days 213, 244, 274, 305, and 335 instead of on Days 217, 251, 285, 319, and 353. The preferred route for obtaining a body temperature was axillary rather than oral as in the adult studies.

Definitions and Criteria for the Assessment of Severity and Causality of AEs

Definitions of AEs and SAEs and reporting requirements were consistent with 21 CFR 312.32. AEs were followed to resolution or stabilization. Solicited AEs and the severity grading scales for solicited and unsolicited AEs are presented in Tables 35, 36 and 37:

Table 35: Severity Grading Scales for Solicited Local Adverse Events – V89_11*

Solicited Local Reactogenicity	Grade 0 (none)	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
Pain	None	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Tenderness	None	Minor light reaction to touch	Cried or protested to touch	Cried when injected limb was moved
Age <6 years: Induration, erythema, or ecchymosis	0 – 9 mm	10 – 25 mm	26 – 50 mm	>50 mm

Solicited Local Reactogenicity	Grade 0 (none)	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
Age ≥6 to <18 years: Induration, erythema, or ecchymosis	1 – 24 mm	25 – 50 mm	51 – 100 mm	>100 mm

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR Section 9.5.1.2 and Appendix 16.1.1, protocol v7.0, Appendix B.
*ClinicalTrials.gov identifier: NCT01776554
Grade 4 toxicity not defined in grading scale; to be defined in the statistical analysis plan as necessary.

Table 36: Severity Grading Scales for Solicited Systemic Adverse Events – V89 11*

Solicited Systemic Events	Grade 0 (none)	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
Fever (axillary)[1,2]	<100.4°F (<38.0°C)	100.4°F-101.1°F (38.0°C-38.4°C)	101.2°F-102.0°F (38.5°C-38.9°C)	102.1-104.0°F (39.0°C-40.0°C)
Change in eating habits[1]	None	Eating <normal for 1-2 feeds	Missed 1-2 feeds	Missed >2 feeds
Sleepiness[1]	None	Increased drowsiness	Sleeps through feeds	Sleeps for most of the time and hard to arouse
Irritability[1]	None	Requires more cuddling and less playful than usual	More difficult to settle	Unable to console
Nausea[2]	None	Present but not interfering with oral intake	Leading to decreased oral intake	Leading to minimal to no oral intake
Myalgia[2]	None	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Arthralgia[2]	None	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Headache[2]	None	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Fatigue[2]	None	No interference with activity	Some interference with activity	Significant; prevents daily activity
Loss of appetite[2]	None	Loss of appetite without decrease in oral intake	Decreased oral intake without weight loss	Decreased oral intake with weight loss
Malaise[2]	None	No interference with activity	Some interference with activity	Significant; prevents daily activity

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR Section 9.5.1.2 and Appendix 16.1.1, protocol v7.0, Appendix B.
*ClinicalTrials.gov identifier: NCT01776554
[1]Applies to children <6 years
[2]Applies to children 6 to <18 years
Grade 4 toxicity not defined in grading scale; to be defined in the statistical analysis plan as necessary.

Table 37: Severity Grading Scales for Unsolicited Adverse Events – V89_11*

Unsolicited Adverse Events	Grade 0 (none)	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
Event	n/a	Transient with no limitation in normal daily activity	Some limitation in normal daily activity	Unable to perform normal daily activity

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR Section 9.5.1.2 and Appendix 16.1.1, protocol v7.0, Appendix B.
*ClinicalTrials.gov identifier: NCT01776554
Grade 4 toxicity not defined in grading scale; to be defined in the statistical analysis plan as necessary.
n/a=not applicable.

Reviewer comment: Solicited AEs and severity grading scales were consistent with those collected in the Applicant's other pediatric influenza vaccine studies.

Reviewer comment: Although the randomization was stratified by three age groups (6 to <36 months, 3 to <6 years, and 6 to <18 years) and immunogenicity

analyses (specified as an "other" analysis set in the protocol, not as secondary or exploratory endpoints) were conducted according to these subgroups, safety analyses were conducted according to the age subgroups 6 months to <6 years and 6 years to <18 years (the protocol stated that safety analyses would be performed by "age group" but specified 6 mos to <6 yrs and 6 yrs to <18 yrs for the solicited parameters). The SAP, including the list of planned Section 14 tables, stated that safety analyses would be performed by age group, groups not specified except for solicited AEs 6 months to <6 years and 6 years to <18 years. Based on different solicited AE parameters, the age subgroup analyses of safety appear reasonable and were agreed to by CBER during review of the protocol and SAP. Subanalyses of safety for V89_11 were not discussed during the pre-BLA meeting. The Package Insert describes solicited AEs for age groups 6 months to <6 years and 6 years to <18 years. To inform dose selection for the planned post-marketing pediatric study in infants from birth to <6 months, the review team requested additional subanalyses of solicited and unsolicited AEs in children 6-35 months and 3 to <6 years.

Definitions of MAAEs and NOCD were identical to study V89_18. The list of AESIs grew larger as clinical development proceeded but was generally similar across studies. Please see V89_11 CSR, Appendix 16.1.1, protocol version 7.0, Appendix A, for the full list of AESIs.

Solicited AEs were not assessed for relatedness. The relationship of all other AEs to study treatment was determined by the investigator based on the same criteria as for study V89_18 (please see Section 6.1.7 of this review).

6.4.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints

Co-primary immunogenicity endpoints as measured by the HI assay against the H5N1 homologous vaccine virus strain at Day 43 were the: 1) SCR and 2) % HI ≥1:40.

Success criteria for the SCR and %HI ≥1:40 were the same as for subjects 18 to <65 years in study V89_18 (please see Section 6.1.8).

Secondary Immunogenicity Endpoints

Secondary immunogenicity endpoints included the following:

- GMTs at Days 1, 22, 43, and 387
- SCRs at Days 22, 43, and 387
- % HI ≥1:40 at Days 22, 43, and 387

Exploratory endpoints included responses to heterologous strains.

Safety Endpoints

Safety endpoints included solicited and unsolicited AE parameters monitored over the same time intervals as described for V89_04 (Section 6.2.8 of this review).

6.4.9 Statistical Considerations & Statistical Analysis Plan

Statistical hypotheses for the primary immunogenicity endpoints were:

- For SCR: H_0: $\pi_i - \pi_0 \leq 0$ vs H_1: H_1: $\pi_i - \pi_0 > 0$
- For %HI≥1:40: H_0: $\tau_i - \tau_0 \leq 0$ vs H_1: H_1: $\tau_i - \tau_0 > 0$

Where π_i represents an unknown SCR and π_0 represents the threshold for seroconversion (0.4), and τ_i represents an unknown %HI ≥1:40 and τ_0 represents the threshold for %HI ≥1:40 (0.7).

The multiplicity adjustment strategy for the primary analysis required that both the %HI ≥1:40 and SCR hypotheses be rejected using a two-sided 97.5% CI in the low dose group, and if successful, the high dose group could be tested using a two-sided 95% CI for each hypothesis. If unsuccessful, the high dose group would also be tested with a two-sided 97.5% CI.

Assuming a dropout rate of 10% and a true %HI ≥1:40 and SCR of 84%, the sponsor calculated that a sample size of n=100 per age/treatment group would provide 84% power to demonstrate the %HI ≥1:40 endpoint (with a two-sided alpha level of 2.5%), >99% power to demonstrate the SCR endpoint, and an overall power of ~83% to demonstrate both endpoints.

Primary immunogenicity analyses were adjusted for dose group, baseline HI titers, and center. Secondary analyses were performed with covariate adjustments for age cohort, gender, race and center. GMTs and proportions of subjects with HI ≥1:40 and seroconversion were calculated with 2-sided 95% CIs.

Safety data were analyzed using descriptive statistics. MedDRA version 17.1 was used to code unsolicited AEs.

Protocol Deviations

Protocol deviations were defined similar to studies V89_18, V89_04, and V89_13. Deviations leading to exclusions from analysis sets were reviewed and defined in the SAP prior to unblinding.

Missing Data

Missing immunogenicity data were not imputed. The primary and secondary immunogenicity analyses were conducted in the Full Analysis Set (FAS). Analyses were conducted in the Per Protocol Set (PPS) as a sensitivity analysis.

Missing safety data were handled in a manner similar to the approach outlined for V89_18 and V89_04 (please see Sections 6.1.9 and 6.2.9 of this review, SAP [CSR Appendix 16.1.9.7, Section 8.2.1] and the statistical review).

Changes in the Planned Analyses

Major changes in the protocol and planned analyses following the first versions of the protocol and SAP, and prior to enrollment of the first subject, included:

- Elimination of a booster dose at Day 387 and related analyses.
- Addition of subanalyses according to prior influenza vaccination; exploratory analyses limited to the high dose group; and updates to the list of AESIs.

6.4.10 Study Population and Disposition

6.4.10.1 Populations Enrolled/Analyzed

The predefined analysis populations for V89_11 were essentially the same as for V89_18 (Section 6.1.10.1 of this review) except for: 1) the age groups defined for immunogenicity subanalyses (6 months to <36 months, 3 years to <9 years, and 9 years to <18 years); and 2) the FAS Day 387 and PPS Day 387 which included subjects in the All Enrolled Set who provided immunogenicity data at Day 1 and Day 387 (instead of at Day 1 and Day 183 as defined in V89_18) and fulfilled the other criteria for inclusion in the FAS or PPS.

Safety data were analyzed as treated, according to actual treatment received. Subjects who provided safety data only for the 30 minute postvaccination periods were analyzed separately and were excluded from all other safety analyses.

6.4.10.1.1 Demographics

Table 38 presents demographic and baseline characteristics of the All Enrolled Set (AES) according to treatment group. Distribution of characteristics between treatment groups was balanced. Countries of enrollment included Thailand (73%) and the U.S. (27%). Males, Asians, and non-Hispanic/Latinos comprised the majority of subjects in the overall study population (52%, 73%, and 96%, respectively). The mean age of all subjects was 78.4 (SD 55.7) months. Overall, 19% of subject reported ever having received an influenza vaccination, 11% within the previous 12 months, with nearly identical proportions between treatment groups.

Table 38: Demographic and Baseline Characteristics – V89_11 (All Enrolled Set)*

Treatment	**Low dose N=330**	**High dose N=332**	**Total N=662**
Mean Age (months) (SD)	78.1 (55.6)	78.7 (55.9)	78.4 (55.7)
Age group	-	-	-
6 months to <36 months, %	32	33	32
3 years to <9 years, %	34	33	33
9 years to <18 years, %	34	34	34
Sex – Male, %	50	54	52
Sex – Female, %	50	46	48
Race, %	-	-	-
American Indian or Alaskan Native	0	<1	<1
Asian	73	72	73
Black or African American	5	4	5
White	20	22	21
Other	2	2	2
Ethnicity, %	-	-	-
Hispanic/Latino	5	4	4
Non-Hispanic/Latino	95	96	96
Country of Enrollment, %	-	-	-
Thailand, %	73	72	73
United States of America, %	27	28	27
Body Mass Index (kg/m2), Mean (SD)	17.4 (3.6)	17.4 (3.4)	17.4 (3.5)
Previous seasonal influenza vaccination, %	19	19	19
Seasonal influenza vaccination in the previous 12 months, %	12	10	11

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR, Tables 11.2-1 and 14.1.1.3.
Abbreviations: SD=standard deviation
*ClinicalTrials.gov identifier: NCT01776554
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

Percentages are based on the number of subjects in each treatment group.

Reviewer comment: Differences between treatment groups in demographic and baseline characteristics were very small and unlikely to impact interpretation of study results. Approximately 73% of subjects were from Thailand and were Asian. In study V89_11, the proportion of whites and blacks/African Americans (21% and 5%, respectively) were underrepresented relative to the U.S. population (76.5% and 13.4%, respectively). The proportion of Asians and non-Hispanics/Latinos in the study (73% and 96%, respectively) were overrepresented relative to the U.S. population (5.9% and 82.4%, respectively). Because consistent correlations between sex, race and ethnicity and the safety and immunogenicity of influenza vaccines have not been established, the study population was deemed sufficiently representative of the U.S. population. [41]

6.4.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Medical history, including proportions of subjects with prior seasonal influenza vaccination, was balanced between dose groups.

6.4.10.1.3 Subject Disposition
Table 39 presents the disposition of subjects and selected analysis populations for immunogenicity and safety, overall and by treatment group.

Table 39: Disposition of Subjects and Analysis Populations for Immunogenicity and Safety by Treatment Group – V89_11, (Enrolled Set)*

Treatment Group	Low Dose N=330 n (%)	High Dose N=332 n (%)	Total N=662 n (%)
Enrolled (as randomized)	330 (100)	332 (100)	662 (100)
Exposed (as randomized)	329 (100)	329 (99)	658 (99)
Completed	307 (93)	315 (95)	622 (94)
Premature withdrawals	23 (7)	17 (5)	40 (6)
Adverse event	0	1 (0.3)	1 (0.2)
Withdrew consent	8 (2)	3 (0.9)	11 (2)
Lost to follow-up	9 (3)	6 (2)	15 (2)
Administrative	5 (2)	2 (0.6)	7 (1)
Protocol deviation or violation	0	1 (0.3)	1 (0.2)
Other	1 (0.3)	4 (1)	5 (0.6)
Immunogenicity Populations (as randomized)	-	-	-
FAS Day 1	300 (91)	304 (92)	604 (91)
FAS Day 43	288 (87)	289 (87)	577 (87)
PPS Day 43	269 (82)	270 (81)	539 (81)
Safety Populations (as treated)	-	-	-
Exposed (as treated)	329 (100)	329 (100)	658 (100)
Overall Safety Set	329 (100)	329 (100)	658 (100)
Solicited Safety Set Overall (6 hr-Day7)	323 (98)	323 (98)	646 (98)
Unsolicited Safety Set[1]	324 (98)	326 (99)	650 (99)

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR, Tables 10.1-1, 11.1-1, 14.1.1.1, 14.1.1.1.2, and 14.1.1.2, and CSR Erratum (31 August 2015) Tables 11.1-1 and 14.1.1.1.
Abbreviations: FAS=Full Analysis Set; PPS=Per Protocol Set; AE=adverse event.
*ClinicalTrials.gov identifier: NCT01776554
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Percentages of subjects in the Subject Disposition,and Immunogenicity Populations are based on denominators using the numbers of subjects in the All Enrolled Set, with exposure/treatment as randomized.

Percentages in the Safety Populations are based on denominators using the numbers of subjects in the Exposed Set (as treated), according to actual treatment.
[1]The Unsolicited Safety Sets for Days 1-43 and Days 1-387 were identical.

Reviewer comment: The V89_11 CSR contained an Erratum that corrected errors in the PPS Day 1 sample sizes, from low dose n=300 to n=299 and from high dose n=305 to n=302 (data not shown in Table 39). Results of immunogenicity analyses on the corrected PPS were unchanged. The error had no impact on immunogenicity or safety results or study conclusions.

Of a total of n=662 enrolled subjects, n=330 and n=332 were randomized to receive low or high dose vaccine, respectively. A total of 99% (n=329) subjects in each group received study vaccine and 94% of all subjects completed the study. One subject in the low dose group and three subjects in the high dose group were not vaccinated. Forty (6%) subjects withdrew prematurely, primarily due to lost-to-follow-up (2%) or withdrawal of consent (2%). One subject (high dose subject (b) (6)) withdrew early (Day 22) due to an AE and another (high dose group) due to a protocol deviation/violation. No subject received the wrong or unassigned dose, and none were excluded from safety analyses.

A total of 25% and 28% of subjects in the low and high dose groups, respectively, had major protocol deviations, primarily due to missing serologies. Fewer than 1% of all subjects received prohibited medications or vaccines.

Reviewer comment: Most subjects (94%) completed the study. Discontinuation rates and analysis set exclusions due to deviations were balanced between treatment groups.

6.4.11 Efficacy Analyses

6.4.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity objective was to select low or high dose aH5N1c to test in Phase 3 based on the co-primary endpoints of SCR and % HI ≥1:40 at 21 days after the second vaccination (Day 43). Table 40 presents GMTs, %HI ≥1:40, and SCR at Day 1 (baseline), Day 22, and Day 43 for subjects in each dose group.

Table 40: Geometric Mean Titers, Seroconversion Rates, and Percentages of Subjects with HI ≥1:40 at Baseline and Post-Vaccination (by HI Assay) – V89_11* (Full Analysis Set)

Treatment Group	**Low dose N=300**	**High dose N=304**
GMT Day 1 (97.5% CI)	5.15 (4.91,5.39) N=300	5.23 (5,5.48) N=294
GMT Day 22 (97.5% CI)	34 (24,48) N=287	64 (46,90) N=283
GMT Day 43 (97.5% CI)	431 (312,595) N=288	1356 (985,1866) N=287
SCR Day 22 (97.5% CI)	38% (31,44) N=287	52% (45,58) N=281
SCR Day 43 (97.5% CI)	86% (81,90) N=288[1]	96% (93,98) N=279
%HI ≥1:40 Day 1 (97.5% CI)	0% (0.4,2) N=300	1% (0,3) N=294
%HI ≥1:40 Day 22 (97.5% CI)	38% (32,45) N=287	51% (44,58) N=283

Treatment Group	Low dose N=300	High dose N=304
%HI ≥1:40 Day 43 (97.5% CI)	86% (81,90) N=288	96% (92,98) N=287

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR, Tables 11.4.1-1, 11.4.1-2, 11.4.1-3, 14.2.1.1, 14.2.1.2, and 14.2.1.3, and V89_11 CSR Erratum (31 August 2015) Table 4 (corrected original CSR Table 11.4.1-1).
Abbreviations: HI=hemagglutinin inhibition; GMT=geometric mean titer; SCR=seroconversion rate; %HI ≥1:40=percentage of subjects with an anti-hemagglutination inhibition antibody titer of at least 1:40; CI=confidence interval; LB=lower bound; N=number of subjects in the denominator.
*ClinicalTrials.gov identifier: NCT01776554
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
SCR defined as percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a 4-fold increase in post-vaccination HI titer.
SCR endpoint criteria: the LB of the 2-sided 97.5% CI for the SCR must be ≥30%.
%HI ≥1:40 endpoint criteria: the LB of the 2-sided 97.5% CI for the %HI ≥1:40 must be ≥60%.
[1]V89_11 CSR Erratum indicated that an error in transcription was made from Table 14.2.1.1 to Table 11.4.1-1 and corrected the SCR Day 43 low dose group sample size from N=287 to N=288.

Both the low and high dose groups met success criteria for the SCR (LB of the 2-sided 97.5% CI for the SCR must be ≥40%) and for the %HI ≥1:40 (LB of the 2-sided 97.5% CI for the %HI ≥1:40 must be ≥70%) at Day 43.

6.4.11.2 Analyses of Secondary Endpoints

Secondary immunogenicity analyses showed that only the high dose group met success criteria for the SCR following a single vaccination (at Day 22 the LB of the 97% CI = 45%) or at twelve months following the second vaccination (at Day 387, the LB of the 97% CI = 40%). Neither group met the % HI ≥1:40 success criteria after a single vaccination or at twelve months after the second vaccination. At Day 387, GMTs in both low and high dose groups declined but remained ~5.6 and 12 times the baseline level.

Primary and secondary analyses of immunogenicity (GMTs, SCRs, and %HI ≥1:40 at Days 22 and 43) conducted on the PPS were very similar to results in the FAS.

Reviewer comment: After reviewing immunogenicity results from V89_11 provided in the pre-BLA meeting package, FDA acknowledged that both 3.75 and 7.5 mcg HA dose levels met pre-defined success criteria for immunogenicity endpoints and that either MF59-adjuvanted dose level could support an indication in children 6 months through 17 years. For licensure, the sponsor selected the 7.5 mcg HA + 0.25 mL MF59 dose which was associated with higher GMTs as compared to the lower dose at the Day 22, 43 and 387 time points.

6.4.11.3 Subpopulation Analyses

Analyses of SCRs and %HI ≥1:40 at Day 43 were performed according to age subgroups of 6 to <36 months (total n=176), 3 to <9 years (total n=192) and 9 to <18 years (total n=207). Table 41 shows that subjects in all three age subgroups, in both low and high dose groups, met the SCR and %HI ≥1:40 endpoints.

Table 41: Geometric Mean HI Titers, Seroconversion Rates and Percentages of Subjects with HI ≥1:40 at Post-Vaccination Day 43 by Age Subgroups – V89_11* (Full Analysis Set)

Age group	6 to <36 mos	6 to <36 mos	3 to <9 yr	3 to <9 yr	9 to <18 yr	9 to <18 yr
Treatment	Low dose N=85	High dose N=91	Low dose N=98	High dose N=94	Low dose N=105	High dose N=102
GMT	674	1842	363	1244	300	961

Age group	6 to <36 mos	6 to <36 mos	3 to <9 yr	3 to <9 yr	9 to <18 yr	9 to <18 yr
Treatment	**Low dose N=85**	**High dose N=91**	**Low dose N=98**	**High dose N=94**	**Low dose N=105**	**High dose N=102**
LB 95% CI on SCR	87%	94%[1]	77%	92%[2]	70%	85%
LB 95% CI on %HI ≥1:40	87%	92%	77%	93%	70%	85%

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR, Tables 14.2.1.1.8, 14.2.1.2.8 and 14.2.1.3.8.
Abbreviations: HI=hemagglutinin inhibition; SCR=seroconversion rate; GMT=geometric mean HI titer; %HI ≥1:40=percentage of subjects with an anti-hemagglutination inhibition antibody titer of at least 1:40; CI=confidence interval; LB=lower bound; N=number of subjects in the denominator.
*ClinicalTrials.gov identifier: NCT01776554
[1]N=84
[2]N=93
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
SCR defined as percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a 4-fold increase in post-vaccination HI titer.
SCR endpoint criteria: the LB of the 2-sided 95% CI for the SCR must be ≥40%.
%HI ≥1:40 endpoint criteria: the LB of the 2-sided 95% CI for the %HI ≥1:40 must be ≥70%.

Reviewer comment: Across age groups, subjects in the high dose group had higher immune responses as compared to the low dose group. In both dose groups, subjects 6 to <36 months had higher immune responses relative to the other two age subgroups. The explanation for this observation is unclear.

