Application Type	BLA
STN	125408/101
CBER Received Date	November 20, 2014
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Division / Office	OVRR
Committee Chair	Melisse Baylor, M.D.
Clinical Reviewer(s)	George Dubrocq, M.D.
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Priority Review	No
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Review Completion Date / Stamped Date	
Supervisory Concurrence	Tsai-Lien Lin, Ph.D. Team Leader, Viral and Bioassay Team
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Applicant	Novartis Vaccines and Diagnostics, Inc.
Established Name	Trivalent, inactivated subunit-influenza vaccine
(Proposed) Trade Name	FLUCELVAX
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	H1N1-15 mcg; H3N2-15 mcg; B-15 mcg / 0.5mL
Dosage Form(s) and Route(s) of Administration	Suspension for intramuscular (IM) injection supplied in 0.5-mL single-dose pre-filled syringes
Dosing Regimen	For 4 through 8 years of age, one or two doses, 0.5 mL each (If 2 doses, administer at least one month apart); For 9 years of age or older, one dose, 0.5 mL
Indication(s) and Intended Population(s)	For use in persons 4 years of age or older for active immunization for the prevention of influenza disease caused by influenza virus subtypes A and type B contained in the vaccine

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1. EXECUTIVE SUMMARY

The application submitted by Novartis is a supplement to the existing Biologics License Application (BLA) for Flucelvax™, approved by the FDA for use in the prevention of influenza in adults 18 years of age and older, seeking extension of the existing indication to include children from 4 to < 18 years of age.

Immunogenicity: The primary objective of establishing non-inferiority between Flucelvax (TIVc) and Fluvirin (TIVf) for all three strains in subjects 4 to < 9 years of age was not met. Ratio of GMTs (Flucelvax/Fluvirin) and 95% CI were 0.89 (0.76 to 1.04) for strain A/H1N1, 0.56 (0.47-0.67) for strain A/H3N2, and 0.85 (0.68-1.06) for strain B. The non-inferiority criterion was a CI lower limit of 0.67 that had to be exceeded. Difference in seroconversion rate (Flucelvax – Fluvirin) and 95% CI were 0% (-3% to 2%) for strain A/H1N1, -7% (-12% to -2%) for strain A/H3N2, and 0% (-6% to 7%) for strain B. The non-inferiority criterion was a CI lower limit of -10%, which had to be exceeded. Thus, non-inferiority was demonstrated for the A/H1N1 and B strains by GMTs and the percentages of subjects achieving seroconversion at day 50; however, the non-inferiority criteria were not met for the A/H3N2 strain.

Although the primary objective was not met, the applicant suggested that relevant immune response was observed following vaccination with TIVc in the 4 to < 9 years age group based on a secondary endpoint analysis that showed five out of six alternative immunogenicity criteria were met. The secondary endpoint analyses on the age group 4 to < 9 years showed that the lower limit of the two-sided 95% CI for percentage of subjects achieving an HI antibody titer ≥ 1:40 was greater than 70% for strains A/H1N1 and A/H3N2; however, TIVc did not meet the criterion for strain B. The lower limit of the two-sided 95% CI for seroconversion rate was greater than 40% for all three strains. For subjects 9 to < 18 years of age, the alternative immunogenicity criteria were met for all three strains. The reviewer defers to other reviewers on the review team for further considerations based on the totality of evidence submitted.

Safety: The integrated safety analysis showed comparable safety profiles between Flucelvax and Fluvirin in children and adolescents 4 to < 18 years of age. There appear to be no major safety concerns from a statistical perspective.

2. CLINICAL AND REGULATORY BACKGROUND

This application, submitted by Novartis, is a supplement to the existing BLA for Flucelvax approved by the FDA on November 20, 2012, for use in the prevention of influenza in adults 18 years of age and older. Flucelvax is a purified, inactivated, trivalent subunit influenza vaccine manufactured in a Madin-Darby Canine Kidney (MDCK) cell line (hereafter referred to as TIVc). This BLA supplement seeks extension of the existing indication to include children from 4 to < 18 years of age.

2.1 Disease or Health-Related Condition(s) Studied

Influenza in children from 4 to < 18 years of age

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

N/A

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

Flucelvax was approved by the FDA on November 20, 2012, for use in the prevention of influenza in adults 18 years of age and older. Novartis is currently the Marketing Authorization Holder in 33 countries worldwide, including 31 European Economic Area countries, the US, and Switzerland.