Subanalyses of the %HI ≥1:40 (95% CIs) at Day 43 among high dose aH5N1c recipients by sex, race and ethnicity showed the following: females 96% (91,99), males 96% (91,98); Asians 95% (91,98), blacks/African Americans 100% (63,100), and whites 97% (89,100); Hispanic/Latinos 92% (62,100) and non-Hispanic/non-Latinos 96% (93,98). SCRs showed patterns very similar to the %HI ≥1:40. GMTs were higher in females [1800 (95% CI: 1148, 2824)] as compared to males [1185 (95% CI: 824, 1705)] but 95% CIs were overlapping. GMTs among racial subgroups were similar with overlapping 95% CIs: Asians [1095 (95% CI: 862,1392)], blacks/African Americans [1036 (95% CI: 298, 3598)], and whites [1055 (95% CI: 727, 1531)]. GMTs in Hispanic/Latinos were higher as compared to non-Hispanic/non-Latinos [2510 (95% CI: 1593, 3954) vs 1212 (95% CI: 893, 1647)], but the sample size of Hispanic/Latinos was small (n=12) and 95% CIs were wide.

Subanalyses of the %HI ≥1:40 (95% CIs) at Day 43 among high dose aH5N1c recipients by country showed the following: U.S. 98% (91,100), Thailand 95% (91,98). SCRs were nearly identical to the %HI ≥1:40. GMTs were higher in U.S. subjects [1440 (95% CI: 1073, 1933)] as compared to Thai subjects [1095 (95% CI: 862, 1392)].

Reviewer comment: Subanalyses of immunogenicity by sex, race, ethnicity and country followed patterns observed in the overall study population. Results are limited by the relatively small sample sizes and descriptive nature of the analyses.

6.4.11.4 Dropouts and/or Discontinuations

Please see Section 6.4.9. The proportions of low and high dose vaccine recipients who comprised the FAS Day 43 (87% in both groups) and PPS Day 43 (82% and 81%, respectively) were similar between treatment groups. Missing data were not imputed and were unlikely to impact the interpretation of immunogenicity results. Sensitivity

analyses showed that %HI ≥1:40, SCRs, and GMTs between the FAS and PPS were nearly identical.

6.4.11.5 Exploratory and Post Hoc Analyses

Exploratory analyses, performed in the high dose group, showed some cross-reactive HI antibody responses to heterologous influenza A/H5 strains. Immune responses as measured by MN assay showed patterns similar to HI antibody responses.

6.4.12 Safety Analyses

6.4.12.1 Methods

The Overall Safety Set Overall (OSS) was used to summarize all safety data, was identical to the Exposed Set (ES), and included all subjects who received any study vaccination and provided any safety data. The OSS was comprised of 658 subjects who received low (n=329) or high (n=329) dose vaccine. Most subjects (97%) received both vaccinations. Data were analyzed according to actual treatment received. Safety data were collected and analyzed by methods similar to studies V89_18, V89_04 and V89_13 (Sections 6.1.12.1, 6.2.12.1 and 6.3.12.1). Table 39 (Section 6.4.10.1.3, Subject Disposition) summarizes safety analyses populations.

Reviewer comment: The SAP pre-specified and the CSR indicated that the Unsolicited Safety Set (USS) would be used for the analyses of unsolicited AEs. However, review of the CSR table headings and their denominators indicated that the sponsor used both the OSS and the USS to summarize unsolicited AEs with onset after any vaccination, overall and by severity and/or relatedness, for various time periods, including the Day 1-43 and Day 1-387 time periods. The difference between the OSS/ES (total n=658, 100%) and the USS (Day 1-43 and Day 1-387) (total n=650, 99%) was very small and use of one or the other did not affect interpretation of the data. Because the sponsor used the OSS for most of the unsolicited AE analyses and the clinical review team viewed the OSS as being the more appropriate analysis set for unsolicited AEs, this review will summarize overall unsolicited AEs based on the OSS. Because the sponsor used only the USS Day 1-Day 387 for analyses of deaths, SAEs, AESIs, NOCDs, MAAEs and AEs leading to premature withdrawal, we will use these analyses for this review.

6.4.12.2 Overview of Adverse Events

The SSS after any vaccination (excluding the 30-minute post-vaccination observation period) was comprised of n=323 (98%) low dose and n=323 (98%) high dose aH5N1c recipients. Overall, 98% and 96% of all enrolled subjects returned solicited AE diary cards after the first and second vaccinations, respectively, similar proportions between treatment groups.

<u>Solicited Local Adverse Events</u>

Tables 42 and 43 summarize the frequencies of solicited local AEs reported in the seven days following vaccinations in children 6 months to <6 years and 6 years through 17 years, respectively, according to treatment group, dose and maximum severity. Excluding the 30-minute post-vaccination observation period, a total of 57% and 56% of children 6 months to <6 years in the low (n=162) and high (n=160) dose groups, respectively, and 71% and 68% of children 6 years through 17 years in the low (n=161) and high (n=163) dose groups, respectively, reported any solicited local AE. Among

children 6 months to <6 years, injection site tenderness was the most frequently reported local AE following any vaccination (56% in both dose groups). Local erythema, induration and ecchymosis occurred infrequently (1%-3% of subjects in either dose group). In both dose groups, all local reactions were mild to moderate in severity except for three subjects who experienced severe tenderness (1% in each group). Among children 6 years to <18 years, injection site pain was the most frequently reported local AE following any vaccination (low dose 72%, high dose 68%). Local erythema, induration, and ecchymosis occurred in 0 to 2% of subjects in either dose group. Local AEs were mild to moderate in severity except for in three subjects (1% in each dose group) who reported severe injection site pain. Within both age cohorts, rates of local AEs were similar between treatment groups and were lower following the second as compared to the first vaccination. In both age cohorts, most local reactions resolved within 3 days of onset.

Table 42: Children 6 Months to <6 Years - Solicited Local Adverse Events Occurring on Day 1 through Day 7 after Any Vaccination (excluding 30-minute post-vaccination observation period) by Vaccination and Maximum Severity (Solicited Safety Set) – V89_11*

Group	**-**	**Low N=162**	**Low N=161**	**Low N=157**	**High N=160**	**High N=159**	**High N=158**
Vaccination	**-**	**Any**	**1st**	**2nd**	**Any**	**1st**	**2nd**
Local AE	**Grade[1]**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Erythema	N	N=162	N=161	N=156	N=159	N=157	N=158
Erythema	Any[2]	2 (1)	2 (1)	0	4 (3)	2 (1)	2 (1)
Erythema	Severe	0	0	0	0	0	0
Induration	N	N=162	N=161	N=157	N=159	N=158	N=158
Induration	Any[2]	2 (1)	0	2 (1)	2 (1)	1 (1)	1 (1)
Induration	Severe	0	0	0	0	0	0
Ecchymosis	N	N=162	N=161	N=157	N=159	N=158	N=158
Ecchymosis	Any[2]	1 (1)	0	1 (1)	0	0	0
Ecchymosis	Severe	0	0	0	0	0	0
Tenderness	N	N=162	N=161	N=156	N=159	N=158	N=158
Tenderness	Any[2]	91 (56)	79 (49)	60 (38)	89 (56)	74 (47)	68 (43)
Tenderness	Severe	1 (1)	1 (1)	0	2 (1)	2 (1)	0

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR, Tables 12.2.1-1, 12.2.3-1a, 14.3.1.1.1, and 14.3.1.2.
*ClinicalTrials.gov identifier: NCT01776554
Percentages are based on number of subjects in each group for whom data were not missing.
[1]Grading scale for measured erythema, induration and ecchymosis (6 months to <6 years): Grade 0: <10mm; Grade 1: 10-25mm; Grade 2: 25-50mm; Grade 3: >50mm.
[2]Any refers to the occurrence of any Grade 1, 2, or 3 reaction.
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

Table 43: Children 6 Years through 17 Years - Solicited Local Adverse Events Occurring on Day 1 through Day 7 after Any Vaccination (excluding 30-minute post-vaccination observation period) by Vaccination and Maximum Severity (Solicited Safety Set) – V89_11*

Group	**-**	**Low N=161**	**Low N=161**	**Low N=159**	**High N=163**	**High N=163**	**High N=159**
Vaccination	**-**	**Any**	**1st**	**2nd**	**Any**	**1st**	**2nd**
Local AE	**Grade[1]**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Erythema	N	N=161	N=160	N=158	N=163	N=162	N=158
Erythema	Any[2]	0	0	0	2 (1)	1 (1)	1 (1)
Erythema	Severe	0	0	0	0	0	0
Induration	N	N=160	N=159	N=158	N=163	N=163	N=159

Group	-	Low N=161	Low N=161	Low N=159	High N=163	High N=163	High N=159
Vaccination	**-**	**Any**	**1st**	**2nd**	**Any**	**1st**	**2nd**
Local AE	**Grade[1]**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Induration	Any[2]	2 (1)	0	2 (1)	4 (2)	3 (2)	1 (1)
Induration	Severe	0	0	0	0	0	0
Ecchymosis	N	N=160	N=159	N=158	N=163	N=163	N=159
Ecchymosis	Any[2]	0	0	0	0	0	0
Ecchymosis	Severe	0	0	0	0	0	0
Pain	N	N=160	N=159	N=158	N=163	N=163	N=159
Pain	Any[2]	115 (72)	109 (69)	65 (41)	111 (68)	109 (67)	61 (38)
Pain	Severe	1 (1)	1 (1)	1 (1)	2 (1)	1 (1)	1 (1)

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR, Tables 12.2.1-2, 12.2.3-1b, 14.3.1.1.1.0, and 14.3.1.2.0.
*ClinicalTrials.gov identifier: NCT01776554
Percentages are based on number of subjects in each group for whom data were not missing.
[1]Grading scale for measured erythema, induration and ecchymosis (6 years through 17 years): Grade 0: <25mm; Grade 1: 25-50mm; Grade 51-100mm; Grade 3: >100mm.
[2]Any refers to the occurrence of any Grade 1, 2, or 3 reaction.
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

Solicited Systemic Adverse Events

Tables 44 and 45 summarize the frequencies of solicited systemic AEs reported in the seven days following vaccinations in children 6 months to <6 years and 6 years through 17 years, respectively, according to treatment group, dose and maximum severity. Excluding the 30-minute post-vaccination observation period, a total of 40% and 43% of children 6 months to <6 years in the low and high dose groups, respectively, and 51% and 48% of children 6 years through 17 years in the low and high dose groups, respectively, reported any solicited systemic AE.

Among children 6 months to <6 years, the most frequently reported solicited systemic AEs (≥20%) following any vaccination in low and high dose vaccine recipients, respectively, were irritability (28% vs 30%) and sleepiness (25% in both groups). Most events were mild to moderate in severity and resolved within 2-3 days of onset. Severe irritability and sleepiness occurred in ≤1% of children. In both dose groups, more subjects had AEs following the first vaccination as compared to the second vaccination. Fever (≥38.0°C, ≥100.4°F) following any vaccination occurred in 8% of low dose and 16% of high dose vaccine recipients. Four (2%) low dose and two (1%) high dose recipients had Grade 3 fever (102.1°F to <104.0°F [39.0°C to <40.0°C]) and one (1%) high dose recipient had Grade 4 fever (≥104.0°F [≥40°C]). Most fevers occurred within two days of vaccinations and resolved within one to two days. A total of 26 (16%) and 37 (23%) of low and high dose recipients, respectively, used analgesics or antipyretics to treat pain or fever in the seven days following any vaccination.

Among children 6 years through 17 years, the most frequently reported solicited systemic AEs (≥20%) following any vaccination in low and high dose vaccine recipients, respectively, were fatigue (30% vs 27%), headache (29% vs 22%), myalgia (23% vs 30%), and malaise (24% vs 25%). Most solicited systemic AEs were mild to moderate in severity and resolved within 2-3 days of onset. Severe solicited systemic AEs occurred in ≤1% of subjects in either group. In both dose groups, more subjects had AEs following the first as compared to the second vaccination. Fever (≥38.0°C, ≥100.4°F) following any vaccination occurred in 3% of low dose and 4% of high dose vaccine

recipients. One (1%) low dose and one (1%) high dose recipient had Grade 3 fever (102.1°F to <104.0°F [39.0°C to <40.0°C]). No children 6 years to <17 years had Grade 4 fever (≥104.0°F [≥40°C]). Most fever occurred within 4 days of vaccinations and resolved within one day. A total of 23 (14%) and 24 (15%) of low and high dose recipients, respectively, used analgesics or antipyretics to treat pain or fever in the seven days following any vaccination.

Table 44: Children 6 Months to <6 Years - Solicited Systemic Adverse Events Occurring on Day 1 through Day 7 after Any Vaccination (excluding 30-minute post-vaccination observation period) by Vaccination and Maximum Severity (Solicited Safety Set) – V89_11*

Group	**-**	**Low N=162**	**Low N=161**	**Low N=157**	**High N=160**	**High N=159**	**High N=158**
Vaccination	**-**	**Any**	**1st**	**2nd**	**Any**	**1st**	**2nd**
Systemic AE	**Grade[1]**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Change in eating habits	N	N=162	N=161	N=157	N=159	N=157	N=158
Change in eating habits	Any[2]	20 (12)	19 (12)	6 (4)	29 (18)	21 (13)	12 (8)
Change in eating habits	Severe	0	0	0	0	0	0
Sleepiness	N	N=162	N=161	N=157	N=159	N=157	N=158
Sleepiness	Any[2]	40 (25)	32 (20)	14 (9)	40 (25)	27 (17)	23 (15)
Sleepiness	Severe	1 (1)	1 (1)	0	0	0	0
Irritability	N	N=162	N=161	N=156	N=159	N=157	N=158
Irritability	Any[2]	45 (28)	35 (22)	26 (17)	47 (30)	35 (22)	29 (18)
Irritability	Severe	2 (1)	2 (1)	0	1 (1)	1 (1)	0
Fever	N	N=162	N=158	N=157	N=160	N=158	N=158
Fever	Any	13 (8)	10 (6)	4 (3)	25 (16)	11 (7)	16 (10)
Fever	Grade 1	7 (4)	5 (3)	2 (1)	9 (6)	4 (3)	7 (4)
Fever	Grade 2	2 (1)	1 (1)	2 (1)	13 (8)	6 (4)	7 (4)
Fever	Grade 3	4 (2)	4 (2)	0	2 (1)	1 (1)	1 (1)
Fever	Grade 4	0	0	0	1 (1)	0	1 (1)

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR, Tables 12.2.1-1, 12.2.3-2a, 14.3.1.1.1, and 14.3.1.2.
*ClinicalTrials.gov identifier: NCT01776554
Percentages are based on number of subjects in each group for whom data were not missing.
[1]Grading scale for body temperature: Fever analyzed by two methods: 1) as None (<38.0°C, <100.4°F) or Any (≥38.0°C, ≥100.4°F); and 2) in 0.5°C increments. The grading scale used in this review is as follows: Grade 0: <38.0°C (<100.4°F); Grade 1: 38.0°C -38.4°C (100.4°F-101.1°F); Grade 2: 38.5°C-38.9°C (101.2°F-102.0°F); Grade 3: 39.0°C to ≤40.0°C (102.1°F to ≤104.0°F); Grade 4: >40.0°C (>104.0°F).
[2]Any refers to the occurrence of any Grade 1, 2, 3, or 4 reaction.
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

Table 45: Children 6 Years through 17 Years - Solicited Systemic Adverse Events Occurring on Day 1 through Day 7 after Any Vaccination (excluding 30-minute post-vaccination observation period) by Vaccination and Maximum Severity (Solicited Safety Set) – V89_11*

Group	**-**	**Low N=161**	**Low N=161**	**Low N=159**	**High N=163**	**High N=163**	**High N=159**
Vaccination	**-**	**Any**	**1st**	**2nd**	**Any**	**1st**	**2nd**
Systemic AE	**Grade[1]**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Nausea	N	N=160	N=158	N=158	N=162	N=162	N=158
Nausea	Any[2]	26 (16)	22 (14)	9 (6)	21 (13)	14 (9)	10 (6)
Nausea	Severe	1 (1)	0	1 (1)	2 (1)	0	2 (1)
Myalgia	N	N=160	N=157	N=157	N=162	N=162	N=158
Myalgia	Any[2]	44 (28)	36 (23)	20 (13)	49 (30)	45 (28)	14 (9)
Myalgia	Severe	1 (1)	1 (1)	1 (1)	0	0	0
Arthralgia	N	N=160	N=157	N=158	N=162	N=162	N=158

Group	-	Low N=161	Low N=161	Low N=159	High N=163	High N=163	High N=159
Vaccination	**-**	**Any**	**1st**	**2nd**	**Any**	**1st**	**2nd**
Systemic AE	**Grade[1]**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Arthralgia	Any[2]	19 (12)	13 (8)	9 (6)	21 (13)	17 (10)	6 (4)
Arthralgia	Severe	1 (1)	0	1 (1)	0	0	0
Headache	N	N=160	N=157	N=157	N=162	N=162	N=158
Headache	Any[2]	47 (29)	36 (23)	23 (15)	36 (22)	28 (17)	14 (9)
Headache	Severe	2 (1)	0	2 (1)	0	0	0
Fatigue	N	N=160	N=157	N=158	N=162	N=162	N=158
Fatigue	Any[2]	48 (30)	43 (27)	22 (14)	43 (27)	34 (21)	19 (12)
Fatigue	Severe	2 (1)	1 (1)	2 (1)	1 (1)	1 (1)	1 (1)
Loss of appetite	N	N=160	N=157	N=157	N=162	N=162	N=158
Loss of appetite	Any[2]	18 (11)	14 (9)	8 (5)	22 (14)	15 (9)	9 (6)
Loss of appetite	Severe	0	0	0	1 (1)	0	1 (1)
Malaise	N	N=160	N=156	N=158	N=162	N=162	N=158
Malaise	Any[2]	38 (24)	33 (21)	13 (8)	40 (25)	34 (21)	16 (10)
Malaise	Severe	1 (1)	1 (1)	1 (1)	2 (1)	1 (1)	1 (1)
Fever	N	N=161	N=161	N=159	N=163	N=162	N=159
Fever	Any	5 (3)	3 (2)	2 (1)	7 (4)	5 (3)	2 (1)
Fever	Grade 1	4 (2)	3 (2)	1 (1)	5 (3)	5 (3)	0
Fever	Grade 2	0	0	0	1 (1)	0	1 (1)
Fever	Grade 3	1 (1)	0	1 (1)	1 (1)	0	1 (1)
Fever	Grade 4	0	0	0	0	0	0

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR, Tables 12.2.1-2, 12.2.3-2b, 14.3.1.1.1.0, and 14.3.1.2.0.
*ClinicalTrials.gov identifier: NCT01776554
Percentages are based on number of subjects in each group for whom data were not missing.
[1]Grading scale for body temperature: Fever analyzed by two methods: 1) as None (<38.0°C, <100.4°F) or Any (≥38.0°C, ≥100.4°F); and 2) in 0.5°C increments. The grading scale used in this review is as follows: Grade 0: <38.0°C (<100.4°F); Grade 1: 38.0°C -38.4°C (100.4°F-101.1°F); Grade 2: 38.5°C-38.9°C (101.2°F-102.0°F); Grade 3: 39.0°C to ≤40.0°C (102.1°F to ≤104.0°F); Grade 4: >40.0°C (>104.0°F).
[2]Any refers to the occurrence of any Grade 1, 2, 3, or 4 reaction.
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

Solicited AEs by Age Sub-Groups 6 Months to <3 Years and 3 Years to <6 Years

In the BLA submission, the sponsor proposed changing the proposed dose of aH5N1c vaccine for infants <6 months in the agreed initial Pediatric Study Plan (iPSP) from 3.75 mcg H5N1 HA/0.125 mL MF59 to 7.5 mcg H5N1 HA/0.25 mL MF59. To determine whether the sponsor's request was acceptable with respect to safety, CBER requested subgroup analyses of solicited AEs in children 6 months to <6 years from study V89_11 to evaluate whether there were large differences in reactogenicity between dose levels in two younger age subgroups 6 months to <3 years and 3 years to <6 years. The sponsor submitted the requested analyses in STN 125692/0/14. A total of n=212 children 6 months to <3 years (6-35 months) and n=118 children 3 to <6 years (36-71 months) were equally randomized to receive either high or low dose vaccine. Rates of any local injection site reaction from 6 hours to 7 days following any vaccination were similar between age and dose groups, ranging from 52% (6-35 months, low dose) to 64% (36-71 months, low dose). Local reactogenicity consisted almost exclusively of tenderness and was mostly mild to moderate in both age groups. Severe tenderness occurred in 2% of children 6-35 months, low dose group, and in 6% of children 36-71 months, high dose group. No other severe local reactions occurred. Rates of solicited systemic AEs overall were more frequent in infants 6-35 months (49% of both the low

and high dose groups) than in infants 36-71 months (25%-32%), with the largest differences noted in rates of sleepiness (26%-28% versus 19%-24%) and irritability (33%-35% versus 15%-24%). Fever ≥100.4°F occurred most frequently in high dose aH5N1c recipients 6-35 months than in the other groups (21% versus 9% of younger low dose recipients and 7% of both low and high dose recipients 36-71 months). However, severe solicited systemic AEs were infrequent (0-6% of 6-35 months and 0-2% of 36-71 months). Grade 3/severe fever (≥102.1°F) occurred in 3% and 2% of low and high dose recipients 6-35 months, respectively, and in 2% of both low and high dose recipients 36-71 months. The frequencies of solicited tenderness and systemic AEs are presented in Table 46.