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

Study V58P12 was originally designed to investigate the immunogenicity and safety of TIVc in subjects 3 to < 18 years of age. Results from the study were submitted as supportive evidence in the original application to the FDA. However, as the comparator vaccine, Fluvirin (hereafter referred as to TIVf), is licensed for use only in individuals 4 years of age and older, CBER recommended adjusting the intended age range for the analysis to children 4 to < 18 years of age (CBER Memorandum, 05 JUN 12). Therefore, reanalysis was performed to support the licensing of TIVc for prevention of influenza in a subset of children 4 years of age and older in the US.

Study V58_31 was a phase 3, observer-blind, randomized, controlled, multicenter study designed to evaluate the safety of TIVc compared to TIVf in subjects 4 to < 18 years of age. This study was designed to extend the safety database of the TIVc in the pediatric population 4 to ≤ 18 years of age, as requested by CBER (Type C Meeting, 15 DEC 10), to reach a safety database of at least 3000 subjects vaccinated with TIVc.

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission is adequately organized for conducting a complete statistical review.

3.2 Compliance with Good Clinical Practices and Data Integrity

The submission generally complied with good data integrity.

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

N/A

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

5.1 Review Strategy

This review focuses on Study V58P12 for efficacy evaluation and the integrated safety summary (studies V58P12 and V58_31) for safety evaluation.

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

- STN 125408/101.0 Module 2.5. Clinical Overview
- STN 125408/101.0 Module 5.3.5.3. Integrated Summary of Efficacy
- STN 125408/101.0 Module 5.3.5.3. Integrated Summary of Safety
- STN 125408/101.0 Module 5.3.5.1. Study V58_31 Clinical Study Report
- STN 125408/82.0 Study V58P12 Clinical Study Report addendum 3, 20 May 2014
- STN 125408/0.0 Module 5.3.5.4. Study V58P12 Clinical Study Report

5.3 Table of Studies/Clinical Trials

Table 1: Overview of Clinical Studies Supporting the sBLA

Study Number	Geographic Location	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Age
V58P12	US and Europe (Croatia, Finland, Hungary, Italy, Lithuania, Romania)	Noninferiority of TIVc vs TIVf	Phase 2/3, observer blind, randomized, active-controlled	TIVc and TIVf, formulation 2007-2008[a], 0.5 mL (1 dose for Cohorts 1 and 2, and 2 doses [given 4 weeks apart] for Cohort 3); IM injection (deltoid)	3- <18 years (original study) 4- <18 years (current submission)
V58_31	US, Australia, New Zealand, Philippines, Thailand	Safety and tolerability of TIVc vs TIVf	Phase 3, observer blind, randomized, active-controlled	TIVc and TIVf, formulation 2013[b] and formulation 2013-2014[c]; 0.5 mL (1 or 2 doses); IM injection (deltoid)	4- <18 years

Note: [a] Northern Hemisphere; [b] Southern Hemisphere; [c] Northern Hemisphere; for subjects enrolled in study V58_31 after July, 2013 only.
Source: adapted from STN 125408/101 Module 2.5. Clinical Overview, Table 2.5.1.3-1.

5.4 Consultations

N/A

5.5 Literature Reviewed (if applicable)

N/A

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study V58P12: A Combined Phase II/III, Observer-Blind, Randomized, Multicenter Study to Evaluate Safety, Tolerability and Immunogenicity of Trivalent Subunit Influenza Vaccines, Produced Either in Mammalian Cell Culture or in Embryonated Hen Eggs (Fluvirin®), in Healthy Children and Adolescents Aged 3 to 17 Years

Study V58P12 was originally designed as a phase 2/3, observer-blind, randomized, multicenter study to evaluate the immunogenicity, safety, and tolerability of TIVc and TIVf in subjects 3 to < 18 years of age. Based on CBER's recommendation, the intended age range for the analysis was adjusted to children 4 to < 18 years of age in the current submission.

6.1.1 Objectives

Immunogenicity Objectives

Co-Primary Objectives:

- To demonstrate non-inferiority of the post-vaccination (day 50) hemagglutination inhibition (HI) geometric mean titer (GMT) of TIVc to the corresponding GMT of TIVf for all three strains, after two injections administered four weeks apart to a subset of children 4 to < 9 years of age.
- To demonstrate non-inferiority of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 following administration of TIVc to the corresponding percentages of subjects following administration of TIVf for all three strains, after two doses administered four weeks apart to a subset of children 4 to < 9 years of age.

Secondary Objectives:

- To evaluate immunogenicity, measured by seroprotection and by percentage of subjects achieving seroconversion or significant increase, of:
    - one injection of either TIVc or TIVf administered to children and adolescents 9 to < 18 years of age.
    - two injections of either TIVc or TIVf, administered 4 weeks apart to a subset of children 4 to < 9 years of age.

Safety Objectives

To evaluate safety and tolerability of one injection of either TIVc or TIVf in children and adolescents 9 to < 18 years of age and of two injections of either TIVc or TIVf, administered four weeks apart to children 4 to < 9 years of age.

6.1.2 Design Overview

The study enrolled subjects into one of three age cohorts as follows:

- Cohort 1 (immunogenicity and safety): healthy subjects 9 to < 18 years of age, US centers only. Subjects 9 to < 18 years of age were randomized in Cohort 1 at a 1:1 ratio to receive either TIVc or TIVf vaccine. All subjects received one 0.5 mL

intramuscular (IM) vaccine. Enrollment of subjects in Cohorts 2 and 3 was to begin after day-3 safety and tolerability data for Cohort 1 were reviewed by the applicant and determined to meet the defined criteria for proceeding to enrollment of Cohorts 2 and 3.

- Cohort 2 (safety only): healthy subjects 9 to < 18 years of age, US and European centers. Subjects 9 to < 18 years of age were randomized at a 3:1 ratio to receive either TIVc or TIVf. All subjects received one 0.5 mL vaccine administered IM.
- Cohort 3 (immunogenicity and safety): healthy subjects 3 to < 9 years of age, US and European centers. Subjects aged 3-8 years were randomized at a 2:1 ratio to receive either TIVc or TIVf. All subjects received two 0.5 mL vaccines, administered 4 weeks apart. Furthermore, approximately 1320 subjects in Cohort 3 were planned to be allocated at a 1:1 ratio to an immunogenicity subset. As per CBER's request for reanalysis of data for 4-17 year old subjects, subjects < 4 years of age were removed from Cohort 3.

6.1.3 Population

Individuals 4 to < 18 years of age in good health as determined by medical history, physical examination, and clinical judgment of the investigator

6.1.4 Study Treatments or Agents Mandated by the Protocol

Each 0.5 mL of MDCK TIVc and 0.5 mL of the conventional TIVf contained: purified viral envelope-glycoproteins, neuraminidase (NA), and hemagglutinin (HA), including 15µg of HA for each strain (A/Solomon Islands/3/2006 [H1N1]-like, A/Wisconsin/67/2005 [H3N2]-like, and B/Malaysia/ 2506/2004-like) recommended for the 2007-2008 influenza season in the Northern Hemisphere.

6.1.6 Sites and Centers

14 sites in Finland, 16 in the US, 9 in Croatia, 5 in Italy, 6 in Lithuania, 2 in Romania, 8 in Hungary.

6.1.7 Surveillance/Monitoring

N/A

6.1.8 Endpoints and Criteria for Study Success

<u>Immunogenicity</u>

Co-Primary Endpoints (Cohort 3, immunogenicity subset):

- TIVc was non-inferior to TIVf in post-vaccination HI GMTs if, for all three strains, the lower limit of the two-sided 95% confidence interval (CI) for day 50 ratio of GMTs (TIVc/TIVf) was > 0.667.
- TIVc was non-inferior to TIVf in terms of the percentages of subjects achieving seroconversion or significant increase in antibody titer at day 50 if for all three strains, the lower limit of the two-sided 95% CI around the differences in the percentages of subjects achieving seroconversion and significant increase (TIVc minus TIVf) was > -10%. Here seroconversion rate is defined as the percentage of subjects with either a pre-vaccination (baseline) HI titer < 1:10 and post-

vaccination HI titer ≥ 1:40 or with a pre-vaccination HI titer ≥ 1:10 and a ≥ 4-fold increase in post-vaccination HI antibody titer.

Secondary Endpoints (Cohort 1 and Cohort 3, immunogenicity subset):

The percentage of subjects sero-protected or achieving seroconversion was considered statistically compliant with the stated CBER immunogenicity criteria if:

- the lower limit of the two-sided 95% CI for the percentage of subjects achieving an HI antibody titer ≥ 40 met or exceeded 70%;
- the lower limit of the two-sided 95% CI for the percentage of subjects achieving seroconversion for HI antibody met or exceeded 40%.

Safety

Safety of the study vaccines was assessed in terms of number of subjects exposed to study vaccine with reported solicited local and systemic reactions, unsolicited reactions, as well as the number of subjects with reported SAEs and/or AEs per vaccine group.