Table 46: Most Frequent Solicited Local and Systemic Adverse Events Reported from 6 Hours to 7 Days following Any Vaccination in Subjects 6-35 Months and 36-71 Months by Treatment Group (Solicited Safety Set) – V89_11*

Age Group	**6-35 months**	**6-35 months**	**36-71 months**	**36-71 months**
Adverse Event	**Low Dose N=103 %**	**High Dose N=100 %**	**Low Dose N=59 %**	**High Dose N=59 %**
Any Local, %	52	57	64	54
Any Systemic, %	49	49	25	32
Any tenderness, %	51	57	64	54
Severe	2	0	0	6
Change in eating habits, %	14	19	10	17
Severe	0	0	0	0
Sleepiness, %	28	26	19	24
Severe	0	0	9	0
Irritability, %	35	33	15	24
Severe	6	3	0	0
Fever, n (%)	n (%)	n (%)	n (%)	n (%)
Any fever ≥38.0°C (100.4°F)	9 (9%)	21 (21%)	4 (7%)	4 (7%)
38.0-38.4 (100.4°F-101.1°F)	4 (4%)	7 (7%)	3 (5%)	2 (3%)
38.5-38.9 (101.2°F-102.0°F)	2 (2%)	12 (12%)	0	1 (2%)
39.0-39.4 (102.1°F-102.9°F)	2 (2%)	1 (1%)	1 (2%)	0
39.5-39.9 (103.0°F-103.8°F)	1 (1%)	1 (1%)	0	0
Any fever ≥40°C (≥104°F)	0	0	0	1 (2%)
Any fever ≥39.0°C (≥102.1°F)	3 (3%)	2 (2%)	1 (2%)	1 (2%)

Source: Adapted from STN 125692/0/14, CSR V89_11, Module 5, Tables 2, 4, 8, 1.2.7.2.1, 1.2.7.4.1, 1.2.8.1.1, 1.2.8.2.1.

*ClinicalTrials.gov identifier: NCT01776554

Percentages are based on number of subjects in each group for whom data were not missing.

[1]Grading scale for body temperature: Fever analyzed by two methods: 1) as None (<38.0°C, <100.4°F) or Any (≥38.0°C, ≥100.4°F); and 2) in 0.5°C increments. The grading scale used in this review is as follows: Grade 0: <38.0°C (<100.4°F); Grade 1: 38.0°C -38.4°C (100.4°F-101.1°F); Grade 2: 38.5°C-38.9°C (101.2°F-102.0°F); Grade 3: 39.0°C to ≤40.0°C (102.1°F to ≤104.0°F); Grade 4: >40.0°C (>104.0°F).

[2]Any refers to the occurrence of any Grade 1, 2, 3, or 4 solicited adverse event.

High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL

Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

Reviewer comment: Age subgroup analyses of solicited AEs showed similar rates of local AEs between age groups regardless of dose level while rates of systemic AEs were somewhat higher in the younger children but mostly mild to moderate in severity. Overall, rates of solicited local and systemic AEs among high dose aH5N1c recipients in both age groups were acceptable and support the sponsor's proposal to change the dose of aH5N1c for infants <6 months in the proposed

deferred pediatric study V89_19 to high dose 7.5 mcg H5N1 HA/0.25 mL MF59. Please see Section 9.1.3, Pediatric Use and PREA Considerations, of this review for additional information.

Unsolicited Adverse Events (Day 1 through Day 43)
Treatment emergent AEs were collected and categorized by methods similar to V89_18, V89_04 and V89_13, using MedDRA version 17.1.

A total of 180 (27%) subjects reported unsolicited AEs in the 21 days following any vaccination (through Day 43), with similar overall rates of AEs between treatment groups (low dose 29%, high dose 26%). No larges imbalances in the rates of individual events as categorized by MedDRA PT or by SOC were observed between treatment groups.

Most unsolicited AEs were mild to moderate in severity (20% and 7% of subjects, respectively) and assessed as unrelated to study vaccine. A total of 1% of subjects in either treatment group reported severe (Grade 3) AEs. A total of 4% of subjects in each group reported unsolicited AEs assessed as related by the investigator, with <1% of subjects assessed as having severe (Grade 3) AEs related to study vaccine.

Reviewer comment: Rates of unsolicited AEs were low, mostly mild to moderate in severity, and generally similar between treatment groups. No large imbalances or unusual patterns of specific events were observed. No febrile seizures or convulsions were reported in the 21 days following any vaccination. One subject had an SAE of a febrile convulsion on Study Day 52 and a second subject had a convulsion, unassociated with fever or pre-existing symptoms of illness, on Study Day 145 (please see Section 6.4.12.4 for details).

Subpopulation Analyses of Solicited and Unsolicited AEs
Subpopulation analyses of solicited and unsolicited AEs were limited by small sample sizes, e.g., in blacks/African Americans and Hispanic/Latinos who comprised 5% and 4% of enrolled subjects, respectively. Generally, after any vaccination (Day 1-7, excluding the 30-minute post-vaccination period), across both treatment groups, females reported more solicited local reactions as compared to males (age 6 months to <6 years: 63% vs 50%, respectively; age 6 through 17 years: 74% vs 66%, respectively) and more solicited systemic AEs (age 6 months to <6 years:43% vs 40%, respectively; age 6 years through 17 years: 56% vs 44%, respectively). In children 6 months to <6 years, the rates of any solicited local reactions after any vaccination (Day 1-7) across treatment groups among whites, blacks/African Americans, and Asians were 71%, 57%, and 53%, respectively, and rates of solicited systemic AEs were 59%, 57%, and 36%, respectively. In children 6 years through 17 years, the rates of any solicited local reactions after any vaccination (Day 1-7) across treatment groups among whites, blacks/African Americans, and Asians were 86%, 55%, and 65%, respectively, and rates of solicited systemic AEs were 59%, 73%, and 45%, respectively. In children 6 months to <6 years, the rates of any solicited local reactions after any vaccination (Day 1-7) in Hispanics/Latinos vs non-Hispanics/Latinos were 71% vs 56%, respectively, and for solicited systemic AEs, 71% and 40%, respectively. In children 6 years through 17 years, the rates of any solicited local reactions after any vaccination (Day 1-7) in Hispanics/Latinos and non-Hispanics/non-Latinos were 86% and 69%, respectively, and for solicited systemic AEs, 79% and 48%, respectively. For subpopulation analyses of unsolicited AEs, the sponsor reported rates covering the 12 months following any vaccination. Across treatment groups, the overall rates of unsolicited AEs after any vaccination in females as

compared to males (Days 1-387) were 43% vs 50%, respectively, and for whites, blacks/African Americans, and Asians, 70%, 38%, and 40%, respectively. Because they were not provided in the CSR, the reviewer requested subpopulation analyses of unsolicited AEs by ethnicity from Day 1 through Day 43. Across treatment groups, the overall rates of unsolicited AEs after any vaccination in Hispanics/Latinos as compared to non-Hispanics/non-Latinos were 42.9% vs 26.7%.

Of 658 subjects in the OSS, n=478 (72.6%) were enrolled in Thailand and n=180 (27.4%) in the U.S. Across age and dose groups, fewer subjects from Thailand than the U.S. reported solicited local AEs after any vaccination (children 6 months to <6 years: 53% vs 66%; children 6 years to <18 years: 65% vs 82%, respectively). Solicited systemic AEs were also reported less frequently in subjects from Thailand than the U.S. (children 6 months to <6 years: 36% vs 57%; children 6 years to <18 years: 45% vs 61%, respectively). In both countries, most solicited AEs were mild to moderate in severity and frequencies of both solicited local and systemic AEs were lower following the second vaccination. Patterns of specific solicited AEs followed those observed in the overall study population. Fever ≥100.4°F (≥38.0°C) in the seven days following any vaccination occurred in 27 (11%) and 11 (13%) children 6 months to <6 years from Thailand and the U.S., respectively, and 9 (4%) and 3 (3%) children 6 years to <18 years, respectively.

Subpopulation analyses of unsolicited AEs by country showed that fewer subjects from Thailand than the U.S. reported any AE in the 21 days following any vaccination (Days 1-43): among children 6 months to <6 years 30.4% vs 46.7%, respectively; among children 6 years to <18 years 11.8% vs 41.1%, respectively. Children in the U.S. generally reported more vomiting, diarrhea and pyrexia, perhaps reflecting geographical and seasonal differences in contagious childhood illnesses prevalent during the study period.

Reviewer comment: Subpopulation analyses were descriptive and limited by small sample sizes. In general, higher percentages of females, whites, and Hispanics/Latinos reported solicited local and systemic AEs as compared to males, blacks/African Americans and Asians, and non-Hispanics/non-Latinos, respectively. Overall rates of unsolicited AEs were slightly lower in females as compared to males, higher in whites as compared to other racial groups, and higher in Hispanics/Latinos as compared to non-Hispanics/non-Latinos. Subjects from the U.S. reported more solicited and unsolicited AEs than subjects from Thailand, but patterns of events were similar. The significance of these differences is unknown due to the descriptive nature of the analyses and small sample sizes.

6.4.12.3 Deaths

No deaths were reported during the study.

6.4.12.4 Nonfatal Serious Adverse Events

A total of 24 SAEs (all non-fatal) occurred from Day 1 through Day 387, including 14 SAEs reported by 11 subjects (3%) in the low dose group and 10 SAEs reported by 8 (2%) subjects in the high dose group. All SAEs were considered unrelated to study vaccine. One subject (low dose) had an SAE with onset in the Day 1-43 post-vaccination period. The remaining SAEs began during the Day 44-387 period. Table 47

summarizes the percentages of subjects who had SAEs according to study period, MedDRA PT and SOC, and treatment group.

Table 47: Subjects with Serious Adverse Events through 366 days following the Second Vaccination (Day 387) by Study Period, Body System, Preferred Term and Treatment Group (Unsolicited Safety Set) – V89_11*

Study Period	Treatment Group	Low Dose N=329	High Dose N=329	Total N=658
D1-387	**Subjects with any SAE, n (%)**	11 (3)	8 (2)	19 (3)
D1-43	**Subjects with any SAE, n (%)**	1 (<1)	0	1 (<1)
D44-387	**Subjects with any SAE, n (%)**	10 (3)	8 (2)	18 (3)
D1-43	**System Organ Class, n (%)** **Preferred Term, n (%)**	-	-	-
D1-43	**Infections and infestations**	1 (<1)	0	1 (<1)
	Influenza	1 (<1)	0	1 (<1)
D44-387	**System Organ Class, n (%)** **Preferred Term, n (%)**	-	-	-
D44-387	**Gastrointestinal disorders**	1 (<1)	1 (<1)	2 (<1)
D44-387	Food poisoning	1 (<1)	1 (<1)	2 (<1)
D44-387	**Infections and infestations**	4 (1)	6 (2)	10 (2)
D44-387	Bronchopneumonia	1 (<1)	0	1 (<1)
D44-387	Cellulitis orbital	0	1 (<1)	1 (<1)
D44-387	Dengue fever	1 (<1)	1 (<1)	2 (<1)
D44-387	Gastroenteritis	1 (<1)	2 (1)	3 (<1)
D44-387	Pneumonia	0	2 (1)	2 (<1)
D44-387	Pneumonia influenza	1 (<1)	0	1 (<1)
D44-387	Streptococcal sepsis	0	1 (<1)	1 (<1)
D44-387	Upper respiratory tract infection	0	1 (<1)	1 (<1)
D44-387	**Injury, poisoning and procedural complications**	3 (1)	0	3 (<1)
D44-387	Clavicle fracture	1 (<1)	0	1 (<1)
D44-387	Femur fracture	1 (<1)	0	1 (<1)
D44-387	Laceration	1 (<1)	0	1 (<1)
D44-387	Tibia fracture	1 (<1)	0	1 (<1)
D44-387	Upper limb fracture	1 (<1)	0	1 (<1)
D44-387	**Musculoskeletal and connective tissue disorders**	1 (<1)	0	1 (<1)
D44-387	Myalgia	1 (<1)	0	1 (<1)
D44-387	**Nervous system disorders**	1 (<1)	1 (<1)	2 (<1)
D44-387	Convulsion	1 (<1)	0	1 (<1)
D44-387	Febrile convulsion	0	1 (<1)	1 (<1)
D44-387	**Respiratory, thoracic and mediastinal disorders**	1 (<1)	0	1 (<1)
D44-387	Apnoeic attack	1 (<1)	0	1 (<1)

Source: Adapted from STN 125692/0, Module 5, V89_11 CSR Tables 14.3.2.2.4, 14.3.2.2.3, and 14.3.2.3.
*ClinicalTrials.gov identifier: NCT01776554
Abbreviations: SAE=serious adverse event; N=denominator or number of subjects in respective treatment group; n=number of subjects with SAE in respective group.
Denominators for Study Days 1-43 and 1-387: Low Dose N=324, High Dose N=326, Total N=650.
Denominators for Study Days 44-387: Low Dose N=317, High Dose N=319, Total N=636.
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

Case narratives of all SAEs were reviewed. Selected narratives, based on a strong temporal relationship or other characteristics raising the possibility of relatedness or otherwise of interest, are summarized below.

- Subject (b) (6) Pneumonia influenza. The subject was a 27-month old female without significant medical history. She received aH5N1c 3.75 mcg HA + 0.125

mL MF59 on (b) (6)
(Study Day 387), she developed fever and had a positive rapid test for influenza A, was diagnosed with pneumonia, and was hospitalized. She recovered on March 23, 2014 following treatment that included oseltamivir. The investigator assessed the SAE as not related to study vaccine.

- Subject (b) (6): Convulsion. The subject was a 60-month old male without significant medical history or medications. He received aH5N1c 3.75 mcg HA + 0.125 mL MF59 on (b) (6). On August 1, 2013 (Study Day 145), he was reported to have a generalized motor seizure lasting a few minutes, witnessed by friends and a teacher. No preceding fever or illness or postictal drowsiness or irritability were reported. He was hospitalized and had an EEG reported as normal. No lumbar puncture or CT were performed, and no anticonvulsants prescribed. He had no further episodes and was discharged on (b) (6) with instructions to follow-up with a neurologist. The investigator assessed the event as not related to study vaccine.

- Subject (b) (6): Influenza. The subject was a 48-month old male without significant medical history. He received aH5N1c 3.75 mcg HA + 0.125 mL MF59 on (b) (6) (Study Day 3), he had a fever of 39.5°C, vomiting and dehydration, and was hospitalized. A rapid test for influenza was positive. He was treated with oseltamivir, discharged on (b) (6) and recovered on March 22, 2013. The investigator assessed the event as not related to study vaccine.

- Subject (b) (6): Febrile convulsion. The subject was a 33-month old male with a medical history of three prior febrile convulsions. He received aH5N1c 7.5 HA mcg + 0.25 mL MF59 on (b) (6)
(Study Day 52), he had cough, headache, penile pain, and presented to a medical clinic where he was had a febrile convulsion and was hospitalized. Examination and blood work were normal except for fever and an EEG showing an epileptic discharge. He was diagnosed with a febrile convulsion and was treated with diazepam and antipyretics. The investigator assessed the event as not related to study vaccine.

- Subject (b) (6): Pregnancy. The subject was a 192-month (16 year) old female without significant medical history or prior pregnancies. She received aH5N1c 7.5 mcg HA + 0.25 mL MF59 on (b) (6). Her LMP was on March 18, 2013. Pregnancy tests prior to each vaccination were negative. On October 31, 2013 (Study Day 208), the subject was confirmed as being pregnant with an estimated due date (EDD) of December 25, 2013. She delivered a healthy infant on (b) (6)

- Subject (b) (6): Dengue fever (SAE #1) and Pregnancy. The subject was a 192-month (16 year) old female without significant medical history, medications, or prior pregnancies. She received aH5N1c 3.75 mcg HA + 0.125 mL MF59 on (b) (6) with negative pregnancy tests prior to each vaccination. Her LMP was August 31, 2013. On July 2, 2013 (Study Day 116), she became ill and was hospitalized with dengue fever on (b) (6). She received supportive care and recovered on July 10, 2013. The dengue fever

was assessed as not related to study vaccine. On October 9, 2013 (192 days after the second vaccination), she was confirmed as pregnant with an EDD of June 7, 2014. She delivered a healthy infant on (b) (6) .

Reviewer comment: SAEs reported in V89_11 consisted of events anticipated in a general pediatric population and in this clinical trial population (e.g., dengue fever) and did not reveal unusual patterns or safety concerns. This reviewer agrees with the investigators' assessments that the SAEs were unrelated to study vaccine due to a lack of biologic plausibility, existence of more likely alternative causal factors, and/or the absence of a close temporal relationship to vaccination.

Subpopulation Analyses of SAEs

The Applicant provided subpopulation analyses of SAEs with onset from Day 1 through Day 43 and Day 44 through Day 387, according to dose group, sex and race. Sub-analyses for Days 1-43 were not meaningful because only one SAE (influenza in an Asian female) was reported in the entire study population during this period. The rates of any SAE (both dose groups combined) in females as compared to males, were 2% (n=7) vs 3% (n=11) for Days 44-387. In the Day 44-387 post-vaccination period, the rates of any SAE, in both treatment groups combined, among Asians, blacks/African Americans, and whites were 4% (n=17), 0, and 1% (n=2), respectively. Hispanics/Latinos (n=28) reported no SAEs during the study. From Day 1-387, SAEs occurred in 3.6% and 2.3% of all subjects from Thailand and the U.S., respectively, without notable differences in the types of SAEs reported.

Reviewer comment: Meaningful interpretation of subpopulation analyses of SAEs is limited by small sample sizes and low rates of events.

6.4.12.5 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest

No Adverse Events of Special Interest were reported during the study.

New Onset of Chronic Diseases

A total of three (0.4%) subjects, all low dose vaccine recipients, reported NOCDs during the study, all with onset between Days 43-387 and all assessed as unrelated to study vaccine. The NOCDs and study day of onset were: bone cyst (Day 384); attention deficit/hyperactivity disorder (Day 48); and dyspepsia (Day 302).

Medically-Attended Adverse Events

Medically-attended adverse events (MAAEs) were reviewed. A total of 223 (34%) of all subjects reported MAAEs with onset from Day 1 through Day 387, with 10.5% (n=69) of subjects experiencing onset of MAAEs in the 21 days after either vaccination (Days 1-43). The rates of MAAEs overall (low dose 35%, high dose 34%) and by body system were balanced between treatment groups. The most frequent (≥5%) MAAEs across treatment groups as categorized by SOC were: infections and infestations (27%); injury, poisoning and procedural complications (6%); and gastrointestinal disorders (5%). The most frequent (≥2%) events as categorized by PT occurring across treatment groups were: upper respiratory tract infection (13%); diarrhea (3%); otitis media (3%); gastroenteritis (2%); laceration (2%); and dermatitis contact (2%). Investigators assessed two MAAEs as possibly related to study vaccine:

- Subject (b) (6) (high dose): vomiting, mild, onset Day 7; and

- Subject (b) (6) (low dose): dermatitis allergic, mild, onset Day 2.

Reviewer comment: Although interpretation of the results is limited by the absence of a placebo group, review of V89_11 CSR Table 14.3.2.9 and MAAE Listing 14.3.2.12.7 suggested that the majority of MAAEs were events that occur commonly in a pediatric population and were unlikely to have been caused by the study vaccine due to a lack of biological plausibility and/or a close temporal relationship. Overall, MAAEs, as categorized by MedDRA SOC and PT, followed patterns similar to all unsolicited AEs with no unusual patterns or additional AEs of interest not already reported as SAEs.

Subpopulation Analyses of MAAEs

Subpopulation analyses of MAAEs by sex and between white and Asian racial groups showed no clear differences. Analyses were not performed for blacks/African Americans or Hispanic/Latinos because small sample sizes precluded meaningful analyses. MAAEs were reported by 31.6% and 41.7% of subjects from Thailand and the U.S., respectively. Between countries, subjects in the U.S. tended to have more MAAEs due to upper respiratory tract infections.

6.4.12.6 Clinical Test Results

Safety laboratories were not collected in this study.

6.4.12.7 Dropouts and/or Discontinuations

A total of 40 (6%) subjects withdrew early from the study, 7% of low dose and 5% of high dose recipients. Reasons for withdrawal were balanced between groups (please see Subject Disposition, Section 6.4.10.1.3). Subject (b) (6) (high dose group) was discontinued from the second vaccination and withdrawn from the study prematurely due to AEs of gastroenteritis rotavirus and skin (facial) rash which began on Study Days 10 and 13, respectively, and were assessed as unrelated to study vaccine.

Discontinuations from the second vaccination (regardless of whether due to AEs) were balanced between treatment groups (4% in each group). An additional two subjects in each treatment group were discontinued from the second vaccination but were not withdrawn from the study due to AEs. In the low dose group, subject (b) (6) had irritability on Study Day 4 (assessed as possibly related) and subject (b) (6) had severe (Grade 3) urticaria at the vaccination site on Study Day 1 (assessed as probably related). In the high dose group, subject (b) (6) had severe (Grade 3) pyrexia on Study Day 3 (assessed as possibly related) and subject (b) (6) had an arthropod bite on Study Day 6 (assessed as not related).

Reviewer comment: Discontinuations were infrequent and did not significantly impact the evaluation of safety.

6.4.13 Study Summary and Conclusions

Immunogenicity Conclusions

The primary immunogenicity objective of the study was to select low (half) dose or high (full) dose aH5N1c vaccine to test in Phase 3. At 21 days after the second vaccination, subjects 6 months through 17 years in both the low and high dose vaccine groups achieved both co-primary endpoints of the %HI ≥1:40 (LB of the 2-sided 97.5% CI must

exceed 70%) and the SCR (LB of the 2-sided 97.5% CI must exceed 40%). Immune responses were higher in the high dose group.

Secondary immunogenicity analyses showed that only the high dose group met success criteria for the SCR following a single vaccination (at Day 22 the LB of the 97% CI = 45%) or at twelve months following the second vaccination (at Day 387, the LB of the 97% CI = 40%). Neither group met the % HI ≥1:40 success criteria at Day 22 or Day 387. At Day 387, GMTs in both low and high dose groups declined but remained ~5.6 and 12 times the baseline level, respectively. As compared to low dose, high dose vaccine was associated with higher GMTs through Day 387. Based on an assumption that higher immune responses may be associated with greater efficacy, the Applicant selected high (full) dose aH5N1c vaccine (7.5 mcg HA + 0.25 mL MF59) for licensure in children 6 months through 17 years.

In age subgroup analyses, children 6 to <36 months, 3 years to <9 years, and 9 to <18 years each met success criteria for the co-primary immunogenicity endpoints.

Exploratory analyses in high dose aH5N1c recipients showed some cross-reactive immune responses to heterologous influenza A/H5 strains.

Safety Conclusions

Rates of solicited AEs were similar between low and high dose groups in both age groups 6 months to <6 years and 6 years through 17 years. Across age and dose groups, most solicited local and systemic AEs were mild to moderate in severity and resolved within 2-3 days. Severe solicited local and systemic AEs each occurred in ≤1% of subjects in both age groups. The most common solicited AEs in children 6 months to <6 years were injection site tenderness, irritability and sleepiness. The most common solicited AEs in children 6 years through 17 years were injection site pain, fatigue, headache, myalgia, and malaise. Higher rates of solicited AEs were observed following the first as compared to the second vaccination.