6.1.9 Statistical Considerations & Statistical Analysis Plan

(1) Blinding

The study was designed as an observer-blind study. During the study, designated un-blinded nurses or physicians were responsible for administering the study vaccines to the subjects, for keeping daily and final accountability records of the vaccine supplies, and were instructed not to reveal the identity of the study vaccines either to the subject, to their parents/legal guardians, or to the investigative site personnel (investigator, study nurse) involved in the monitoring or conduct of the study, except in an emergency.

(2) Statistical Methods

GMT and ratio of GMTs (TIVc/TIVf) and their associated 95% CIs for each strain and each vaccine group were calculated using the least squares method from analysis of variance with vaccine group and center as factors. Centers with fewer than 10 subjects were combined. The difference of seroconversion rates (TIVc-TIVf) and its two-sided 95% confidence interval were calculated for each strain, using the usual normal approximation to the binomial or the method of Miettinen – Nurminen - Mee. Percentages of subjects with HI dilution ≥ 1:40, 4-fold increase, and seroconversion and associated 95% CIs for each strain and each vaccine group were calculated. The 95% CIs were calculated using the Clopper-Pearson method.

(3) Sample size

The study was powered to demonstrate non-inferiority of TIVc to TIVf for immunogenicity in children aged 3 to 8 years (Cohort 3). The null hypotheses for the primary immunogenicity objectives state that for at least one strain, TIVc does not meet the non-inferiority criteria. With respect to the GMT criteria, assuming a standard deviation of HI titers of 0.8 (calculated as the upper limit of the 80% CI of the standard deviation reported in a previous Novartis Vaccines' exploratory study, M71P1), and a randomization ratio of 1:1 (TIVc : TIVf), 1200 evaluable subjects, 600

subjects in each vaccine group, was considered to be sufficient to demonstrate non-inferiority with power of 90.6% (96.75% for each strain; one-sided α=0.025). Assuming a percentage of subjects achieving seroconversion or significant increase equal to 55% (as in previous Novartis Vaccines' exploratory study, M71P1), 1200 evaluable subjects with 600 subjects in each vaccine group was considered to be sufficient to demonstrate non-inferiority with power of 82% (93.6% for each strain; one-sided α=0.025). Considering an approximate 10% dropout rate, 1320 subjects were planned to be enrolled in the immunogenicity subset (660 in each vaccine group).

(4) Definitions of analysis populations

- All Randomized population: all enrolled subjects who have a record in the DEMOG panel.
- Intent-to-Treat (ITT) population, Immunogenicity: all randomized subjects who received at least one dose of vaccine and provided at least one evaluable serum sample before (baseline) or one after vaccination.
- Per Protocol (PP) population, Immunogenicity: all subjects in the ITT population who received all the doses of vaccine correctly, provided evaluable serum samples at the relevant time points, and had no major protocol violation as defined prior to unblinding.
- Safety population: all subjects with at least one vaccination and with some post-vaccination safety data.

(5) Missing data handling

Missing data were not imputed. Missing values were considered by the applicant as completely missing at random and left out of the analysis.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A subset of subjects 4 to < 18 years of age from the original study V58P12 was used for the immunogenicity analysis. Subjects enrolled in the immunogenicity subset were randomized and analyzed separately according to their age group: 4 to < 9 years of age or 9 to < 18 years of age. The primary immunogenicity objective was based on the analysis of the 4 to < 9 years age group. The primary population analyzed for all immunogenicity analyses was the Per-Protocol Set (PPS).

6.1.10.1.1 Demographics

Subjects 4 to < 9 years (Per Protocol Set): in both vaccine groups (TIVc and TIVf), the mean age was 5.9 (±1.3) years. Half of the subjects in this age group were male. Most subjects in both vaccine groups were Caucasian (84% to 86%), and most subjects (88% to 90%) in both vaccine groups did not receive an influenza vaccination in the previous year.

Subjects 9 to < 18 years (Per Protocol Set): the mean age was 12.6 (±2.4) to 12.7 (±2.6) years in the TIVf and TIVc vaccine groups, respectively. In both vaccine groups, the

majority of subjects were male (57% to 58%), Caucasian (68% to 69%), and did not receive an influenza vaccination in the previous year (62% to 66%).

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.1.10.1.3 Subject Disposition

Table 2 summarizes number of subjects planned, actually enrolled, and included in the analysis sets. The data for 3 to <9 years of age in the original study are also included as reference.