Among children 6 months to < 6 years, solicited fever (≥38.0°C, ≥100.4°F) in the seven days following any vaccination occurred in 8% of low dose and 16% of high dose vaccine recipients. Four (2%) low dose and two (1%) high dose recipients had Grade 3 fever (102.1°F to <104.0°F [39.0°C to <40.0°C]) and one (1%) high dose recipient had Grade 4 fever (≥104.0°F [≥40°C]). Most fever occurred within two days of vaccinations and resolved within one to two days. Among children 6 through 17 years, fever in the seven days following any vaccination occurred in 3% of low dose and 4% of high dose vaccine recipients. One (1%) low dose and one (1%) high dose recipient had Grade 3 fever and none had Grade 4 fever.

Among children 6 months through 17 years, the frequency and types of unsolicited AEs occurring in the 21 days following any vaccination (through Day 43) were similar between low and high dose groups and were typical of a pediatric population. Overall, 29% and 26% of subjects in each group, respectively, reported unsolicited AEs, with 1% of subjects in each group experiencing severe AEs, and 4% in each group experiencing AEs assessed as at least possibly related to study vaccine.

Three subjects were discontinued from the second vaccination due to AEs assessed as possibly or probably related to study vaccine: irritability; severe urticaria at the vaccination site; and severe pyrexia.

No deaths occurred during the study. A total of 24 non-fatal SAEs occurred from Day 1 through Day 387, including 14 SAEs reported by 11 subjects (3%) in the low dose group and 10 SAEs reported by 8 (2%) subjects in the high dose group. All but one SAE (influenza) had onset during the Day 44-387 period. SAEs consisted of events anticipated in the pediatric population represented in the clinical trial, were unrelated to study vaccine, and did not reveal unusual patterns or safety concerns. Similarly, NOCDs and MAAEs consisted of events that occur commonly in a pediatric population and did not reveal unusual patterns or safety concerns. No AESIs were reported during the study.

Subpopulation analyses of solicited and unsolicited AEs showed no clear differences between sexes or between whites and Asians. Subjects from the U.S. reported more solicited and unsolicited AEs relative to those from Thailand. Small sample sizes precluded meaningful analyses of blacks/African Americans or Hispanics/Latinos.

Overall, aH5N1c vaccine at either dose level of 7.5 mcg HA + 0.25 mL MF59 or 3.75 mcg HA + 0.125 mL MF59, administered IM to persons 6 months through 17 years as two doses 21 days apart, appeared immunogenic with an acceptable safety profile.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The Integrated Summary of Safety (ISS) included safety data from a main pooled analysis of one pivotal Phase 3 and two Phase 2 adult studies of the full (high) dose of aH5N1c vaccine intended for licensure, and an expanded pooled analysis of the same studies that included data from subjects who received either the full or half (high or low) dose of aH5N1c vaccine, as delineated in Section 8.2 below. Safety data collection methods were similar across studies. Subjects were observed for 30 minutes following each vaccination to record any immediate adverse reactions. Following the observation period, a diary card was used to collect pre-specified solicited AEs and any unsolicited AEs that occurred from Day 1-Day 7 and Day 22-Day 28, inclusive. Diary cards were also used to capture any ongoing solicited AEs or unsolicited AEs from Days 8-21 and Days 29-42. SAEs, MAAEs, NOCDs, and AESIs were collected immediately after the first vaccination through 12 months after the last vaccination, via telephone contacts, site visit interviews, and medical records. Definitions of AEs were the same across studies. The list of AESIs identified by CBER was expanded between conduct of V89_04 and V89_13 and V89_18. However, all three studies followed subjects for 12 months after the last vaccination to identify potential immune-mediated conditions that might be associated with the novel MF59 adjuvant. Solicited AE parameters and criteria for grading the severity and relatedness of AEs were the same across studies.

Reviewer comment: The Applicant's ISS referred to active treatment as full (7.5 mcg HA + 0.25 mL MF59) and half (3.75 mcg HA + 0.125 mL) dose vaccines whereas V89_04 and V89_13 CSRs referred to high (full) and low (half) dose vaccines. To avoid confusion and for consistency with the Applicant's ISS, in this section of the review we will refer to dose levels as full or half dose and to the pooled analyses as full dose or full + half dose, however, the terms are interchangeable.

The Applicant's ISS focused on exposure to the full dose vaccine intended for licensure (main pooled analysis) but also provided integrated analyses of both full and half dose vaccine recipients versus placebo (expanded pool) in adults ≥18 years and by age subgroup, 18-64 years and ≥65 years. Half dose recipients comprised 24.8% of aH5N1c vaccine recipients in the expanded pool. Including subjects exposed to half dose increased the likelihood of detecting an uncommon safety signal that is not necessarily dose-dependent. However, the expanded pool also lowered rates of AEs by increasing the denominator. Rates of AEs in the main pooled analyses (full dose alone) were more conservative. This review will summarize results of both analyses (full dose versus placebo and full + half dose versus placebo).

Because the individual study data adequately characterized commonly occurring solicited AEs in adults overall and by age subgroup (18-64 years and ≥65 years), and the ISS showed similar patterns, this review will describe integrated analyses of solicited AEs only briefly and the integrated analyses of less frequently occurring unsolicited AEs, deaths, SAEs, MAAEs, NOCDs and AESIs, in greater detail. Please refer to Sections 6.1.12.2, 6.2.12.2 and 6.3.12.2 for additional information regarding solicited AEs.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The ISS pooled data from the pivotal Phase 3 adult study V89_18 and two Phase 2 adult studies, V89_04 and V89_13 (see Section 5.3 for a tabular summary of clinical trials). The Phase 1/2 dose-ranging study of adults 18 through 40 years, V89P1 (please see Section 5.1), included 64 subjects exposed to full dose and 62 subjects who received half dose vaccine but was not integrated because of differences in study design, data collection and database structure, and use of a different A/H5N1 vaccine virus strain. Pediatric study V89_11 (Section 6.4) was not integrated because of the different age population and types of safety data collected.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Extent of Exposure

Table 48 summarizes the extent of exposure to aH5N1c vaccine by study, age and dose group. A total of 3,579 adults ≥18 years received at least one full dose, 1,179 received half dose, 4758 received either full or half dose vaccine, and 796 received placebo.

Table 48: Summary of Exposure in the Integrated Summary of Safety by Individual and Pooled Studies, Age and Dose Groups*

Study	Age group	Pooled Age Group	Pooled Dose Group	Exposed Full dose n	Exposed Half dose N	Exposed Full or Half Dose n	Exposed Placebo n
V89_18	18-64	≥18 yrs	Full	1198	-	-	398
V89_18	≥65	≥18 yrs	Full	1197	-	-	398
V89_04	18-64	≥18 yrs	Full	485	-	-	-
V89_13	≥65	≥18 yrs	Full	699	-	-	-
Total ≥18	**≥18**	**≥18 yrs**	**Full ≥18**	**3579**	**-**	**-**	**796**
V89_18	18-64	18-64	Full	1198	-	-	398
V89_04	18-64	18-64	Full	485	-	-	-
Total 18-64	**18-64**	**18-64**	**Full 18-64**	**1683**	**-**	**-**	**398**
V89_18	≥65	≥65	Full	1197	-	-	398

Study	Age group	Pooled Age Group	Pooled Dose Group	Exposed Full dose n	Exposed Half dose N	Exposed Full or Half Dose n	Exposed Placebo n
V89_13	≥65	≥65	Full	699	-	-	-
Total ≥65	**≥65**	**≥65**	**Full ≥65**	**1896**	**-**	**-**	**398**
V89_18	18-64	≥18 yrs	Full + half	1198	-	-	398
V89_18	≥65	≥18 yrs	Full + half	1197	-	-	398
V89_04	18-64	≥18 yrs	Full + half	485	490	975	-
V89_13	≥65	≥18 yrs	Full + half	699	689	1388	-
Total ≥18	**≥18**	**≥18 yrs**	**Full + half ≥18**	**3579**	**1179**	**4758**	**796**

Source: Adapted from STN 125692/0, Module 5, ISS Table 2, CSR V89_18 Table 14.1.1.1.1, CSR V89_04 Table 14.1.1.1.1, and CSR V89_13 Table 14.1.1.1.2.
*ClinicalTrials.gov identifiers: NCT02839330, NCT01776541, and NCT1766921.

In the main pooled analysis (full dose only) 97.0% and 97.9% of all full dose and placebo recipients ≥18 years, respectively, were exposed to the second vaccination. In the expanded pooled analysis (full + half dose), 96.5% and 97.9% of all full or half dose and placebo recipients ≥18 years, respectively, were exposed to the second vaccination. Vaccination rates were also similar between treatment groups within age subgroups.

Subject Disposition and Analysis Populations

Subjects included or excluded from the ISS were all those who were included or excluded from the ES, SSS, USS, and OSS defined in the individual studies (definitions were essentially the same across studies). Subjects were analyzed according to treatment actually received.

- Exposed Set (ES): All subjects who received any study vaccine or placebo.
- Solicited Safety Set (SSS): All subjects in the ES with solicited AE data and/or assessment of any use of analgesics/antipyretics.
- Unsolicited Safety Set (USS): All subjects in the ES with unsolicited AE data.
- Overall Safety Set (OSS): All subjects in the SSS and/or USS.

Across studies, a total of 88.8% to 96.9% of full dose, half dose or placebo recipients completed the protocol, with comparable rates between treatment groups within each study. Fewer than 0.5% of subjects in any treatment group across studies died during the study or withdrew from the study due to an AE. Table 49 presents analysis populations used in the ISS for both full, full + half dose, and placebo treatment groups in the main and expanded pooled analyses. The integrated SSS is not included in the table because integrated solicited AEs are addressed only briefly in this review of the ISS (Sections 8.4.6 and 8.4.7).

Table 49: Analysis Populations Used in the Main and Expanded Pooled Analyses – Pooled All Exposed Set*

Age (yrs)	≥18	≥18	≥18	18-64	18-64	18-64	≥65	≥65	≥65
Treatment	**Full N=3579 n (%)**	**Full+ Half N=4758 n (%)**	**PBO N=796 n (%)**	**Full N=1683 n (%)**	**Full+ Half N=2173 n (%)**	**PBO N=398 n (%)**	**Full N=1896 n (%)**	**Full+ Half N=2585 n (%)**	**PBO N=398 n (%)**
Exposed Set	3579 (100)	4758 (100)	796 (100)	1683 (100)	2173 (100)	398 (100)	1896 (100)	2585 (100)	398 (100)
Unsolicited Safety Set Day 1-43	3523 (98.4)	4683 (98.4)	784 (98.5)	1642 (97.6)	2117 (97.4)	388 (97.5)	1881 (99.2)	2566 (99.3)	396 (99.5)
Unsolicited Safety Set Day 1-387	3564 (99.6)	4725 (99.3)	796 (100)	1674 (99.5)	2149 (98.9)	398 (100)	1890 (99.7)	2576 (99.7)	398 (100)

Overall Safety Set	3579 (100)	4758 (100)	796 (100)	1683 (100)	2173 (100)	398 (100)	1896 (100)	2585 (100)	398 (100)

Source: Adapted from STN 125692/0, Module 5, ISS Tables 13, 14, 1.1.1.1, 2.1.1, and 2.1.1.1.
*Pooled studies V89_18, V89_04, and V89_13.
*ClinicalTrials.gov identifiers: NCT02839330, NCT01776541, and NCT1766921.
Abbreviations: Full= full (high) dose vaccine groups; Full+Half= full+half (high+low) dose vaccine groups; PBO=placebo; yrs=years; vax=vaccination.
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Exposed Set: All subjects who received a study vaccine or placebo.
Unsolicited Safety Set: All subjects in the ES with unsolicited AE data.
Overall Safety Set: All subjects who were in the Solicited Safety Set or Unsolicited Safety Set.
Percentages based on numbers of subjects in each treatment group.

Reviewer comment: In response to our January 24, 2019 IR (STN 125692/0/14), the Applicant confirmed that some ISS unsolicited AE table headings were incorrect, and that the OSS (identical to the ES), not the USS, was used for all ISS analyses of unsolicited AEs regardless of treatment period. Differences between the USS (Day 1-43 treatment period) and OSS/ES populations were small (98.4% vs 100%, respectively) and clinically insignificant for non-serious AEs. The Applicant's approach was acceptable to the review team.

Demographic and Baseline Characteristics

Table 50 presents the demographic and baseline characteristics of subjects.

Table 50: Demographic and Baseline Characteristics of Subjects, Main and Expanded Pooled Analyses – Pooled Exposed Set*

Age (yrs)	**≥18**	**≥18**	**≥18**	**18-64**	**18-64**	**18-64**	**≥65**	**≥65**	**≥65**
Treatment	**Full N=3579**	**Full+ Half N=4758**	**PBO N=796**	**Full N=1683**	**Full+ Half N=2173**	**PBO N=398**	**Full N=1896**	**Full+ Half N=2585**	**PBO N=398**
Age (yrs) Mean (SD)	57.8 (18.1)	57.7 (18.3)	57.7 (18.3)	41.9 (13.7)	41.1 (13.9)	42.8 (14.0)	71.9 (5.4)	71.6 (5.3)	72.6 (5.4)
Age 18-64 yrs N (%)	1683 (47.0)	2173 (45.7)	398 (50.0)	1683 (100)	2173 (100)	398 (100)	0	0	0
Age ≥65 yrs N (%)	1896 (53.0)	2585 (54.3)	398 (50.0)	0	0	0	1896 (100)	2585 (100)	398 (100)
Male %	43.8	43.5	45.0	42.5	43.5	43.5	45.0	43.6	46.5
Female %	56.2	56.5	55.0	57.5	56.5	56.5	55.0	56.4	53.5
Ethnicity %	-	-	-	-	-	-	-	-	-
Hispanic/Latino	8.3	8.6	6.9	14.3	15.6	8.5	3.0	2.7	5.3
Non-Hispanic/Latino	91.0	90.9	91.7	84.9	83.8	89.7	96.4	96.8	93.7
Race %	-	-	-	-	-	-	-	-	-
American Indian/ Alaskan Native	0.5	0.4	0.4	0.7	0.6	0.8	0.4	0.3	0
Asian	10.1	14.6	0.9	6.8	9.7	1.0	13.0	18.7	0.8
Black/ African American	11.8	11.1	14.1	20.0	20.0	22.4	4.5	3.7	5.8
Native Hawaiian/ Pacific Islander	0.2	0.1	0.5	0.2	0.2	0.8	0.1	0.1	0.3
White	76.9	73.2	83.3	71.4	68.6	73.9	81.8	77.0	92.7
Other	0.6	0.5	0.9	1.0	0.9	1.3	0.2	0.2	0.5
Country %	-	-	-	-	-	-	-	-	-
Australia	5.5	8.3	0	6.3	10.0	0	4.9	6.8	0
New Zealand	2.3	3.4	0	0	0	0	4.3	6.2	0
Thailand	9.0	13.6	0	5.1	7.9	0	12.5	18.3	0
USA	83.2	74.8	100	88.6	82.1	100	78.3	68.6	100

Source: Adapted from STN 125692/0, Module 5, ISS Tables 1.2.2, 1.2.2.1, 2.2.2, and 2.2.2.1.

*Pooled studies V89_18, V89_04, and V89_13.
*ClinicalTrials.gov identifiers: NCT02839330, NCT01776541, and NCT1766921.
Abbreviations: Full= full (high) dose vaccine groups; Full+Half= full+half (high+low) dose vaccine groups; PBO=placebo; yrs=years; SD=standard deviation.
High dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Low dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Percentages based on numbers of subjects in each treatment group.

Reviewer comment: Differences in age and sex across treatment groups were small and unlikely to impact interpretation of study results. Across treatment groups, the placebo group was comprised of more whites and fewer Asians as compared to the full and full + half dose groups, because a placebo group was included only in study V89_18, the only study conducted solely in the U.S. Across the aH5N1c vaccine treatment groups, Asians and non-Hispanics were overrepresented relative to the U.S. population (5.9% and 82.4%, respectively). Relative to aH5N1c recipients 18-64 years, subjects ≥65 years were comprised of more Asians, whites and non-Hispanics, and fewer blacks/African Americans and Hispanics. Because consistent correlations between sex, race and ethnicity and the safety and immunogenicity of influenza vaccines have not been established, the study population was deemed sufficiently representative of the U.S. population. [41]

8.2.3 Categorization of Adverse Events

Pooled studies collected the same types of safety data and used the same criteria for assessing severity and relatedness of AEs to study treatment. Unsolicited AEs were recoded, if applicable, to preferred terms using MedDRA version 20.0. Because CBER had updated the AESI list for V89_18, new AESI terms were searched for in studies V89_04 and V89_13 and retrospectively updated.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

V89_18, V89_04 and V89_13 shared similar features and safety endpoints that support pooling of safety data. However, differences among the studies included:

- The study populations differed geographically and by age. V89_18 was conducted solely in the U.S. while V89_04 and V89_13 were conducted in the U.S., Australia, New Zealand (V89_13 only) and Thailand. V89_18 included adults ≥18 years while V89_04 included adults 18 through 64 years and V89_13 included adults ≥65 years.
- V89_18 included a placebo control while V89_04 and V89_13 evaluated two dose levels of aH5N1c without a control group. Pooling of safety data increases the overall randomization ratio between vaccine and placebo recipients.
- Although no large differences in unsolicited safety data were apparent between full and half dose aH5N1c vaccine recipients in the individual studies, there may be dose-dependent safety findings that could theoretically be diluted by the larger denominator in the expanded pooled analysis.
- Including subjects exposed to half dose increased the likelihood of detecting an uncommon signal that is not necessarily dose-dependent. However, it also lowered the rates of AEs by increasing the denominator. Rates of AEs in the main pooled analyses (full dose alone) were more conservative.
- The studies were conducted in different seasons using different versions of MedDRA. V89_18 was conducted in 2016-2017 and used MedDRA version 20.0

while V89_04 and V89_13 were conducted in 2013-2014 and used MedDRA version 17.0. AE preferred terms required recoding to version 20.0.

Despite potential limitations associated with pooling, the purpose of performing the ISS analyses was to increase the likelihood of identifying a safety concern that might be overlooked when similar AEs occurring across studies are analyzed separately. However, because the ISS contributed only aH5N1c recipients and no additional placebo recipients to subjects in the pivotal study population (i.e., V89_18), thereby increasing the randomization ratio between aH5N1c and placebo recipients, interpretation of differences between the two groups should be interpreted carefully. Additionally, no studies other than those already reviewed in Section 6 are included in the ISS.

8.4 Safety Results

8.4.1 Deaths

Table 51 presents the proportions of subjects who had any AE leading to death during the studies in the main and expanded pooled analyses, by age and treatment groups.

Table 51: Adverse Events Leading to Deaths from Day 1 through Day 387 in the Main (Full Dose) and Expanded (Full and Half Dose) Pooled Analyses – Pooled Unsolicited Safety Set*

Age (yrs)	**≥18**	**≥18**	**≥18**	**18-64**	**18-64**	**18-64**	**≥65**	**≥65**	**≥65**
Treatment	**Full N=3579 n (%)**	**Full+ Half N=4758 n (%)**	**PBO N=796 n (%)**	**Full N=1683 n (%)**	**Full+ Half N=2173 n (%)**	**PBO N=398 n (%)**	**Full N=1896 n (%)**	**Full+ Half N=2585 n (%)**	**PBO N=398 n (%)**
Deaths, n (%)	16 (0.4)	17 (0.4)	1 (0.1)	5 (0.3)	5 (0.2)	0	11 (0.6)	12 (0.5)	1 (0.3)

Source: Adapted from STN 125692/0, Module 5, ISS Tables 16, 21, 1.6.1, 1.6.1.1, 2.6.1, 2.6.1.1.
*Pooled studies V89_18, V89_04, and V89_13.
*ClinicalTrials.gov identifiers: NCT02839330, NCT01776541, and NCT1766921.
Abbreviations: Full= full (high) dose vaccine groups; Full+Half= full+half (high+low) dose vaccine groups; PBO=placebo; yrs=years.
Full (high) dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Half (low) dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Percentages based on numbers of subjects in each treatment group.

A total of 18 deaths were reported in the pooled data for all subjects ≥18 across studies and treatment groups (full dose n=16, half dose n=1, and placebo n=1). Frequencies of deaths in subjects ≥18 years were low but were higher in the active treatment groups (0.4%) as compared to placebo (0.1%). Deaths occurred more frequently among aH5N1c recipients ≥65 years as compared to 18-64 years (0.5% [n=12] vs 0.2% [n=5]). Most subjects who died had underlying medical conditions and most deaths occurred >21 days after the last vaccination received, with an average time of death >7 months postvaccination. No deaths were considered related to study treatment by the investigator or the Applicant. Among full and half dose aH5N1c recipients, the most frequently reported SOCs leading to death were cardiac disorders (0.2%, n=7). Table 52 summarizes all deaths in subjects ≥18 years across studies by treatment and MedDRA SOC and PT. Please see Sections 6.1.12.3, 6.1.12.3 and 6.3.12.3 of this review for individual case narratives.