Table 2: Number of Enrolled Subjects Planned and Number of Subjects Included in the Actual Analysis Sets

	3 to < 9 Years (Original)		**4 to < 9 Years**		**9 to < 18 Years**	
	TIVc	TIVf	TIVc	TIVf	TIVc	TIVf
Enrollment planned	2000	1000	NA	NA	600	300
Enrolled actual	1608	1022	1330	836	656	318
Safety Set	1599	1013	1324	831	652	316
Enrollment planned for Immunogenicity	660	660	NA	NA	150	150
Enrollment Immunogenicity subset as randomized	657	662	546	545	151	154
ITT immunogenicity subset	637	640	530	531	149	151
PPS immunogenicity subset	524	513	441	430	142	144

Source: STN 125408/101 Module 5.3.5. Integrated Summary of Efficacy, Table 2-2

For subjects 4 to < 9 years of age, exclusions from the PPS were balanced between the vaccine groups. In total, 105 subjects (19%) and 115 subjects (21%) in the TIVc and TIVf vaccine groups, respectively, were excluded from the enrolled immunogenicity subset due to major protocol deviations. The two most common major protocol deviations leading to exclusion from the PPS in the immunogenicity subset was that not all serum samples (6% of subjects in either vaccine group) and not all immunogenicity results were available from the subject (6% of subjects in either vaccine group).

Within the 9 to < 18 years age group, 9 subjects (6%) and 10 subjects (6%) in the TIVc and TIVf vaccine groups, respectively, were excluded from the enrolled immunogenicity subset. The most common major protocol deviation in the immunogenicity subset was that subjects received an excluded concomitant medication (3% of subjects in either vaccine group).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Primary endpoint analysis was performed on the immunogenicity data of subjects 4 to < 9 years of age. The criteria for non-inferiority are that (1) the lower bound of the two-sided 95% CI on the day 50 ratio of the GMTs (TIVc/TIVf) is > 0.667, and (2) the lower bound of the two-sided 95% CI on the difference between the day 50 seroconversion rates (TIVc - TIVf) is > -10%. Non-inferiority of TIVc versus TIVf was demonstrated for 4 of 6 non-inferiority endpoints. Non-inferiority was demonstrated for the A/H1N1 and B strains as measured by GMTs and the percentages of subjects achieving seroconversion by day 50. However, non-inferiority criteria were not met for the A/H3N2 strain (Table 3).

Table 3: Noninferiority Based on Day 50 GMTs and Seroconversion Rates Using the HI Cell-Derived Antigen Assay in Subjects 4 to < 9 Years of Age - PPS

		TIVc	**TIVf**	**Ratio of GMTs TIVc/TIVf (95% CI)**	**Difference TIVc – TIVf (95% CI)**
		N=441	**N=430**		
A/H1N1	GMT (95% CI)	609 (540-686)	685 (608-773)	0.89 (**0.76**-1.04)	
	Seroconversion rate (95% CI)	96% (94%-98%)	97% (94%-98%)		0% (**-3%** to 2%)
A/H3N2	GMT (95% CI)	976 (855-1114)	1743 (1527-1989)	0.56 (0.47-0.67)	
	Seroconversion rate (95% CI)	80% (76%-84%)	87% (84%-90%)		-7% (-12% to -2%)
B	GMT (95% CI)	60 (51-71)	71 (60-84)	0.85 (**0.68**-1.06)	
	Seroconversion rate (95% CI)	62% (57-66%)	62% (57-66%)		0% (**-6%** to 7)

Source: modified from STN 125408/101 Module 5.3.5.3. Integrated Summary of Efficacy, Table 3.2-1. It should be noted that 95% CI of difference TIVc – TIVf for B strain was presented as (-6% to -7%) in the original table; it has been corrected by the reviewer and confirmed by the applicant.

Reviewer Comment:
The two-sided 95% CI for the difference in seroconversion rate between TIVc and TIVf for the B strain in subjects 4 to < 9 years old was reported as -6% to -7% in Table 2.5.4.4.1-1 in the clinical overview and in Table 3.2-1 in the integrated summary of efficacy. The upper limit of the CI is incorrect. An information request was sent to the applicant on June 15, 2015 to ask for clarification. The applicant's response is as follows:

> *The correct two-sided 95% CI for the difference in seroconversion rate between TIVc and TIVf for B strain in the subjects 4 to <9 years is -6% to 7%. Consequently, the correct upper limit of the CI is 7%. There has been a transcription error in Table 2.5.4.4.1-1 in the clinical overview and in Table 3.2-1 in the integrated summary of efficacy.*

The applicant indicated that non-inferiority of TIVc versus TIVf, as assessed by HI assay using cell culture-derived test antigen, was demonstrated for 5 of 6 non-inferiority endpoints in subjects 3 to < 9 years of age; for the A/H3N2 strain, non-inferiority was achieved based on percentages of subjects achieving seroconversion rate at day 50. However, TIVc was inferior to TIVf as measured by GMT ratio. The applicant suggested that the outcome difference may be due to reduction of sample size; the sample size for the study was calculated for non-inferiority assessment in subjects 3 to < 9 years, and not for the analyses in subjects 4 to < 9 years.

Reviewer Comment: *In the primary endpoint analysis with subjects 3 to <4 years of age included, reported in the original BLA (STN 125408/0), the lower bound of the two-sided 95% CI on the difference between the day 50 seroconversion rates (TIVc - TIVf) was > -10% for A/H3N2, while GMT ratio for the strain did not meet the non-inferiority criteria (Table 4). On the other hand, neither seroconversion rate difference nor GMT ratio met the non-inferiority criteria in the current analysis with subjects 3 to <4 years of age excluded (STN 125408/101). The applicant suggested that reduction of sample size may lead to the difference in outcome. The reviewer performed additional analysis on subjects 3 to <4 years of age. The point estimates of seroconversion rate difference (TIVc-TIVf) and GMT ratio (TIVc/TIVf) were substantially higher than those of subjects 4 to <9 years of age, although the confidence intervals were wide due to small sample size for the 3 to < 4 age subgroup, which may suggest potential difference in immune response to the vaccines between subjects 3 to <4 years and subjects 4 to <9 years (Table 4). It is possible that different immune responses to the vaccines between subjects 3 to <4 years and subjects 4 to <9 years may also contribute to the outcome difference between the analyses with and without subjects 3 to <4 years of age.*

Table 4: Summary of A/H3N2 Non-inferiority Results Based on Day 50 GMTs and Seroconversion Rates Using the HI Cell-Derived Antigen Assay for Subjects 4 to < 9 Years of Age, Subjects 3 to <9 Years of Age, and Subjects 3 to <4 Years of Age

		TIVc	TIVf	Ratio of GMTs TIVc/TIVf (95% CI)	Difference TIVc – TIVf (95% CI)
4 to <9 Years of Age[1]	GMT (95% CI)	976	1743	0.56 (0.47-0.67)	
	Seroconversion rate (95% CI)	80%	87%		-7% (-12% to -2%)
3 to <9 Years of Age[2]	GMT (95% CI)	858	1329	0.65 (0.54 – 0.78)	
	Seroconversion rate (95% CI)	80%	85%		-5% (-9.5% to 0%)
3 to <4 Years of Age[3]	GMT (95% CI)	333	373	0.89 (0.49, 1.64)	
	Seroconversion rate (95% CI)	79%	74%		5% (-7% to 17%)

Source:

1. *Subjects 4 to <9 Years of Age: STN 125408/101 Module 5.3.5.3. Integrated Summary of Efficacy, Table 3.2-1; STN 125408/82.0 Module 5.3.5.4. Study V58P12 - Study Report Addendum 3, Table 11.4.1-1.*
2. *Subjects 3 to <9 Years of Age: STN 125408/0 Module 5.3.5.4. Study V58P12 – Study Report, Table 11.4.1.1-1.*
3. *Subjects 3 to <4 Years of Age: Reviewer's analysis based on the A/H3N2 data for subjects 3 to <4 years of age, provided in STN 125408/101 (N=107 for TIVc and N=109 for TIVf). The GMT results presented in the table were obtained from the analysis with adjustment of study center, following the approach used in the study. Considering small number of subjects within certain centers, an additional analysis was conducted without adjustment of study center. Without adjustment of center, GMT ratio (TIVc/TIVf) was 1.13 with 95% CI (0.62 to 2.05).*

6.1.11.2 Analyses of Secondary Endpoints

The applicant also evaluated immunogenicity based on alternative immunogenicity criteria. The alternative criteria for adults < 65 years old and for the pediatric population, included in the FDA Guidance "Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccine," are that (1) the lower bound of the two-sided 95% CI for the percent of subjects achieving seroconversion for HI antibody should meet or exceed 40%, and (2) the lower bound of the two-sided 95% CI for the percent of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 70%.