Table 52: Adverse Events Leading to Deaths from Day 1 through Day 387 in the Main (Full Dose) and Expanded (Full and Half Dose) Pooled Analyses by MedDRA SOC and PT – Pooled Overall Safety Set*

Age	**≥18 years**	**≥18 years**	**≥18 years**

System Organ Class Preferred Term	Full Dose N=3579 n (%)	Full+Half Dose N=4758 n (%)	Placebo N=796 n (%)
Subjects with any AE leading to death	16 (0.4)	17 (0.4)	1 (0.1)
Cardiac disorders	7 (0.2)	7 (0.1)	1 (0.1)
Cardio-respiratory arrest	2 (0.1)	2 (0.0)	0
Hypertensive heart disease	2 (0.1)	2 (0.0)	0
Myocardial infarction	2 (0.1)	2 (0.0	0
Acute myocardial infarction	1 (0.0)	1 (0.0)	0
Cardiogenic shock	0	0	1 (0.1)
Infections and infestations	3 (0.1)	4 (0.1)	0
Sepsis	2 (0.1)	2 (0.0)	0
Pneumonia	1 (0.0)	2 (0.0)[1]	0
Septic shock	1 (0.0)	1 (0.0)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.0)	0
Lung adenocarcinoma	0	1 (0.0)[1]	0
Nervous system disorders	2 (0.1)	2 (0.0)	0
Cerebral haemorrhage	1 (0.0)	1 (0.0)	0
Cerebral infarction	1 (0.0)	1 (0.0)	0
Respiratory, thoracic and mediastinal disorders	2 (0.1)	2 (0.0)	0
Acute respiratory failure	1 (0.0)	1 (0.0)	0
Respiratory failure	1 (0.0)	1 (0.0)	0
General disorders and administration site conditions	1 (0.0)	1 (0.0)	0
Death (PT unknown)	1 (0.0)	1 (0.0)	0
Injury, poisoning and procedural complications	1 (0.0)	1 (0.0)	0
Subdural haematoma	1 (0.0)	1 (0.0)	0
Renal and urinary disorders	1 (0.0)	1 (0.0)	0
Renal failure	1 (0.0)	1 (0.0)	0

Source: Adapted from STN 125692/0, Module 5, ISS Tables 52, 53, 1.6.1, 1.6.1.1, 2.6.1, 2.6.1.1, and electronic datasets.
*Pooled studies V89_18, V89_04, and V89_13.
*ClinicalTrials.gov identifiers: NCT02839330, NCT01776541, and NCT1766921.
Abbreviations: Full= full (high) dose vaccine groups; Full+Half= full+half (high+low) dose vaccine groups; SOC=system organ class; PT=preferred term.
Full (high) dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Half (low) dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Percentages based on numbers of subjects in each treatment group.
[1]One half dose aH5N1c recipient (V89_13, (b) (6), ≥65 years) contributed to all deaths in the full + half dose treatment group. Two AEs lead to death in this subject: lung adenocarcinoma onset on Day 24 and pneumonia onset Day 142.

Reviewer comment: The number of deaths reported in the ISS were consistent with the individual study reports and the electronic datasets. Although the frequencies of deaths in the two aH5N1c vaccine groups were four times higher than the placebo group, overall rates were low. The clinical reviewer agreed with the investigator and Applicant's assessments that no deaths were related to study treatment.

8.4.2 Nonfatal Serious Adverse Events

SAEs – Full Dose aH5N1c vaccine versus Placebo

Across studies, a total of n=225 (6.3%) of full dose aH5N1c recipients and n=74 (9.3%) placebo recipients experienced SAEs, with onset occurring primarily during the follow-up

period (full dose aH5N1c 5.8%; placebo 8.4%). Most SAEs occurred among subjects ≥65 years (full dose aH5N1c 9.0%; placebo 15.3%) as compared to 18-64 years (3.3% in both full dose aH5N1c and placebo groups). The most frequently reported SAEs (≥1%) by full dose and placebo recipients ≥18 years, respectively, over the entire study period, as categorized by MedDRA SOC, were: cardiac disorders (1.1 vs 2.8%), musculoskeletal and connective tissue disorders (1.0% in both groups), infections and infestations (0.9% vs 1.1%), neoplasms benign, malignant and unspecified (0.8% vs 1.3%), and gastrointestinal disorders (0.6% vs 1.1%). Among all subjects ≥18 years, one full dose aH5N1c recipient had an SAE assessed as at least possibly related to study treatment: Subject (b) (6) (V89_04, full dose aH5N1c): Abortion spontaneous, 30-year-old female, onset Day (b) (6)

Among subjects ≥65 years, the most frequent SAEs ≥(1%), as categorized by MedDRA SOC, reported by full dose and placebo recipients, respectively, were cardiac disorders (1.6% vs 5.0%), musculoskeletal and connective tissue disorders (1.7% vs 1.8%), infections and infestations (0.9% vs 1.8%), neoplasms benign, malignant, and unspecified (1.2% vs 2.0%), nervous system disorders (1.2% vs 1.5%), gastrointestinal disorders (0.9% vs 2.0%), nervous system disorders (1.2% vs 1.5%), gastrointestinal disorders (0.9% vs 2.0%), and respiratory, thoracic and mediastinal disorders (0.4% vs 1.3%). Among subjects 18 to <65 years, neither treatment group reported SAEs with a frequency of ≥1% as categorized by SOC.

Reviewer comment: Other than an imbalance of subjects who reported cardiac disorders, lower in the full dose aH5N1c group than placebo (1.1% vs 2.8%, respectively), and driven by subjects ≥65 years (1.6% vs 5.0%, respectively), no large imbalances or unusual patterns of SAEs were observed in the ISS of full dose aH5N1c recipients versus placebo. Please see the reviews of SAEs for the individual studies, Sections 6.1.12.4, 6.2.12.4 and 6.3.12.4, for additional information on selected SAEs.

<u>SAEs – Full and Half Dose aH5N1c Vaccine versus Placebo</u>

Across studies, a total of n=286 (6.0%) of full and half dose aH5N1c recipients and n=74 (9.3%) placebo recipients experienced SAEs, with onset occurring primarily during the follow-up period (full and half dose aH5N1c 5.5%; placebo 8.4%). Most SAEs occurred among subjects ≥65 years (full and half dose aH5N1c 8.6%; placebo 15.3%) as compared to 18-64 years (full and half dose aH5N1c 2.9%; placebo 3.3%). The most frequent SAEs (≥1%) reported by all full and half dose aH5N1c and placebo recipients ≥18 years, respectively, over the entire study period, as categorized by MedDRA SOC, were: cardiac disorders (1.0 vs 2.8%), musculoskeletal and connective tissue disorders (0.8% vs 1.0%), infections and infestations (0.8% vs 1.1%), neoplasms benign, malignant and unspecified (0.8% vs 1.3%), and gastrointestinal disorders (0.6% vs 1.1%). Like the analysis of full dose alone vs placebo recipients, the only relatively large imbalance observed between treatment groups was among subjects who reported cardiac disorders: 1.0% vs 2.8% among aH5N1c vs placebo recipients ≥18 years, respectively, driven by subjects ≥65 years, 1.5% vs 5.0%, respectively. Atrial fibrillation was the only SAE, as categorized by PT, that occurred with a frequency of ≥1% among all full and half dose aH5N1c recipients or in either age subgroup: among aH5N1c recipients and placebo recipients ≥18 years, respectively, (0.3% vs 1.0%) and among subjects ≥65 years, respectively, (0.5% vs 2.0%). No additional subjects in the half dose group (or expanded pool analysis) had SAEs assessed by the investigator as related to study treatment as compared to the full dose group alone (main pooled analysis).

Table 53 summarizes the integrated analysis of all SAEs reported for full and half dose aH5N1c and placebo recipients from Day 1 through the end of each study (Day 387), as categorized by MedDRA SOC and PT (for PTs with a frequency of >1%), overall in subjects ≥18 years, and by age subgroup (18-64 years and ≥65 years).

Reviewer comment: Results of the full and half dose analyses of SAEs were similar to analyses of full dose alone versus placebo. Please see the review of SAE case narratives for each individual study in Sections 6.1.12.4, 6.2.12.4, and 6.3.12.4 of this review. Most SAEs occurred in subjects ≥65 years and consisted of events typical of an elderly population and did not reveal unusual patterns, large imbalances between treatment groups, or safety concerns. For the majority of SAEs, this reviewer agrees with the investigator's assessments of relatedness to the aH5N1c vaccine due to lack of a biological plausibility, existence of more likely alternative causal factors, and/or the absence of a close temporal relationship. In study V89_18, for a few SAEs, a temporal association between vaccination and onset of the event made it difficult to completely exclude a causal relationship (e.g., acute non-STEMI, fall/cerebral hematoma, PMR, worsening sarcoid). Notably, close temporal relationships were also observed between receipt of placebo and SAEs/AESIs, but in these cases causality could be excluded due to the lack of biological plausibility given receipt of a placebo.

Table 53: Subjects with Serious Adverse Events through 366 days following the Second Vaccination (Day 387) by Study Period, Body System, Preferred Term (≥1%), Age and Treatment Group in the Expanded (Full + Half Dose) Pooled Analyses – (Pooled Overall Safety Set)*

-	Age Group	18-64 yrs	18-64 yrs	≥65 yrs	≥65 yrs	≥18 yrs	≥18 yrs
-	Treatment, N	Full+Half aH5N1c N=2173	Placebo N=398	Full+Half aH5N1c N=2585	Placebo N=398	Full+Half aH5N1c N=4758	Placebo N=796
Study Period	System Organ Class, n (%) Preferred Term, n (%)	All SAEs n (%)	All SAEs n (%)	All SAEs n (%)	All SAEs n (%)	All SAEs n (%)	All SAEs n (%)
D1-387	Subjects with any SAE, n (%)	63 (2.9)	13 (3.3)	223 (8.6)	61 (15.3)	286 (6.0)	74 (9.3)
D1-43	Subjects with any SAE, n (%)	n/a	n/a	n/a	n/a	24 (0.5)	8 (1.0)
D44-387	Subjects with any SAE, n (%)	n/a	n/a	n/a	n/a	264 (5.5)	67 (8.4)
D1-43	Infections and infestations	n/a	n/a	n/a	n/a	7 (0.1)	2 (0.3)
D1-43	Nervous system disorders	n/a	n/a	n/a	n/a	5 (0.1)	0
D1-43	Cardiac disorders	n/a	n/a	n/a	n/a	3 (0.1)	3 (0.4)
D1-43	Gastrointestinal disorders	n/a	n/a	n/a	n/a	2 (0.0)	3 (0.4)
D1-43	Neoplasms benign, malignant and unspecified	n/a	n/a	n/a	n/a	2 (0.0)	1 (0.1)
D1-43	Blood and lymphatic system	n/a	n/a	n/a	n/a	1 (0.0)	0
D1-43	General disorders and administration site conditions	n/a	n/a	n/a	n/a	1 (0.0)	0
D1-43	Hepatobiliary disorders	n/a	n/a	n/a	n/a	1 (0.0)	0
D1-43	Injury, poisoning and procedural complications	n/a	n/a	n/a	n/a	1 (0.0)	0
D1-43	Metabolism and nutritional disorders	n/a	n/a	n/a	n/a	1 (0.0)	0
D1-43	Renal and urinary disorders	n/a	n/a	n/a	n/a	1 (0.0)	0
D1-43	Respiratory, thoracic and mediastinal disorders	n/a	n/a	n/a	n/a	1 (0.0)	0
D1-43	Surgical and medical procedures	n/a	n/a	n/a	n/a	1 (0.0)	0
D1-387	Cardiac disorders	10 (0.5)	2 (0.5)	39 (1.5)	20 (5.0)	49 (1.0)	22 (2.8)
D1-387	Atrial fibrillation	1 (0.0)	0	12 (0.5)	8 (2.0)	13 (0.3)	8 (1.0)

-	Age Group	18-64 yrs	18-64 yrs	≥65 yrs	≥65 yrs	≥18 yrs	≥18 yrs
-	Treatment, N	Full+Half aH5N1c N=2173	Placebo N=398	Full+Half aH5N1c N=2585	Placebo N=398	Full+Half aH5N1c N=4758	Placebo N=796
Study Period	System Organ Class, n (%) Preferred Term, n (%)	All SAEs n (%)	All SAEs n (%)	All SAEs n (%)	All SAEs n (%)	All SAEs n (%)	All SAEs n (%)
D1-387	Musculoskeletal and connective tissue disorders	2 (0.1)	1 (0.3)	38 (1.5)	7 (1.8)	40 (0.8)	8 (1.0)
D1-387	Infections and infestations	14 (0.6)	2 (0.5)	23 (0.9)	7 (1.8)	37 (0.8)	9 (1.1)
D1-387	Nervous system disorders	5 (0.2)	1 (0.3)	32 (1.2)	6 (1.5)	37 (0.8)	7 (0.9)
D1-387	Neoplasms, benign, malignant and unspecified	6 (0.3)	2 (0.5)	30 (1.2)	8 (2.0)	36 (0.8)	10 (1.3)
D1-387	Gastrointestinal disorders	5 (0.2)	1 (0.3)	25 (1.0)	8 (2.0)	30 (0.6)	9 (1.1)
D1-387	Injury, poisoning and procedural complications	9 (0.4)	0	20 (0.8)	1 (0.3)	29 (0.6)	1 (0.1)
D1-387	Respiratory, thoracic and mediastinal disorders	6 (0.3)	1 (0.3)	11 (0.4)	5 (1.3)	17 (0.4)	6 (0.8)
D1-387	General disorders and administration site conditions	4 (0.2)	0	7 (0.3)	1 (0.3)	11 (0.2)	1 (0.1)
D1-387	Renal and urinary disorders	4 (0.2)	0	7 (0.3)	1 (0.3)	11 (0.2)	1 (0.1)
D1-387	Hepatobiliary disorders	5 (0.2)	0	5 (0.2)	3 (0.8)	10 (0.2)	3 (0.4)
D1-387	Vascular disorders	1 (0.0)	1 (0.3)	9 (0.3)	3 (0.8)	10 (0.2)	4 (0.5)
D1-387	Metabolism and nutrition disorders	0	0	5 (0.2)	2 (0.5)	5 (0.1)	2 (0.3)
D1-387	Pregnancy, puerperium and perinatal disorders	4 (0.2)	2 (0.5)	0	0	4 (0.1)	2 (0.3)
D1-387	Blood and lymphatic system disorders	0	0	3 (0.1)	1 (0.3)	3 (0.1)	1 (0.1)
D1-387	Immune system disorders	0	0	3 (0.1)	0	3 (0.1)	0
D1-387	Skin and subcutaneous tissue disorders	0	0	3 (0.1)	0	3 (0.1)	0
D1-387	Ear and labyrinth disorders	0	0	2 (0.1)	1 (0.3)	2 (0.0)	1 (0.1)
D1-387	Psychiatric disorders	1 (0.0)	3 (0.8)	1 (0.0)	0	2 (0.0)	3 (0.4)
D1-387	Reproductive system and breast disorders	0	0	2 (0.1)	1 (0.3)	2 (0.0)	1 (0.1)
D1-387	Surgical and medical procedures	0	0	2 (0.1)	0	2 (0.0)	0
D1-387	Eye disorders	0	0	1 (0.0)	0	1 (0.0)	0

Source: Adapted from STN 125692/0, Module 5, ISS Tables 2.6.2 and 2.6.2.1 and electronic datasets.
*Pooled studies V89_18, V89_04, and V89_13.
*ClinicalTrials.gov identifiers: NCT02839330, NCT01776541, and NCT1766921.
Abbreviations: Full= full (high) dose vaccine groups; Full+Half= full+half (high+low) dose vaccine groups; SAE=serious adverse event; SOC=system organ class; PT=preferred term; D=day; yrs=years.
n/a=Applicant did not provide analyses of SAEs by onset period (Days 1-43 or 44-387) for age subgroups.
Full (high) dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Half (low) dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Percentages based on numbers of subjects in each treatment group.

8.4.3 Study Dropouts/Discontinuations

Across the three integrated studies, a total of 19 (0.4%) full and half dose recipients (full dose n=18, half dose n=1) and 3 (0.4%) placebo recipients had AEs that led to premature withdrawal. The most frequently reported AEs leading to premature withdrawal, as categorized by SOC, were cardiac disorders, 0.1% in each group (aH5N1c n=7, placebo n=1), and infections and infestations, aH5N1c 0.1% (n=4) and placebo n=0. Most subjects withdrew during the Day 44-387 follow-up period. Two aH5N1c recipients and one placebo recipient withdrew during the treatment period, before Day 22. Of the two aH5N1c recipients (subjects (b) (6) and (b) (6) both full dose, study V89_18), one had rash (Day 4) and the other had constipation (Day 6). Placebo recipient (b) (6) (V89_18) had pyrexia, gastrointestinal and constitutional

symptoms (Days 4-6). These AEs were assessed as related to study treatment. No other subjects withdrew due to AEs considered related to study treatment.

8.4.4 Common Adverse Events

Unsolicited AEs through Day 43 – Full Dose aH5N1c Vaccine versus Placebo
Among subjects ≥18 years in the ISS who received full dose aH5N1c vaccine or placebo, a total of 920 (25.7%) and 180 (22.6%) full dose aH5N1c and placebo recipients, respectively, reported unsolicited AEs through Day 43 (21 days following any vaccination). Among full dose aH5N1c and placebo recipients, respectively, the most frequently reported AEs (≥3%) as categorized by MedDRA SOC were: Infections and Infestations (6.9% vs 6.5%), General Disorders and Administration Site Conditions (5.9% vs 5.0%), Musculoskeletal and Connective Tissue Disorders (4.9% vs 4.1%), Nervous System Disorders (3.4% vs 3.9%), and Gastrointestinal Disorders (3.2% vs 3.4%). No large differences in the rates of events, as categorized by SOC, were observed between treatment groups. The proportions of subjects with AEs assessed as related to study treatment were similar (full dose aH5N1c 8.2%; placebo 6.2%). Evaluation of individual AEs as categorized by MedDRA PT revealed similar frequencies between treatment groups. The most frequently reported AEs by PT (≥1% in either group, range 0.4% to 2.2%) were headache, injection site bruising, fatigue, arthralgia, upper respiratory tract infection, viral upper respiratory tract infection, myalgia, back pain, and urinary tract infection. Most AEs were mild to moderate in severity. Severe AEs were reported by 1.0% and 1.3% of full dose aH5N1c and placebo recipients, respectively. The most frequently reported severe unsolicited AEs reported in the full dose aH5N1c group were fatigue (0.1%, n=5), headache (0.1%, n=5), and arthralgia (0.1%, n=4).

Among subjects 18 to <65 years in the ISS, a total of 382 (22.7%) and 86 (21.6%) full dose aH5N1c and placebo recipients, respectively, reported any unsolicited AE through Day 43. The frequencies of events as categorized by SOC and PT were similar to the overall population of subjects ≥18 years with no large imbalances between treatment groups. Severe unsolicited AEs occurred in 0.8% of full dose aH5N1c and 1.5% of placebo recipients. The most frequently reported severe AEs in the full dose aH5N1c group were headache (0.2%, n=4) and arthralgia (0.2%, n=4). A total of 7.2% and 5.5% of full dose aH5N1c and placebo recipients, respectively, had AEs considered at least possibly related to study vaccine.

As compared to the younger age cohort, slightly higher proportions of subjects ≥65 years experienced unsolicited AEs, 28.4% (n=538) of full dose aH5N1c and 23.6% (n=94) of placebo recipients. The proportions of subjects assessed as having AEs at least possibly related to study treatment were also slightly higher than in the younger cohort, 9.1% and 6.8%, respectively. Frequencies of AEs as categorized by SOC and PT followed patterns similar to the overall ISS population ≥18 years without large imbalances observed between treatment groups. Severe AEs occurred in 1.2% and 1.0% of full dose aH5N1c and placebo recipients, respectively. The most frequently reported severe AE among elderly full dose aH5N1c recipients was fatigue (0.2%, n=3). No other severe AEs occurred in >2 (0.1%) subjects in the full dose aH5N1c group.

Unsolicited AEs through Day 43 – Full + Half Dose aH5N1c versus Placebo
Among subjects ≥18 years in the ISS who received full or half dose aH5N1c vaccine or placebo, a total of 1283 (27.0%) of full + half dose aH5N1c and 180 (22.6%) of placebo

recipients reported unsolicited AEs in the 21 days after any vaccination (through Day 43). Overall, 8.9% and 6.2% of subjects in the active treatment and placebo groups, respectively, had AEs assessed as at least possibly related to study treatment. Similar to the ISS of full dose alone, among full + half dose aH5N1c and placebo recipients, respectively, the most frequently reported AEs (≥3%) as categorized by MedDRA SOC were: Infections and Infestations (7.3% vs 6.5%), General Disorders and Administration Site Conditions (6.4% vs 5.0%), Musculoskeletal and Connective Tissue Disorders (5.2% vs 4.1%), Nervous System Disorders (3.8% vs 3.9%), Gastrointestinal Disorders (3.3% vs 3.4%), and Injury, Poisoning and Procedural Complications (3.0% vs 2.0%). No large differences in the rates of events, as categorized by SOC, were observed between treatment groups although the differences in rates between active treatment and placebo groups were slightly greater overall than observed in the analysis of full dose alone versus placebo due to the additional n=1179 subjects in the active treatment group in the combined analysis.

Evaluation of individual AEs as categorized by MedDRA PT revealed similar frequencies between treatment groups. The most frequently reported AEs by PT (≥1% in either group, range 0.3% to 2.2%) were headache, injection site bruising, upper respiratory tract infection, fatigue, arthralgia, viral upper respiratory tract infection, myalgia, oropharyngeal pain, back pain, and urinary tract infection. Most AEs were mild to moderate in severity. Severe AEs were reported by 1.0% and 1.3% of full + half dose aH5N1c and placebo recipients, respectively. The most frequently reported severe unsolicited AEs reported in the full + half dose aH5N1c group were fatigue (0.2%, n=8), headache (0.1%, n=5), and arthralgia (0.1%, n=5). The placebo group showed similar results.

Among subjects 18 to <65 years in the ISS, a total of 514 (23.7%) and 86 (21.6%) full + half dose aH5N1c and placebo recipients, respectively, reported any unsolicited AE through Day 43. The frequencies of events as categorized by SOC and PT were similar to those in the overall population of subjects ≥18 years with no unusual or large imbalances between treatment groups. Severe unsolicited AEs occurred in 0.9% of full + half dose aH5N1c and 1.5% of placebo recipients. The most frequently reported severe AEs in the full + half dose aH5N1c group were arthralgia (0.2%, n=4), headache (0.2%, n=4), and fatigue (0.1%, n=3). A total of 7.5% and 5.5% of full + half dose aH5N1c and placebo recipients, respectively, had AEs considered at least possibly related to study vaccine.

As compared to the younger age cohort, slightly higher proportions of subjects ≥65 years experienced unsolicited AEs, 29.7% (n=769) of full + half dose aH5N1c and 23.6% (n=94) of placebo recipients. The proportions of subjects assessed as having AEs at least possibly related to study treatment were also slightly higher than in the younger cohort, 10.1% and 6.8%, respectively. Frequencies of AEs as categorized by SOC and PT followed patterns similar to the overall ISS population ≥18 years without large imbalances observed between treatment groups. Severe AEs occurred in 1.1% and 1.0% of full + half dose aH5N1c and placebo recipients, respectively. The most frequently reported severe AE among elderly full dose aH5N1c recipients was fatigue (0.2%, n=5). No other severe AEs occurred in ≥3 (0.1%) subjects in the active treatment groups.