Subjects 4 to < 9 Years of Age:
Overall, 5 of 6 alternative immunogenicity criteria were met for subjects 4 to < 9 years of age for TIVc (Table 5). After two vaccinations, both criteria were met for A/H1N1 and A/H3N2 strains, while only the seroconversion criterion was met for the B strain. Similarly, 5 of 6 CBER immunogenicity criteria were met for subjects 4 to < 9 years of age for TIVf, with only the seroconversion criterion being met for the B strain.

Table 5: Immunogenicity Results of Subjects 4 to < 9 Years of Age - PPS

	Day 50	**TIVc**	**TIVf**
		N=441	**N=430**
A/H1N1	HI ≥ 40 (95% CI)	99% (**97%**-99%)	98% (**97%**-99%)
	Seroconversion rate (95% CI)	96% (**94%**-98%)	97% (**94%**-98%)
A/H3N2	HI ≥ 40 (95% CI)	99% (**97%**-100%)	97% (**95%**-98%)
	Seroconversion rate (95% CI)	80% (**76%**-84%)	87% (**84%**-90%)
B	HI ≥ 40 (95% CI)	64% (60%-69%)	66% (61%-70%)
	Seroconversion rate (95% CI)	62% (**57%**-66%)	62% (**57%**-66%)

Source: adapted from STN 125408/101 Module 5.3.5.3. Integrated Summary of Efficacy, Table 3.2-2.

Subjects 9 to < 18 Years of Age:
At day 29, 3 weeks after vaccination, both CBER criteria (seroconversion and HI titer ≥ 40) were met by both TIVc and TIVf for all three influenza strains (Table 6).

Table 6: Immunogenicity Assessment Results for Subjects 9 to < 18 Years of Age - PPS

	Day 29	**TIVc**	**TIVf**
		N=141	**N=144**
A/H1N1	HI ≥ 40 (95% CI)	99% (**96%**-100%)	98% (**94%**-100%)
	Seroconversion rate (95% CI)	74% (**66%**-81%)	74% (**66%**-81%)
A/H3N2	HI ≥ 40 (95% CI)	100% (**97%**-100%)	100% (**97%**-100%)
	Seroconversion rate (95% CI)	52% (**44%**-61%)	78% (**70%**-84%)
B	HI ≥ 40 (95% CI)	95% (**90%**-98%)	94% (**89%**-98%)
	Seroconversion rate (95% CI)	63% (**55%**-71%)	69% (**61%**-76%)

Source: adapted from STN 125408/101 Module 5.3.5.3. Integrated Summary of Efficacy, Table 3.2-3.

Reviewer Comment: *The number of subjects 9 to <18 years receiving TIVc was reported as 141 (N=141) in the analyses of the per-protocol set (Table 2.5.4.4.2-1 in the clinical overview and Table 3.2-3 in the integrated summary of efficacy). However, the applicant's overview of the study population indicates that the number of subjects 9 to <18 years receiving TIVc in the PPS is 142 (Table 2.5.4.3-1 in the clinical overview and Table 3.1-1 in the integrated summary of efficacy). An information request was sent to the applicant on June 15, 2015 to ask for clarification. The applicant's response is as follows:*

> *The overview of study population (Table 2.5.4.3-1 in clinical overview and Table 3.1-1 in integrated summary of efficacy) provides the per-protocol set (PPS) numbers, i.e., 142 subjects. This PPS was used for immunogenicity assessments as evaluated by HI antibody response, measured using either egg derived or cell derived antigens. In this PPS one subject (081020) did not have the pre-vaccination titers for HI assay measured with cell derived antigen. Table 2.5.4.4.2-1 in the clinical overview and Table 3.2-3 in the integrated summary of efficacy present the results of the cell based antigen HI assay. Hence, N=141 (excluding the one subject whose pre-vaccination titers were not available) is represented in Table 2.5.4.4.2-1 and Table 3.2-3.*

6.1.11.3 Subpopulation Analyses

Subgroup analyses of immune response by sex, race/ethnicity, region, and baseline immune status (subjects with pre-vaccination HI titers < 10 or ≥ 10) were performed.