Reviewer comment: The integrated analyses of unsolicited AEs with onset during the active treatment period (through 21 days after any vaccination) showed similar

frequencies of AEs as categorized by MedDRA SOC and PT in both the analyses of full dose alone and full and half dose aH5N1c recipients combined as compared to placebo. Analyses by age cohort 18 to <65 years and ≥65 years were also similar to the overall populations of subjects ≥18 years in both integrated analyses. No unusual or large clinically significant imbalances were observed. No safety concerns were identified.

Reviewer comment: The reviewer also used FDA's MedDRA Adverse Event Diagnosis (MAED) tool to evaluate the Applicant's electronic datasets for elevated relative risks (RR) in SOC or PT categories between treatment groups. Specifically, MAED was used to evaluate the ADAE datasets for the pivotal study V89_18 (full dose aH5N1c vs placebo) and for the ISS, full + half dose aH5N1c combined vs placebo. Among all 7,901 AEs included in the ISS ADAE dataset and evaluated by MAED, the only SOC with a RR >2 was Endocrine Disorders. However, the 95% CIs on the RRs for endocrine disorders in aH5N1c recipients as compared to placebo in both the ISS and V89_18 alone analyses crossed 1 and were not statistically significant: ISS RR=2.760 (95% CI 0.664, 11.481), p=0.222; V89_18 RR=2.327 (95% CIs: 0.530, 10.214), p-value = 0.385. Further evaluation of RRs for thyroid disorders using high level terms and MedDRA broad and narrow standard MedDRA queries (SMQs) all yielded statistically insignificant results. MAED identified other SMQs for which RRs were >1 but were statistically insignificant (95% CIs crossed 1) and/or the events did not appear to have plausible relationships to vaccination.

8.4.5 Clinical Test Results

Clinical safety laboratories were only monitored in the Phase 1/2 dose-finding study V89P1 (Section 5.1) and are not applicable to the ISS.

8.4.6 Systemic Adverse Events

For detailed analyses, please see Sections 6.1.12.2, 6.2.12.2 and 6.3.12.2. In subjects ≥18 overall, solicited systemic AEs in the seven days following any vaccination were reported slightly more frequently by full dose (39.0%) and full and half dose recipients combined (38.7%) as compared to placebo recipients (32.8%). Frequencies of events followed patterns observed in the individual studies. The most frequent events following any vaccination in the full dose aH5N1c groups were fatigue (21.7%), headache (19.5%) and malaise (19.4%). Rates in placebo recipients were generally similar except for malaise (11.9%) Solicited systemic AEs among full dose aH5N1c recipients were less frequent after the second vaccination (21.6%) as compared to the first (31.8%). Most systemic AEs were mild to moderate in severity (severe AEs <1%). Most systemic AEs began within two days of vaccinations and resolved within 3 to 4 days. Fever occurred in 1.2% of full dose, 1.2% of full and half dose aH1N1c, and 1.3% of placebo recipients. Fever ≥102.1°F (≥39.0°C) occurred in 0.3% of full dose, 0.2% of full and half dose combined, and in no placebo recipients. As in the individual adult studies, more subjects 18 through 64 years (full dose aH5N1c 44.9%; placebo 38.5%) reported solicited systemic AEs overall as compared to subjects ≥65 years (full dose aH5N1c 33.8%; placebo 27.2%).

8.4.7 Local Reactogenicity

For detailed analyses, please see Sections 6.1.12.2, 6.2.12.2 and 6.3.12.2. In subjects ≥18 overall, solicited local AEs in the seven days following any vaccination were reported more frequently by full dose (51.6%) and full and half dose recipients combined (48.5%) as compared to placebo recipients (14.7%). Frequencies of events followed patterns observed in the individual studies. The most frequent local AE following any vaccination was pain (full dose aH5N1c 51.2%; placebo 14.7%). Solicited local AEs among full dose aH5N1c recipients were less frequent after the second vaccination (34.8%) as compared to the first (44.9%). Most local AEs were mild to moderate in severity (severe AEs ≤0.2%). Most local AEs began within two days of vaccinations and resolved within 3 to 4 days. As in the individual adult studies, more subjects 18 through 64 years (full dose aH5N1c 65.5%; placebo 19.9%) reported solicited local AEs as compared to subjects ≥65 years (full dose aH5N1c 39.6%; placebo 9.6%).

8.4.8 Adverse Events of Special Interest

Subjects in the three integrated studies were assessed for AESIs, defined as any new medical events or signs or symptoms that might indicate potential immune-mediated diseases. AESIs were prospectively defined and reported according to a list of medical terms provided by FDA and pre-specified in the protocols. Studies V89_04 and V89_13 used the same list but V89_18 used an updated list. Because the pre-defined list was not the same for all three studies, the ISS of AESIs was conducted as a retrospective analysis for which each study was searched according to the most recent AESI list provided by FDA, using MedDRA PTs, version 20.0.

Reviewer comment: The list of AESIs used for the ISS analysis contains MedDRA terms equivalent to the most current list of potential immune-mediated medical conditions that we recommend for monitoring of vaccines with novel adjuvants.

AESIs – Full Dose aH5N1c Vaccine versus Placebo

In the main pooled analysis, a total of 18 subjects reported AESIs, 11 (0.3%) full dose aH5N1c and 7 (0.9%) placebo recipients. No subjects in the half dose aH5N1c group had an AESI. All AESIs were reported during the follow-up period (after Day 43) except for one case of colitis ulcerative reported in the placebo group on Day 42 (20 days after the second vaccination). Three AESIs occurred in subjects 18 to <65 years, Raynaud's phenomenon, cardiomyopathy, and Basedow's disease, while the remainder occurred in subjects ≥65 years. Table 54 presents the frequency of AESIs among full dose aH5N1c vaccine and placebo recipients across studies according to age, treatment and MedDRA SOC and PT.

Table 54: Subjects Reporting New Onset of Adverse Events of Special Interest from Day 1 through 366 Days after the Second Vaccination (Day 387) by Age, Treatment, Body System, and Preferred Term, in the Main (Full Dose and Placebo) Pooled Analyses – (Pooled Overall Safety Set)*

Age Group	**≥18 yrs**	**≥18 yrs**	**18-64 yrs**	**18-64 yrs**	**≥65 yrs**	**≥65 yrs**
Treatment**	**aH5N1c N=3759**	**Placebo N=796**	**aH5N1c N=1683**	**Placebo N=398**	**aH5N1c N=1896**	**Placebo N=398**
System Organ Class Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with any AESI	11 (0.3)	7 (0.9)	3 (0.2)	0	8 (0.4)	7 (1.8)
Musculoskeletal and connective tissue disorders	2 (0.1)	3 (0.4)	0	0	2 (0.1)	3 (0.8)
Ankylosing spondylitis	1 (0.0)	0	0	0	1 (0.1)	0

Age Group	≥18 yrs	≥18 yrs	18-64 yrs	18-64 yrs	≥65 yrs	≥65 yrs
Treatment**	**aH5N1c N=3759**	**Placebo N=796**	**aH5N1c N=1683**	**Placebo N=398**	**aH5N1c N=1896**	**Placebo N=398**
System Organ Class Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Polymyalgia rheumatica	1 (0.0)	2 (0.3)	0	0	1 (0.1)	2 (0.5)
Rheumatoid arthritis	0	1 (0.1)	0	0	0	1 (0.3)
Nervous system disorders	2 (0.1)	0	0	0	2 (0.1)	0
Chronic inflammatory demyelinating polyradiculopathy	1 (0.0)	0	0	0	1 (0.1)	0
Facial paralysis	1 (0.0)	0	0	0	1 (0.1)	0
Skin and subcutaneous tissue disorders	2 (0.1)	0	0	0	2 (0.1)	0
Psoriasis	2 (0.1)	0	0	0	2 (0.1)	0
Cardiac disorders	1 (0.0)	0	1 (0.1)	0	0	0
Cardiomyopathy	1 (0.0)	0	1 (0.1)	0	0	0
Endocrine disorders	1 (0.0)	0	1 (0.1)	0	0	0
Basedow's disease	1 (0.0)	0	1 (0.1)	0	0	0
Eye disorders	1 (0.0)	0	0	0	1 (0.1)	0
Uveitis	1 (0.0)	0	0	0	1 (0.1)	0
Immune system disorders	1 (0.0)	0	0	0	1 (0.1)	0
Sarcoidosis	1 (0.0)	0	0	0	1 (0.1)	0
Vascular disorders	1 (0.0)	0	1 (0.1)	0	0	0
Raynaud's phenomenon	1 (0.0)	0	1 (0.1)	0	0	0
Blood and lymphatic system disorders	0	1 (0.1)	0	0	0	1 (0.3)
Immune thrombocytopenic purpura	0	1 (0.1)	0	0	0	1 (0.3)
Gastrointestinal disorders	0	2 (0.3)	0	0	0	2 (0.5)
Coeliac disease	0	1 (0.1)	0	0	0	1 (0.3)
Colitis ulcerative	0	1 (0.1)	0	0	0	1 (0.3)
Hepatobiliary disorders	0	1 (0.1)	0	0	0	1 (0.3)
Biliary cirrhosis primary	0	1 (0.1)	0	0	0	1 (0.3)

Source: Adapted from STN 125692/0, Module 5, ISS Tables 57, 58, 1.6.8, and 1.6.8.1, and Listing 1.8.1.8; V89_18 CSR Listing 16.2.4.1, V89_04 CSR Listing 16.4.2.1, and V89_13 CSR Listing 16.2.4.1; case narratives; and evaluation of electronic datasets.
*Pooled studies V89_18, V89_04, and V89_13.
*ClinicalTrials.gov identifiers: NCT02839330, NCT01776541, and NCT1766921.
Abbreviations: AESI=adverse events of special interest; yrs=years.
**aH5N1c and associated denominators include only full dose recipients. No half dose recipients reported AESIs.
Full (high) dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Half (low) dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL
Percentages based on numbers of subjects in each treatment group.

Table 55 summarizes each AESI by study, subject ID, age, day of onset, outcome and assessment of relatedness. As noted most subjects were ≥65 years and had onset of AESIs after Day 43. Twelve of the 18 AESIs were also reported as SAEs and most were assessed as unrelated to study treatment.

Table 55: Listing of AESIs Reported by Subjects ≥18 Years in the Expanded Pooled Analysis (Full and Half Dose aH5N1c Vaccine and Placebo)* from Day 1 through Day 387 (End of Study) – Pooled Overall Safety Set**

Study	Subject	Age/ Sex	Tx	AESI Preferred Term	Onset (Day)	Resolved	Related	Serious
18-64 yrs	(b) (6)	-	-	-	-	-	-	-
V89_04		24/F	Full	Raynaud's phenomenon	281	No	No	Yes
V89_18		49/M	Full	Cardiomyopathy	248	No	No	No
V89_18		58/F	Full	Basedow's disease	54	No	No	No
≥65 yrs		-	-	-	-	-	-	-
V89_13		71/M	Full	Psoriasis	75	No	No	No

Study	Subject	Age/ Sex	Tx	AESI Preferred Term	Onset (Day)	Resolved	Related	Serious
V89_13	(b) (6)	71/F	Full	Facial paralysis	61	Yes	No	Yes
V89_13	(b) (6)	81/F	Full	Psoriasis	227	No	No	Yes
V89_18	(b) (6)	72/F	Full	Uveitis	255	No	No	No
V89_18	(b) (6)	78/F	Full	Sarcoidosis	99	Yes	No	Yes
V89_18	(b) (6)	67/M	PBO	Colitis ulcerative	42	No	No	Yes
V89_18	(b) (6)	78/F	PBO	Biliary cirrhosis primary	318	No	No	Yes
V89_18	(b) (6)	78/F	Full	Chronic inflammatory demyelinating polyradiculoneuropathy	310	No	No	Yes
V89_18	(b) (6)	73/F	PBO	Polymyalgia rheumatica	56	No	Possibly	Yes
V89_18	(b) (6)	83/M	PBO	Immune thrombocytopenic purpura	75	Yes	Possibly	Yes
V89_18	(b) (6)	72/M	Full	Ankylosing spondylitis	304	No	No	No
V89_18	(b) (6)	66/M	PBO	Coeliac disease	78	No	No	Yes
V89_18	(b) (6)	71/M	PBO	Rheumatoid arthritis	114	No	No	Yes
V89_18	(b) (6)	68/M	Full	Polymyalgia rheumatica	395	No	No	Yes
V89_18	(b) (6)	67/M	PBO	Polymyalgia rheumatica	305	No	No	No

Source: STN 125692/0, Module 5, ISS Table 58 and electronic datasets.
*Listing derived from all full and half dose aH5N1c vaccine and placebo recipients across studies. However, no AESIs occurred in half dose aH5N1c vaccine recipients.
**Pooled studies V89_18, V89_04, and V89_13.
**ClinicalTrials.gov identifiers: NCT02839330, NCT01776541, and NCT1766921.
Abbreviations: AESI=adverse events of special interest; Tx=study treatment; yrs=years; full=full dose aH5N1c vaccine; PBO=placebo.
**aH5N1c includes full and half dose recipients, however, no half dose recipients reported AESIs.
Full (high) dose: 7.5 mcg HA and 0.25 mL MF59 in a total volume of 0.5 mL
Half (low) dose: 3.75 mcg HA and 0.125 mL MF59 in a total volume of 0.25 mL

Reviewer comment: Please see Sections 6.1.12.4 [subjects (b) (6) ***, and*** (b) (6) ***], 6.1.12.5 [subject*** (b) (6) ***], 6.2.12.5 [subject*** (b) (6) ***], and 6.3.12.4 [subject*** (b) (6) ***of this review for summaries of case narratives and reviewer comments regarding the relatedness of serious and non-serious AESIs reported in the aH5N1c vaccine groups. Although evidence to support causality was insufficient, this reviewer was unable to completely exclude a possible relationship between certain AESIs in the aH5N1c vaccine group such as worsening of sarcoidosis (*** (b) (6) ***, polymyalgia rheumatica (PMR, #*** (b) (6) ***), and facial paralysis (#*** (b) (6) ***). These cases highlight the importance of a placebo group because the occurrence of AESIs was higher among placebo recipients, included similar events (e.g., PMR and psoriasis), and causality was clearly unrelated to placebo due to a lack of biological plausibility.***

AESIs – Full and Half Dose Vaccine versus Placebo

In the expanded pooled analysis of AESIs, half dose aH5N1c vaccine recipients contributed to larger denominators but, because half dose recipients reported no AESIs, the frequencies of AESIs in the expanded analysis were lower overall and by individual SOC and PT. Similar to the main pooled analysis, the overall rates of any AESI among all subjects ≥18 years were lower among full + half dose aH5N1c recipients as compared to placebo (0.2%, n=11 versus 0.9%, n=7). Rates of AESIs among subjects ≥18 years, whether categorized by SOC or PT, were 0.0% (range of 0-2 subjects) for the aH5N1c groups and 0 to 0.4% (range 0-3 subjects) in the placebo group. Among full + half dose aH5N1c and placebo recipients 18 to <65 years, the rates of any AESIs were 0.1% (n=3) and 0 (n=0), respectively. Among subjects ≥65 years, the rates of any AESIs were 0.3% (n=8) and 1.8% (n=7).

Reviewer comment: In both the main and expanded pooled analyses, rates of AESIs were low in general and were lower among aH5N1c recipients than in the placebo group. No patterns or clusters were observed that would strengthen an assessment of causality. No safety signals were identified. Evaluation of the electronic datasets confirmed the sponsor's report.

New Onset of Chronic Diseases – Full Dose aH5N1c Vaccine versus Placebo
Overall, among subjects ≥18 years, similar proportions of full dose aH5N1c (9.7%, n=348) and placebo (9.2%, n=73) recipients in the ISS reported NOCDs from Day 1 through study termination. Most NOCDs occurred after Day 43 during the follow-up period (aH5N1c 8.9%, placebo 8.5%). The most frequently reported NOCDs (≥1% in either group, respectively) as categorized by SOC were: Musculoskeletal and Connective Tissue Disorders (aH5N1c 2.0%, placebo 1.8%), Metabolism and Nutrition Disorders (1.4% vs 0.4%), Vascular Disorders (1.1% vs 0.6%), Cardiac Disorders (0.9% vs 1.4%), and Gastrointestinal Disorders (0.6% vs 1.6%). The most frequently reported NOCDs (≥0.5% in either group, respectively) as categorized by PT were: hypertension (0.9% vs 0.5%), osteoarthritis (0.5% vs 0), atrial fibrillation (0.4% vs 0.5%), and coronary artery disease (0.2% vs 0.6%). Three full dose recipients had NOCDs assessed as possibly related to study treatment: two subjects had hypothyroidism and one had cellulitis/dermatitis and plantar fasciitis of the feet. One placebo recipient had PMR (subject (b) (6)) previously described as an SAE and AESI in Section 6.1.12.4.

Among subjects 18-64 years, NOCDs occurred in 6.2% (n=105) and 5.0% (n=20) of full dose aH5N1c and placebo recipients, respectively. No large imbalances in specific types of events as categorized by SOC or PTs were observed between treatment groups. The most frequently (≥1%) reported NOCDs in full dose aH5N1c recipients 18 to <65 years, as categorized by SOC were: Musculoskeletal and Connective Tissue Disorders and Vascular Disorders, both 1.1%, and Metabolism and Nutrition Disorders (1.0%). NOCDs occurred more frequently in subjects ≥65 years than in the younger age group, 12.8% (n=243) and 13.3% (n=53) of full dose aH5N1c and placebo recipients, respectively, without large imbalances between treatment groups. The most frequently (≥1%) reported NOCDs in full dose aH5N1c recipients ≥65 years were: Musculoskeletal and Connective Tissue Disorders (2.7%), Metabolism and Nutrition Disorders (1.7%), Vascular Disorders (1.2%), Cardiac Disorders (1.3%), Eye Disorders (1.1%), and Gastrointestinal Disorders (1.0%).

NOCDs – Full and Half Dose aH5N1c Vaccine versus Placebo
A total of 9.6% (full dose n=348, half dose n=108) of aH5N1c and 9.2% (n=73) of placebo recipients reported NOCDs through the end of the studies. Most events occurred during the follow-up period after Day 43 (8.7% and 8.5%, respectively). Frequencies of events were balanced between treatment groups and patterns of events were similar to the analyses of full dose alone versus placebo. Among half dose recipients, another four subjects were assessed by the investigator as having NOCDs related to study treatment: hypertension; osteoarthritis (erosive inflammatory arthritis right wrist, V89_13, ID(b) (6)); gastroesophageal reflux disease; and hypothyroidism (V89_13, ID(b) (6)). Please see Section 6.3.12.5 for comment on Subjects (b) (6) and (b) (6).

Reviewer comment: Integrated analyses of NOCDs identified no additional insights beyond individual study observations. NOCDs were conditions

commonly seen in adults, low in frequency, without large imbalances between treatment groups or unusual patterns. Most events were assessed by the investigator as unrelated to vaccination. No safety concerns were identified. Evaluation of the electronic datasets were consistent with the Applicant's report.

MAAEs – Full Dose aH5N1c Vaccine versus Placebo

Overall, among subjects ≥18 years, similar proportions of full dose aH5N1c (47.1%, n=1687) and placebo (46.0%, n=366) recipients in the ISS reported MAAEs from Day 1 through study termination. Most MAAEs occurred after Day 43 during the follow-up period (aH5N1c 42.7%, placebo 42.5%). The most frequently reported MAAEs (≥5% in either group, respectively) as categorized by SOC were: Infections and Infestations (21.4% vs 24.7%); Injury, Poisoning and Procedural Complications (10.1% vs 7.8%); Musculoskeletal and Connective Tissue Disorders (9.8% vs 8.0%); and Gastrointestinal Disorders (5.9% vs 6.3%). The most frequently reported MAAEs (≥3% in either group, respectively) as categorized by PT were: upper respiratory tract infection (3.7% vs 5.0%); urinary tract infection (3.2% vs 4.0%); sinusitis (3.0% vs 3.4%); and bronchitis (2.6% vs 4.3%). MAAEs occurred in 37.8% (n=637) and 37.2% (n=148) of full dose aH5N1c and placebo recipients 18 to <65 years, respectively, and in 55.4% (n=1050) and 54.8% (n=218) of full dose aH5N1c and placebo recipients ≥65 years, respectively. The most frequently reported events within each age subgroup, as categorized by SOC and PT, followed patterns observed in the overall population ≥18 years. Overall and within age subgroups, no large imbalances in specific types of events as categorized by SOC or PTs were observed between treatment groups.

MAAEs – Full and Half Dose aH5N1c Vaccine versus Placebo

The full and half dose aH5N1c vaccine analyses showed patterns very similar to the full dose only analyses. Among subjects ≥18 years, a total of 46.9% (n=2230) of full and half dose aH5N1c and 46.0% (n=366) of placebo recipients reported MAAEs through study termination. Most MAAEs occurred after Day 43 during the follow-up period (aH5N1c 42.5%, placebo 42.5%). Frequencies of events were balanced between treatment groups and patterns of events were similar to the analyses of full dose alone versus placebo. MAAEs occurred in 36.4% (n=791) and 37.2% (n=148) of full and half dose aH5N1c and placebo recipients 18 to <65 years, respectively, and in 55.7% (n=1439) and 54.8% (n=218) of full and half dose aH5N1c and placebo recipients ≥65 years, respectively. The most frequently reported events within each age subgroup, as categorized by SOC and PT, followed patterns observed in the overall population ≥18 years. Overall and within age subgroups, no large imbalances in specific types of events as categorized by SOC or PTs were observed between treatment groups. A total of 60 subjects across studies had MAAEs assessed as at least possibly related, 1.1% (n=38 full dose, n=15 half dose) of full and half dose aH5N1c recipients and 0.9% (n=7) of placebo recipients. Of these subjects, two had also been identified as having AESIs (subject (b) (6) with ITP and #(b) (6) with PMR, both V89_18), one as having a NOCD (subject #(b) (6) with hypothyroidism, V89_13) and one not identified as having an SAE/AESI or NOCD (subject (b) (6) a 75 year-old male with diagnosed with hypothyroidism on Study Day 62, V89_13).

Reviewer comment: Frequencies of MAAEs reported in the analyses of full dose and full and half dose vaccine were similar to and without large imbalances as compared to placebo. Evaluation of the electronic datasets confirmed the ISS report. Most MAAEs were common medical conditions and appeared unrelated to study treatment. No new safety concerns were identified.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

See Sections 8.4.6 and 8.4.7.

8.5.2 Time Dependency for Adverse Events

See Sections 8.4.6 and 8.4.7.

8.5.3 Product-Demographic Interactions

Integrated summaries of solicited and unsolicited AEs, including long-term safety, in aH5N1c recipients ≥18 years according to sex, race, ethnicity and country were performed for the full dose and full and half dose combined aH5N1c populations (main and expanded pooled analyses, respectively). Review of the integrated subpopulation analyses are presented for the full dose formulation intended for licensure. Full and half dose aH5N1c analyses showed similar results and are discussed very briefly with respect to long-term safety. Both analyses mirrored trends observed in the subpopulation analyses of the individual adult studies.

Subpopulation Analyses of Solicited Adverse Events

Sex

Of a total of n=1987 female and n=1531 male aH5N1c full dose vaccine recipients in the ISS (Solicited Safety Set), 57.1% and 44.5% of females and males, respectively, reported solicited local AEs in the seven days following any vaccination. The most common solicited local AE was pain, reported more frequently in females than males (56.5% vs 44.3%), with severe pain reported by 0.4% (n=7) and 0, respectively. A total of 42.6% and 34.3% of females and males, respectively, reported solicited systemic AEs after any vaccination with aH5N1c. The most common (≥10%) solicited systemic AEs among female and male aH5N1c recipients, respectively, were fatigue (24.3% vs 18.3%), malaise (21.7% vs 16.3%), headache (23.0% vs 15.0%), myalgia (15.2% vs 11.6%), arthralgia (12.2% vs 8.6%), and nausea (10.1% vs 6.8%). Fever was reported by 1.4% and 1.0% of females and males, respectively. Among subjects of both sexes, severe solicited symptoms were infrequent, ranging from 0 to 1.1% (fatigue).

Reviewer comment: Rates of solicited AEs between males and females in the ISS were very similar to subanalyses by sex reported in V89_18.

Race

A total of n=2707 whites, n=411 blacks/African Americans, and n=357 Asians received full dose aH5N1c vaccine in the main pooled ISS analysis (Solicited Safety Set). Sample sizes of other racial subgroups were too small to make meaningful comparisons and were not included in the analyses. Overall, whites reported only slightly more solicited local and/or systemic AEs (52.2% and 38.8%, respectively) as compared to blacks/African Americans (48.7% and 40.4%, respectively) and Asians (49.9% and 38.7%, respectively). The most common (≥10%) solicited AEs among whites were local pain (51.8%), fatigue (22.3%), headache (20.2%), malaise (19.2%), and myalgia (12.2%). The most common (≥10%) solicited AEs among blacks/African Americans were local pain (47.9%), fatigue (20.7%), malaise (19.7%), headache (17.5%), myalgia (14.8%), and arthralgia (12.9%). The most common (≥10%) solicited AEs among Asians were local pain (49.3%), fatigue (17.4%), malaise (19.3%), headache (16.2%), myalgia

(23.0%), and arthralgia (12.9%). Fever occurred in 0.7% of whites, 1.0% of blacks/African Americans, and 4.8% of Asians. Severe solicited AEs were infrequent, ranging from 0 to 0.8% (fatigue) among the three racial subgroups.

Reviewer comment: Rates of solicited AEs in the ISS were similar to those reported in the pivotal study V89_18 and were generally similar among racial subgroups except for myalgia and fever which occurred in disproportionately more Asians than whites or blacks/African Americans (myalgia: 23.0% versus 12.2% and 12.2%, respectively) (fever: 4.8% versus 0.7% and 1.0%, respectively). Interpretation of these differences is limited by differences in sample sizes among racial subgroups.

Ethnicity
A total of n=287 Hispanic/Latino and n=3208 non-Hispanic/non-Latino full dose aH5N1c recipients comprised the ISS Solicited Safety Set. Overall, 56.8% and 51.1% of Hispanic/Latino and non-Hispanic/non-Latino aH5N1c recipients, respectively, reported solicited local AEs, most commonly pain (56.1% vs 50.6%, respectively). A total of 43.6% and 38.5% of Hispanic/Latinos and non-Hispanic/non-Latinos, respectively, reported solicited systemic AEs after any vaccination with aH5N1c, most commonly (≥10%): malaise (26.8% vs 18.8%), fatigue (23.0% vs 21.5%), headache (23.3% vs 19.1%), myalgia (19.9% vs 13.1%), arthralgia (14.3% vs 10.3%), loss of appetite (11.1% vs 6.9%) and nausea (10.8% vs 8.4%). Rates of any fever were 1.4% and 1.2%, respectively. Most solicited local and systemic AEs were mild to moderate in severity. The percentage of subjects who had severe solicited AEs ranged from 0 to 2.1% (fatigue).

Reviewer comment: Hispanic/Latino recipients of full dose aH5N1c vaccine reported slightly more solicited AEs than non-Hispanic/non-Latinos, overall, particularly for malaise, myalgia, and loss of appetite. Results were similar to the subgroup analyses conducted for study V89_18 and were limited by the relatively small sample size of Hispanics/Latinos.

Country
Of the three pooled studies, V89_18 was conducted exclusively in the U.S. while V89_04 and V89_13 also included sites in Australia, New Zealand (V89_13 only) and Thailand. U.S. sites comprised 83.2% of full dose aH5N1c recipients in the main pooled analysis (full dose aH5N1c, n=3579 and placebo, n=796) and 74.8% of subjects in the expanded pooled analysis (full + half dose aH5N1c, n=4758 and placebo, n=796). Thailand contributed 9.0% and 13.6% of subjects to the main and expanded pooled analyses, respectively, while Australia contributed 5.5% and 8.3%, respectively, and New Zealand contributed 2.3% and 3.4%, respectively.

Rates of local and systemic solicited AEs by country were reviewed. Among full dose aH5N1c and placebo recipients (main pooled analysis) overall, New Zealand had the lowest proportions of subjects reporting local (35.4%) and systemic (32.9%) AEs in the seven days following any vaccination while Australia had the highest proportions (65.0% and 45.7%, respectively). As in the overall pooled safety population, injection site pain was the most frequently reported solicited local AE (ranging from 32.9% of subjects in New Zealand to 64.5% in Australia). Frequencies of subjects with solicited systemic AEs also followed the overall pooled safety population, with generally lower rates reported in New Zealand. Fever among full dose aH5N1c recipients in the seven days

following any vaccination was notably higher in Thailand, 5.3%, as compared to the other three countries (ranging from 0.8% in the U.S. to 1.2% in New Zealand), following the pattern of higher proportions of Asians reporting fever as compared to whites and blacks/African Americans (4.8% versus 0.7%-1.0%, respectively), and consistent with the higher proportion of Asians (100% of full and half dose aH5N1c recipients) comprising the Thailand sites. Similar patterns of solicited AEs were observed in the full and half dose expanded pooled analyses.

Reviewer comment: Although there were some differences in overall rates of solicited AEs among countries, except for fever in aH5N1c recipients in Thailand, proportions of subjects from different countries reporting individual solicited AEs followed similar patterns. Because U.S. sites contributed the majority of subjects in the ISS, differences among countries do not change the overall interpretation of the data or relevance to the U.S. population.

Subpopulation Analyses of Unsolicited Adverse Events

Sex

Analyses of unsolicited AEs according to sex showed patterns similar to the overall ISS of unsolicited AEs and analyses from the pivotal study V89_18. A total of n=1568 (43.8%) male and n=2011 (56.2%) female aH5N1c recipients were included in the ISS analyses of full dose aH5N1c (n=3579) and placebo (n=796) (Exposed Set/Overall Safety Set).

Over the entire study period, small differences but no large imbalances were observed in long-term safety events between male and female full dose aH5N1c recipients, respectively: Deaths (0.6% vs 0.3%), SAEs (6.7% vs 6.0%), AESIs (0.3% in both groups), NOCDs (8.9% vs 10.4%), MAAEs (43.4% vs 50.0%), and AEs leading to premature withdrawal (0.7% vs 0.3%). The ISS of full and half dose aH5N1c recipients revealed one additional death in a male half dose recipient and no additional AESIs. Proportions of males and females, respectively, who experienced other long-term AEs were similar to the full dose analyses: SAEs (6.5% vs 5.7%), NOCDs (9.5% vs 9.7%), MAAEs (43.4% vs 49.6%), and AEs leading to premature withdrawal (0.6% vs 0.3%).

Reviewer comment: ISS analyses by sex showed that females generally reported more unsolicited AEs than males and that patterns followed those observed for the overall pooled safety population and the individual study V89_18.

Race

A total of n=2752 (76.9%) whites, n=422(11.8%) blacks/African Americans, and n=360 (10.1%) Asians received full dose aH5N1c vaccine in the ISS analysis (Exposed Set/Overall Safety Set). Sample sizes of other racial subgroups were too small to make meaningful comparisons and were not included in the analyses. Subgroup analyses showed that more whites than blacks/African Americans or Asians reported unsolicited AEs in the 21 days following any vaccination (Day 1 through Day 43) (27.8%, 16.6% and 20.0%, respectively). Percentages of whites, blacks/African Americans and Asians reporting AEs as categorized by SOC were highest (≥5%) for Infections and Infestations (7.6%, 4.7% and 5.0%, respectively), Musculoskeletal and Connective Tissue Disorders (5.2%, 2.8% and 4.7%, respectively), and General Disorders and Administration Site Disorders (6.5%, 3.3%, and 3.6%, respectively). The AEs reported most frequently by PT in each group were: headache (whites 2.4%, blacks/African Americans 1.7%) and viral upper respiratory tract infection (Asians 1.7%). Most AEs were mild to moderate in

severity. Severe AEs were reported by 4.3%, 0.7% and 0.6% of white, black/African American and Asian full dose aH5N1c recipients, respectively. A total of 8.8%, 6.6% and 5.3% of white, black/African American and Asian full dose aH5N1c recipients, respectively, reported unsolicited AEs assessed as possibly or probably related to study vaccine.

Over the entire study period, the following long-term safety events were reported among white, black/African American and Asian full dose aH5N1c recipients, respectively: Deaths (0.5%, 0.5% and 0), SAEs (6.9%, 5.0% and 3.6%), AESIs (0.3%, 0.2% and 0.3%), NOCDs (10.5%, 6.4% and 8.6%), MAAEs (50.8%, 33.4% and 37.2%), and AEs leading to premature withdrawal (0.6%, 0.5% and 0). The ISS of full and half dose aH5N1c recipients revealed one additional death in a white half dose recipient and no additional AESIs. Proportions of white, black/African American, and Asian full and half dose aH5N1c recipients, respectively, who experienced other long-term AEs were similar to the full dose analyses: SAEs (6.7%, 5.5% and 3.5%), NOCDs (10.7%, 5.7% and 7.5%), MAAEs (51.5%, 31.5% and 36.3%), and AEs leading to premature withdrawal (0.5%, 0.4% and 0).

Reviewer comment: ISS analyses by race showed that numerically more white than black/African American or Asian recipients of aH5Nc vaccine reported unsolicited AEs, including more MAAEs, without notable differences in specific types of AEs. Asians had slightly lower rates of SAEs than the other two racial groups. Full and half dose aH5N1c analyses showed patterns similar to full dose alone.

Ethnicity

Analyses of unsolicited AEs according to ethnicity showed patterns similar to the overall ISS of unsolicited AEs and analyses from the pivotal study V89_18. A total of n=298 (8.3%) Hispanics/Latinos and n=3257 (91.0%) non-Hispanic/non-Latinos were included in the ISS analyses of full dose aH5N1c (Exposed Set/Overall Safety Set). In the 21 days following any vaccination (Day 1 through Day 43), similar proportions of Hispanic/Latino and non-Hispanic/non-Latino full dose aH5N1c recipients reported unsolicited AEs (23.8% vs 25.8%, respectively). The most frequently reported AEs (≥5%) by Hispanic/Latino and non-Hispanic/non-Latino full dose aH5N1c recipients, respectively, were in the SOC categories of Infections and Infestations (7.4% vs 6.8%), General Disorders and Administration Site Conditions (7.0% vs 5.7%), and Musculoskeletal and Connective Tissue Disorders (6.7% vs 4.8%). The most frequently reported AEs as categorized by PT were myalgia (3.0%) in Hispanic/Latinos and headache (2.1%) in non-Hispanic/non-Latinos. Most events were mild to moderate in severity, with a total of 0.7% and 1.0% of Hispanic/Latino and non-Hispanic/non-Latino full dose aH5N1c recipients, respectively, reporting severe unsolicited AEs. Unsolicited AEs assessed as at least possibly related to aH5N1c vaccine were reported in 9.1% and 8.1% of Hispanic/Latinos and non-Hispanics/non-Latinos, respectively.

Over the entire study period, the proportions of Hispanic/Latino and non-Hispanic/Latino full dose aH5N1c recipients, respectively, who reported long-term safety events were as follows: Deaths (0.7% vs 0.4%), SAEs (5.0% vs 6.4%), AESIs (0.3% in both groups), NOCDs (4.7% vs 10.2%), MAAEs (34.2% vs 48.3%), and AEs leading to premature withdrawal (0.7% vs 0.5%). The ISS of full and half dose aH5N1c recipients revealed one additional death in a non-Hispanic/non-Latino half dose recipient and no additional AESIs. Proportions of Hispanic/Latino and non-Hispanic/Latino full and half dose

aH5N1c recipients, respectively, who experienced other long-term AEs were similar to the full dose analyses: SAEs (4.1% vs 6.2%), NOCDs (4.4% vs 10.1%), MAAEs (29.4% vs 48.5%), and AEs leading to premature withdrawal (0.5% vs 0.4%).

Reviewer comment: ISS analyses of unsolicited AEs by ethnicity were generally similar between Hispanic/Latinos and non-Hispanic/non-Latinos but showed numerically lower lower rates of NOCDs and MAAEs among Hispanic/Latino vaccine recipients. Interpretation of these results is limited by the large difference in sample sizes between the two groups.

Country
Integrated analyses of unsolicited AEs by country were reviewed. Subjects who received full dose aH5N1c vaccine (n=3579) were from the following countries: U.S. (n=2976, 83.2%), Australia (n=198, 5.5%), New Zealand (n=82, 2.3%), and Thailand (n=323, 9.0%). In the main pooled analysis of full dose aH5N1c recipients, the proportions of subjects who had unsolicited AEs in the 21 days following any vaccination (Day 1 through Day 43) were higher among subjects in Australia (41.9%) and New Zealand (40.2%) than in Thailand (21.1%) or the U.S. (24.7%). The U.S. was the only site that had a placebo group (V89_18), and a similar rate of unsolicited AEs was observed (22.6%) among placebo recipients. As compared to the pooled Overall Safety Set, no unusual or large imbalance in AEs as categorized by SOC or PT was observed by country. Within each country, most AEs were assessed as mild to moderate. Percentages of full dose aH5N1c recipients who reported AEs assessed as severe were low and similar to the pooled Overall Safety Set (1.0%): Australia 1.0%, New Zealand (0), Thailand (0.3%), and U.S. (1.1%). Higher percentages of subjects in Australia (16.7%) and New Zealand (19.5%) than in Thailand (5.6%) and the U.S. (7.6%) had AEs assessed as related to study treatment. Similar patterns were observed in the full and half dose aH5N1c expanded analyses.

Over the entire study period (through Day 387), no notable differences were observed among countries in the rates of deaths, SAEs, AESIs or AEs leading to premature withdrawal. Rates of NOCDs were notably higher among full dose aH5N1c recipients in New Zealand (22.0%) than in Australia (5.1%), Thailand (9.3%) or the U.S. (9.7%), or in the placebo group (9.2%). Rates of MAAEs in the main pooled analysis of full dose aH5N1c recipients were: Australia (53.5%), New Zealand (74.4%), Thailand (38.4%) and the U.S. (46.9%), and 46.0% in the placebo group. The higher rates of NOCDs and MAAEs in New Zealand may have been due to the fact that all subjects from New Zealand were ≥65 years (and were only enrolled in study V89_13). However, no unusually high rate of MAAEs or NOCDs as categorized by SOC or PT relative to the pooled OSS was observed or safety signal identified. The expanded pooled analyses (full and half dose) of long-term safety by country showed similar patterns.

Reviewer comment: No safety concerns were identified in the integrated analyses by country.

8.6 Safety Conclusions

Overall, the ISS reflected safety profiles observed in the individual BLA studies and identified no new safety concerns. The most frequent solicited AEs were injection site pain, fatigue, headache, and malaise. While local pain and malaise were reported more

frequently by aH5N1c vaccine than placebo recipients, rates of other solicited AEs were generally similar between treatment groups. Rates decreased following the second vaccination. Solicited AEs were mostly mild to moderate and of short duration. Unsolicited AEs occurred in ~25% of all subjects in the ISS, with similar rates of events between aH5N1c vaccine and placebo recipients. No unusual patterns or imbalances or safety signals were identified.

A total of 16 (0.4%) full or half dose aH5N1c vaccine and 1 (0.1%) placebo recipients died across studies. No deaths appeared related to study treatment. SAEs occurred less frequently in full or half dose aH5N1c recipients (6.0%) as compared to placebo (9.3%). Most SAEs occurred in subjects ≥65 years, consisted of events typical of an elderly population, and did not reveal unusual patterns, large imbalances between treatment groups, or safety concerns. Rates of AESIs were low and also occurred less frequently among full and half dose aH5N1c recipients than in the placebo group (0.2% vs 0.9%). In this reviewer's opinion, the majority of SAEs and AESIs appeared unrelated to the aH5N1c vaccine due to lack of a biological plausibility, existence of more likely alternative causal factors, and/or the absence of a close temporal relationship. A few SAEs/AESIs had a close temporal relationship to vaccination making it difficult to exclude causality with certainty. Importantly, similar events and temporality were observed in the placebo group. Frequencies of NOCDs and MAAEs, overall and as categorized by MedDRA SOC and PT, were balanced between treatment groups and raised no additional concerns.

Integrated subgroup analyses showed trends for younger subjects to report more solicited AEs than elderly subjects while elderly subjects had more unsolicited AEs including SAEs, NOCDs and MAAEs. Females reported more solicited and unsolicited AEs as compared to males. Whites reported more unsolicited AEs than other racial groups. Hispanic/Latinos reported more solicited AEs than non-Hispanic/non-Latinos. Subanalyses by race and country showed numerically higher rates of fever during the solicited AE period among Asians and Thai aH5N1c recipients. Subgroup analyses were limited by small sample sizes and/or large relative differences in sample sizes and should be interpreted with caution.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnancy was an exclusion criterion in all five trials supporting licensure. Thus, the aH5N1c vaccine has not been evaluated systematically in pregnant females. Across studies, a total of n=55 subjects became pregnant, n=25 following exposure to high/full (7.5 mcg HA/0.25 mL MF59) or low/half (3.75 mcg HA/0.125 mL MF59) dose aH5N1c, n= 22 following other dose levels of antigen and adjuvant evaluated in Phase 1, n=3 following unadjuvanted vaccine, and n=5 following placebo. Pregnancies were not considered AEs; however, case narratives were provided for all pregnancies and reviewed. Please see Sections 6.1.12.4 and 6.2.12.4 of this review for case summaries of pregnancies with adverse outcomes.

Study V89_18: Six (0.25%) aH5N1c and five (0.63%) placebo recipients became pregnant in V89_18, two between Days 1 and 43 and nine after vaccinations. Three

pregnancies (one aH5N1c and two placebo recipients) ended in SAEs of spontaneous abortions. A fourth pregnancy-associated non-serious AE (afterbirth pain) was reported. Five aH5N1c recipients and one placebo recipient reported normal deliveries. No outcome data were available for the remaining two placebo recipients.

Study V89_04: A total of 15 pregnancies (8 high dose and 7 low dose aH5N1c recipients) were reported in study V89_04. Four subjects delivered healthy infants, eight subjects had no information on outcome, and three subjects had spontaneous or missed abortions (two during the treatment period (Day 1-43) and one during the follow-up period (Day 44-387).

Study V89_11: Two subjects became pregnant in study V89_11, one (high dose recipient) during the treatment period and one (low dose) during the follow-up period. Both subjects delivered healthy infants.

Study V89P1: A total of 27 subjects became pregnant during study V89P1, n=8 during the treatment period and n=19 during the follow-up period (Day 44-546). Of the 8 subjects who became pregnant during the treatment period, two delivered healthy infants and six elected to have a therapeutic abortion. Of the 19 subjects who became pregnant during the follow-up period, 12 delivered healthy infants, 3 had therapeutic abortions, and no outcome information was available for the remaining 4 subjects. V89P1 evaluated adjuvanted and unadjuvanted vaccine at various dose levels of antigen and adjuvant. Of subjects who became pregnant, 24 received adjuvanted vaccine including one who received the high (full) dose vaccine intended for licensure and one who received low (half) dose vaccine evaluated in Phase 2 trials. Both high and low (full and half) dose aH5N1c recipients delivered healthy infants.

Reviewer comment: In V89_18, one of six pregnancies (16.7%) in aH5N1c recipients and two of five pregnancies (40%) in placebo recipients resulted in spontaneous abortions. In V89_04, 3 of 15 reported pregnancies (20%) resulted in spontaneous or missed abortion. The rate of spontaneous abortion in early pregnancy (<20 weeks gestation) in females <35 years of age is approximately 15% and increases with age. Rates are higher in females with risk factors such as prior miscarriage and smoking and are much higher in studies where clinically unrecognized pregnancy was diagnosed by measuring daily urine hCG levels. There is no established causal relationship between inactivated influenza vaccines and spontaneous abortion or other adverse pregnancy outcomes. Influenza vaccination is recommended in pregnant females because they are at greater risk for complications of influenza infection. Vaccination of pregnant women may also protect infants in the first six months of life before they are eligible for vaccination. A pregnancy registry will be established for the aH5N1c vaccine in the event of a pandemic. [1,2,36]

Please see Section 4.3 for nonclinical reproductive and developmental toxicity information.

9.1.2 Use During Lactation

The aH5N1c vaccine has not been evaluated in lactating females.

9.1.3 Pediatric Use and PREA Considerations

Seqirus submitted an initial Pediatric Study Plan (iPSP) on January 9, 2015 requesting deferral of studies in infants <6 months until after the declaration of an A/H5N1 pandemic at which time they would evaluate the safety and immunogenicity of two doses of 3.75 mcg H5N1 HA + 0.125 mL MF59 administered IM 3 weeks apart. The rationale for a deferred study in this age group was that the product would be ready for approval for use in persons ≥6 months before a pediatric study in infants <6 months was completed. FDA agreed to the iPSP on February 6, 2015.

The BLA submission proposed the following modifications to the agreed iPSP:

- A change in the deferred study population from infants <6 months to infants 6 weeks to <6 months, and
- A change in the proposed dose level for the deferred study from 3.75 mcg HA + 0.125 mL MF59 (half dose) to 7.5 mcg HA + 0.25 mL MF59 (full dose).

In response, FDA requested a justification for the Applicant's proposals and stated that we did not agree with a waiver for infants <6 weeks because mothers would likely be immunologically naïve to the influenza A/H5N1 virus in the setting of a pandemic and infants would not be protected by transfer of maternal antibodies. Thus, the aH5N1c vaccine may represent a meaningful therapeutic benefit over existing products for pediatric patients in the entire age group <6 months. With respect to the proposed increase in dose level to 7.5 mcg HA + 0.25 mL MF59, we agreed that the higher dose was likely to elicit higher immune responses but requested additional analyses of solicited AEs in study V89_11 by age subgroups (6 months to <3 years and 3 years to <6 years) to better inform our decision. [35,39]

In response to our requests, the Applicant: 1) agreed to study infants from birth to <6 months and submitted a revised pediatric study synopsis (V89_19); and 2) submitted subanalyses of solicited reactogenicity to support increasing the dose in V89_19 to 7.5 mcg HA + 0.25 mL MF59.

Please see V89_11 Sections 6.4.11.3 and 6.4.12.2 for review of subpopulation analyses of immunogenicity and safety supporting the selected dose of 7.5 mcg HA + 0.25 mL MF59 in infants <6 months. Briefly, analyses of SCRs and %HI ≥1:40 at Day 43 were performed according to age subgroups of 6 to <36 months, 3 to <9 years and 9 to <18 years. In all three age subgroups, subjects in both the low and high dose groups met both the SCR and %HI ≥1:40 endpoints; however, across age groups, subjects in the high dose group had higher immune responses as compared to the low dose group. Age subgroup analyses of solicited AEs (6 months to <3 years and 3 years to <6 years) showed similar rates of local AEs between age groups regardless of dose level while rates of systemic AEs (e.g., sleepiness and irritability) were somewhat higher in the younger children but mostly mild to moderate in severity. Fever ≥100.4°F occurred most frequently in high dose aH5N1c recipients 6-35 months than in the other groups (21% versus 9% of younger low dose recipients and 7% of both low and high dose recipients 3 years to <6 years). However, severe solicited systemic AEs were infrequent (0-6% of 6 months to <3 years and 0-2% of 3 years to <6 years). Severe fever (≥102.1°F) occurred in 3% and 2% of low and high dose recipients 6 months to <3 years, respectively, and in 2% of both low and high dose recipients 3 years to <6 years. Given the high mortality associated with influenza A/H5N1 infection and an expectation that higher immune responses may be more protective, the rates of solicited local and systemic AEs among

high dose aH5N1c recipients in both age subgroups were acceptable to this reviewer and support the sponsor's proposal to increase the dose of aH5N1c in infants <6 months in the proposed deferred pediatric study V89_19 to full dose 7.5 mcg H5N1 HA/0.25 mL MF59.

Submission of the BLA required a PeRC review because it contained a new indication, data from a completed pediatric assessment (V89_11), and a deferral request for infants <6 months. On October 29, 2019, the PeRC concurred with the review team's assessment that data from study V89_11 support licensure of the aH5N1c vaccine in children and adolescents 6 months through 17 years and agreed with deferral of the study in infants <6 months.

PREA-Related Postmarketing Requirements

Approval of the BLA will include a Postmarketing Requirement (PMR) to conduct the following pediatric study:

1. V89_19, a Phase 3, open-label, multicenter study to evaluate the immunogenicity and safety of the aH5N1c influenza vaccine (7.5 mcg HA + 0.25 mL MF59 administered as two doses intramuscularly 3 weeks apart) in healthy infants <6 months.
    a. Final protocol submission: 60 days after notification by FDA to finalize the protocol which will be related to an imminent H5N1 influenza virus pandemic (sustained human to human H5N1 transmission).
    b. Study completion date: 24 months after initiation of the study.
    c. Final report submission: 8 months after completion of data collection.

Revised Protocol Synopsis V89_19

The revised protocol synopsis for V89_19 is entitled "Open-Label, Multicenter Study to Evaluate the Safety and Immunogenicity of Adjuvanted, Cell Culture-Derived, H5N1 Subunit Influenza Virus Vaccine in Healthy Infants <6 Months of Age", version 2.0, dated 29 May 2019. The primary objectives are to evaluate the safety and antibody response on Day 43 of a 2-dose series of the aH5N1c vaccine (7.5 mcg HA + 0.25 mL MF59, 0.5 mL per dose) three weeks apart. Immunogenicity endpoints, as measured by the HI assay, will include GMTs on Day 1 (prevaccination) and Day 43, SCR at Day 43, and %HI ≥1:40 at Day 43. Safety endpoints will include solicited AEs (for 7 days) and unsolicited AEs (for 21 days) after each vaccination, and SAEs, AESIs, MAAEs, and AEs leading to discontinuation through ~180 days after the final vaccination. The study will enroll ~100 healthy infants <6 months. Exclusion criteria will include children with: suspected AESIs as defined in the protocol; immunosuppressive conditions or therapies; or prior illness, exposure to, or vaccination against the A/H5N1 virus (including mothers vaccinated against or who had suspected illness due to an A/H5N1 virus during the last trimester of pregnancy). Informed consent and screening procedures may occur up to 10 days prior to vaccination on Day 1. Study contacts will include: four clinic visits (Days 1, 22, 43, and 202); two diary reminder calls (3-5 days post-vaccinations); and two scripted safety follow-up calls (Days 91 and 152). Statistical analyses will be descriptive. Depending on the nature of the pandemic and rate of enrollment, one or more interim analyses of safety and immunogenicity may be performed on all or a subset of subjects who have completed the Day 43 visit. A Data Monitoring Committee is not planned for the study.

Reviewer comment: Outline of the deferred pediatric study is acceptable.

9.1.4 Immunocompromised Patients

The aH5N1c vaccine has not been evaluated in immunocompromised individuals. Effectiveness in this population may be lower than in healthy individuals due to impaired immune responses.

9.1.5 Geriatric Use

Please see the results of studies V89_18 and V89_13 (Sections 6.1 and 6.3) which included subjects ≥65 years.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

Immunogenicity and safety data submitted to this efficacy supplement support approval of the aH5N1c vaccine for active immunization to prevent disease caused by the influenza A/H5N1 virus subtype contained in the vaccine for use in persons ≥6 months who are at risk for exposure to the A/H5N1 virus. Approval of the aH5N1c vaccine in adults ≥18 years will be through the "traditional" pathway because efficacy may be inferred by clinical endpoint data in adults for the Flucelvax seasonal influenza vaccine which is manufactured by the same process. Approval in children and adolescents 6 months through 3 years and 4 through 17 years will be according to accelerated approval regulations (21 CFR 601.40-46) because seasonal Flucelvax and Flucelvax Quadrivalent are approved under accelerated approval regulations. Please see Section 2.5 of this review for the regulatory history supporting the respective approval pathways.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 56 presents Risk-Benefit Considerations relating to approval of the aH5N1c vaccine in persons ≥6 months.

Table 56: Risk-Benefit Considerations		
Decision Factor	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Influenza is a highly contagious respiratory viral infection that causes significant morbidity and mortality. Due to a segmented genome, multiple subtypes, numerous animal reservoirs, frequent mutations, and genetic reassortment, novel influenza A virus (IAV) subtypes are continually emerging and represent a persistent pandemic threat. • The H5N1 subtype is one of two avian influenza A subtypes with the greatest pandemic potential. Human-to-human transmission is currently inefficient but is associated with a mortality rate of ~53%. Most cases have occurred in persons <40 years, ~50% in persons <20 years, and ~22.4% in persons 20-29 years. The highest mortality rates are reported in persons 10-40 years. Because most people lack immunity, if the H5N1 virus acquires genes that enhance human transmission, many people would experience severe disease, complications and/or death (potential global mortality estimated at 175-350 million). In addition to the usual high risk groups, young healthy persons would be disproportionately affected.	• An H5N1 pandemic would result in great morbidity and mortality worldwide with serious socioeconomic consequences.
Unmet Medical Need	• The aH5N1c vaccine will be the third H5N1 vaccine licensed and stockpiled in the U.S. All will require two doses given 21-28 days apart. No single manufacturer will be able to produce sufficient vaccine for the entire U.S. population, and reliance on one or two manufacturers may be a risk in the event of unforeseen manufacturing problems. One of the two currently available vaccines is unadjuvanted, requires 90 mcg of HA antigen/dose to elicit an immune response, and is only licensed in adults. The second vaccine contains 3.75 mcg HA/dose, is adjuvanted with AS03, and is licensed in persons ≥6 months. Because an AS03-adjuvanted H1N1 vaccine produced by the same manufacturer was associated with narcolepsy in persons <20 years during the 2009 H1N1 pandemic, narcolepsy remains a potential safety concern for the AS03-adjuvanted H5N1 vaccine. • The MF59-adjuvanted aH5N1c vaccine allows for antigen sparing by eliciting higher HI titers, and enhances immunogenicity by inducing cellular and cross-reactive antibody responses, important characteristics in a pandemic vaccine. aH5N1c may offer an alternative to the AS03-adjuvanted H5N1 vaccine in children during a pandemic. • The aH5N1c cell-culture-based manufacturing process may shorten production time and facilitate large scale production relative to egg-based methods and would be unaffected by threats to the chicken flock or egg supply. • The risk of anaphylaxis following egg-based IIVs is rare (~0.5-2.0%). Several studies have clearly demonstrated that the risk of allergic reactions, including anaphylaxis, following administration of egg-based IIVs is no greater in egg-allergic individuals than in those without egg allergy. However, during a pandemic where close post-vaccination monitoring of large numbers of vaccinees may be limited, a non-egg-based vaccine may be useful in persons with serious egg allergies.	• The aH5N1c vaccine meets an unmet medical need.

Clinical Benefit	• One pivotal phase 3 study in adults ≥18 years, two phase 2 dose confirmation studies in young and elderly adults, and one phase 2 dose confirmation study in children 6 months through 17 years were submitted in the BLA. Subjects in all four studies met both immunogenicity endpoints of HI titer ≥1:40 and seroconversion following the selected (full) dose of 7.5 mcg HA/0.25 mL MF59 administered 21 days apart. In children but not adults, a single dose was also sufficient to meet the immunogenicity endpoints. In age subgroup analyses, children 6 to <36 months, 3 years to <9 years, and 9 to <18 years each met success criteria for the co-primary immunogenicity endpoints. • HI titers declined towards baseline at 6-12 months post-vaccinations. Only pediatric subjects had persistent HI titers sufficient to meet the SCR endpoint (but not the %HI ≥1:40) at 12 months post-vaccinations. • Immunogenicity endpoints were derived from studies of seasonal IIVs which have demonstrated that an HI titer of ≥1:40 is likely to predict protection against clinical disease. • Because human transmission of H5N1 influenza is currently very limited, clinical effectiveness of the aH5N1c vaccine cannot be demonstrated until the onset of a pandemic. However, clinical endpoint efficacy data support the clinical benefit of Flucelvax in adults and, because Flucelvax is manufactured by the same process as the aH5N1c vaccine, these data also provide evidence to support clinical benefit of the aH5N1c vaccine.	• Two doses of aH5N1c vaccine administered 21 days apart elicited an HI antibody response reasonably likely to predict clinical benefit against a homologous H5N1 virus at 21 days post-vaccination. • Clinical benefit, persistence of a protective response, and protection against heterologous or drifted strains remain uncertain.
Risk	• Among adults ≥18 years across studies, the most frequent AEs following any aH5N1c vaccination were local and systemic reactogenicity events, primarily, injection site pain (51.2%), fatigue (21.7%), headache (19.5%) and malaise (19.4%). Reactogenicity was less frequent after the second vaccination and less common among adults ≥65 years. Most local and systemic AEs were mild to moderate in severity. Severe local and systemic AEs occurred in ≤0.2% and <1% of adults, respectively, across studies. Fever occurred in 1.2% of full dose recipients, severe fever (≥102.1°F or 39.0°C) in 0.3%. Most local and systemic AEs began within two days of vaccinations and resolved within 3 to 4 days. • In children, rates of solicited AEs were similar between full and half dose groups in both age groups 6 months to <6 years and 6 years through 17 years. In both age and vaccine dose groups, most solicited local and systemic AEs were mild to moderate in severity, and most resolved within 2-3 days. Severe solicited local and systemic AEs each occurred in ≤1% in both age groups. The most common solicited AEs following any full dose vaccination in children 6 months to <6 years were injection site tenderness (56%), irritability (30%) and sleepiness (25%). The most common solicited AEs in children 6 years through 17 years were injection site pain (68%), myalgia (30%), fatigue (27%), malaise (25%), and headache (22%). Rates of solicited AEs were lower following the second as compared to the first vaccination. • Among children 6 months to <6 years, fever (≥38.0°C, ≥100.4°F) in the seven days following any vaccination occurred in 8% of half dose and 16% of full dose recipients. Four (2%) half dose and 3 (2%) full dose recipients had fever ≥102.1°F (≥39.0°C). Most fever occurred within two days of vaccinations and resolved within one to two days. Among children 6 through 17 years, fever (≥38.0°C, ≥100.4°F) in the seven days following any vaccination occurred in 3% of half dose and 4% of full dose vaccine recipients. One (1%) half dose and 1 (1%) full dose recipient had fever ≥102.1°F (≥39.0°C). No febrile seizures or convulsions were reported in the 21 days following any vaccination. • Additional age subanalyses (6 months to <3 years and 3 to <6 years) of solicited AEs showed similar rates of local AEs between age groups regardless of dose level. Rates of solicited systemic AEs overall were more frequent in infants 6-35 months (49% in both the low and high dose groups) than in infants 36-71 months (25%-32%), with the largest differences noted in rates of sleepiness (26%-28% versus 19%-24%) and irritability (33%-35% versus 15%-24%). Fever	• Inclusion of the MF59 adjuvant is associated with greater reactogenicity than unadjuvanted vaccine. However, local and systemic reactogenicity following full or half dose aH5N1c vaccine in the clinical trials supporting licensure were acceptable. Unsolicited AEs and long-term safety data also appear acceptable but the safety database was not large enough to detect rare AEs. • In the event of an A/H5N1 pandemic, the potential benefit of higher immunogenicity following full as compared to half dose vaccine outweighs the higher rates of solicited AEs in the youngest pediatric age subgroup (6 months to <3 years). Age subanalyses of immunogenicity and safety also support the selection of full dose aH5N1c to administer and study in infants <6 months at the onset of a pandemic. • Although the MF59 adjuvant may in theory be associated with induction of potential immune-mediated medical conditions (PIMMCs) or AEs, no safety signals were identified in the aH5N1c clinical trial data. Seqirus pharmacovigilance and Fluad PSURs (estimated cumulative exposure of 127,140,919 individuals through March 15, 2019), likewise, have not identified unexpected safety concerns.

	≥100.4°F occurred most frequently in high dose aH5N1c recipients 6-35 months than in the other groups (21% versus 9% of younger low dose recipients and 7% of both low and high dose recipients 36-71 months). However, severe solicited systemic AEs were infrequent (0-6% of 6-35 months and 0-2% of 36-71 months). • In the individual pivotal study (V89_18) and the ISS, rates of unsolicited AEs were similar between aH5N1c and placebo recipients. No safety signals or unusual patterns of deaths, SAEs, AESIs, NOCDs, MAAEs or AEs leading to premature study withdrawal were identified in the adult or pediatric safety data. • Safety was not systematically evaluated in pregnant or lactating females.	
Risk Management	• Development of the aH5N1c vaccine was supported by the U.S. government. The Applicant will not market the vaccine until requested by the U.S. government in response to a pandemic threat. • The aH5N1c vaccine is indicated for use in persons at increased exposure to the H5N1 virus. • Any potential for increased reactogenicity, anaphylaxis or other potential risks of vaccination with influenza vaccines (e.g., Guillain Barre Syndrome, encephalitis) can be further described in postmarketing surveillance. • Because no new or unexpected safety signals were identified in the clinical trial data, the clinical review team and OBE/DE determined that a safety PMR, REMS or a Black Box warning were not required for the aH5N1c vaccine. • The Applicant will work with FDA to establish a pregnancy registry in the event of an A/H5N1 pandemic.	• Any theoretical concerns over the safety of the MF59 adjuvant are mitigated by restriction to use of the vaccine during an A/H5N1 pandemic when potential benefits clearly outweigh potential risks of vaccination. • Risk management can be adequately addressed by describing the known safety profile of aH5N1c in the PI and through routine postmarketing surveillance.

11.2 Risk-Benefit Summary and Assessment

In clinical studies submitted to the BLA, the aH5N1c vaccine demonstrated immune responses suggesting that it is reasonably likely to provide protection against disease due to an influenza A/H5N1 virus contained in the vaccine in persons ≥6 months. Clinical endpoint efficacy data for Flucelvax seasonal influenza vaccine in adults allow additional inference of clinical benefit of the aH5N1c vaccine in adults to support "traditional" approval. Immune responses in children, adults and the elderly led to statistically significant rises in the HI antibody titer, a surrogate endpoint for influenza vaccine effectiveness based on seasonal influenza data. The aH5N1c vaccine will not be marketed until requested by the U.S. government in response to an influenza A/H5N1 pandemic threat. Therefore, it is unlikely that the clinical effectiveness of the aH5N1c vaccine will be able to be evaluated until the vaccine is deployed in response to a declared influenza pandemic when it may be studied further in epidemiologic studies.

Safety appeared acceptable in all age groups with local and systemic reactogenicity comprising the most common adverse events. Inclusion of a placebo group in the pivotal adult study indicated no large imbalances of serious or immune-mediated AEs. While no unusual patterns of unsolicited AEs or safety concerns were identified, the ability to detect rare adverse events was limited by the relatively small size of the database. The cumulative global exposure to seasonal Flucelvax and Flucelvax Quadrivalent and to the MF59 adjuvant, manufactured by the same processes as the aH5N1c vaccine, provide supportive data and some reassurance regarding safety of the aH5N1c vaccine. Given the expected high morbidity and mortality of an influenza A/H5N1 pandemic, it is reasonable to conclude that the potential benefits of the aH5N1c vaccine would outweigh potential risks in persons ≥6 months.

11.3 Discussion of Regulatory Options

The Applicant has requested and the data support approval of the aH5N1c vaccine in persons 6 months and older, via "traditional" approval in adults ≥18 years and via accelerated approval in children and adolescents 6 months to <18 years. Please see Sections 11.1 and 2.5.

11.4 Recommendations on Regulatory Actions

From the clinical perspective, data submitted to the BLA support approval of the aH5N1c vaccine in persons ≥6 months. Please see Sections 11.1 and 2.5 for further discussion.

11.5 Labeling Review and Recommendations

Major revisions recommended to product labeling included the following:

- The approved trade name for the aH5N1c vaccine, Audenz, was added to the PI.
- The (b) (4) presentation was removed from the Highlights, Section 3, Dosage Forms and Strengths, and Section 16, How Supplied/Storage and Handling.
- Section 6.1, Adverse Reactions, Clinical Trials Experience: Additional text was added to describe the rates of solicited AEs by age group, and brief descriptions of long-term safety. In order to avoid an implied indication for a half dose (3.75 mcg H5 HA/0.125 mL MF59) of Audenz, references to the half dose and

description of safety data for the half dose were removed from the description of pediatric clinical trial experience.

- Section 6.2, Postmarketing Experience: Although no postmarketing experience exists for Audenz, the sponsor was asked to identify for inclusion in the PI potential risks based on the postmarketing experience for seasonal and pandemic influenza vaccines that contain the same MF59 adjuvant or share the same manufacturing platform as Audenz.
- Section 14, Clinical Studies: References to and description of immunogenicity results for the half dose of Audenz were removed from this section to avoid an implied indication for the half dose. If this information is of interest in the event of a pandemic, it may be found in the clinical review which will be available in the public domain.

11.6 Recommendations on Postmarketing Actions

The review team recommended a deferred pediatric PMR to study the safety and immunogenicity of the aH5N1c vaccine in infants <6 months at the onset of an influenza A/H5N1 pandemic.

Please see Section 2.5 for the regulatory basis of accelerated approval of the aH5N1c vaccine in children 6 months to <18 years. For "traditional" approval in this population, the following postmarketing studies will be required: for traditional approval in children 6 months to < 4 years, the Applicant will need to 1) successfully complete and submit data from Flucelvax study V130_10 that demonstrate immunogenicity and safety of Flucelvax in children 6 months to < 4 years (PMR #2 from 125408/127 approval letter dated May 23, 2016: Final Protocol Submission: June 30, 2019, Study Completion: August 30, 2020, Final Report Submission: February 28, 2021) and 2) demonstrate efficacy, safety and immunogenicity of Flucelvax in children 4 years to <18 years in the clinical disease endpoint study V130_12 (PMR #1 from 125408/127 approval letter dated May 23, 2016). Study V130_12 will also be the PMR to support traditional approval of the aH5N1c vaccine in children 4 years to <18 years.

Postmarketing commitments will be determined at the time of approval. As we did for the approval of Q-Pan H5N1, it is likely that we will ask Seqirus to work with government agencies to:

- Establish a pregnancy registry in the event that the U.S. Government declares an H5N1 pandemic.
- Collect additional safety and effectiveness data if the vaccine is used in the U.S. during an H5N1 pandemic.

Please see Sections 1, Executive Summary, and 9.1.3, Pediatric Use and PREA Considerations, and the OBE/DE review for additional information.