- Sex: Subjects 4 to < 9 years of age in the PPS were balanced between groups (~50% male in the TIVc and TIVf groups). For subjects 9 to < 18 years of age, there were more males included in the PPS (57%~58% male in the TIVc and TIVf groups, respectively). There was a slight tendency of higher point estimates of GMTs in female subjects compared to male subjects on day 50 (for subjects 4 to < 9 years) or day 29 (for subjects 9 to < 18 years).
- Race/Ethnicity: Subgroup analyses for race/ethnicity were performed only on Caucasian, Black, and Hispanic populations because Asian and "other" comprised only 1% and fewer subjects. The immune response appears to be similar in the 3 populations for both A-strains in subjects in the 4 to < 9 age group and for all 3 strains in subjects in the 9 to < 18 age group. For the B strain in the TIVc vaccine group for subjects in the 4 to < 9 years of age group, there appears to be a

tendency for a higher immune response in the Black population (88% [68-97]) compared to the Caucasian population (62% [57-67]).

- Geographic Region: for subjects in the 4 to < 9 years of age group, there was a tendency of higher immune response in the US population compared to the European population regarding GMTs. No subgroup analysis by geographic region was performed in subjects 9 to < 18 years of age since they were only enrolled in the US.
- Baseline immune status (subjects with pre-vaccination HI titers < 10 or ≥ 10): For both age subgroups, the percentages of subjects seropositive (HI titer ≥ 10) at baseline were balanced between the 2 vaccine groups for each strain.

6.1.11.4 Dropouts and/or Discontinuations

In both age groups the percentages of subject who withdrew prematurely were balanced between the vaccine groups. The most common reason for withdrawal in both age groups across vaccine groups was loss to follow up (8% and 7% of subjects 4 to < 9 years of age in the TIVc and TIVf vaccine group, respectively, and 2% of subjects 9 to < 18 years of age in both vaccine groups). Two subjects (< 1% of subjects, age group 4 to < 9 years in the TIVf vaccine group) withdrew due to an adverse event. Missing values were considered by the applicant as missing completely at random and left out of the analysis.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

The safety data obtained from this study and study V58_31 were pooled for integrated safety analysis. The integrated safety analysis will be discussed in section 8.

6.1.12.1 Methods

Evaluation of the safety endpoints was of descriptive nature.

6.1.12.3 Deaths

No deaths were reported in this study.

6.1.12.4 Nonfatal Serious Adverse Events

Among subjects 4 to < 9 years of age, two subjects (both in the TIVc group) experienced any SAE after the first vaccination, and 10 subjects (TIVc: 6, TIVf: 4) experienced any SAE after the second vaccination. Among subjects 9 to < 18 years of age, there were eight subjects (TIVc: 5, TIVf: 3) who experienced an SAE. These SAEs were judged by the investigator as unrelated to vaccine administration.

6.1.12.5 Adverse Events of Special Interest (AESI)

N/A

6.1.12.6 Clinical Test Results

N/A

6.1.12.7 Dropouts and/or Discontinuations

Please refer to section 6.1.11.4.

6.2 Study V58_31: A Phase III, Observer-blind, Randomized, Controlled, Multicenter Study to Evaluate the Safety of a Trivalent Subunit Influenza Vaccine Produced either in Mammalian Cell Culture or in Embryonated Chicken Eggs (Fluvirin®), in Healthy Children and Adolescents 4 to 17 Years of Age

This study was designed to extend the safety database of the TIVc in the pediatric population 4 to ≤ 18 years of age, as requested by CBER (Type C Meeting, 15 DEC 10), to reach a safety database of at least 3000 subjects vaccinated with TIVc. The safety data obtained from this study and study V58P12 were pooled for integrated safety analysis. The integrated safety analysis will be discussed in section 8.

6.2.1 Objectives (Primary, Secondary, etc.)

To evaluate safety and tolerability of one or two doses (administered 4 weeks apart) of mammalian cell culture-derived influenza vaccine (TIVc) and Fluvirin (TIVf) in children and adolescents 4 to ≤ 17 years of age.

6.2.2 Design Overview

The study enrolled children who were designated as “previously vaccinated” or “not previously vaccinated” based on their previous influenza vaccination history. “Previously vaccinated” was defined as any child ≥ 9 years of age, or any child < 9 years of age who has (since 2010) received 2 doses of seasonal influenza vaccine. “Not previously vaccinated” was defined as any child < 9 years of age in any country who does not meet the conditions for designation as previously vaccinated.

Subjects were enrolled and stratified by age cohort (4 through 8 years and 9 through 17 years) in a 1:1 ratio. Subjects within the 4 through 8 year age cohort were further divided into strata “previously vaccinated” or “not previously vaccinated.” Subjects in the 9 to 17 years and the 4 to 8 years (“previously vaccinated”) groups received 1 dose of study vaccine, and subjects in the 4 through 8 years (“not previously vaccinated”) group received 2 doses of study vaccine separated by 4 weeks. Subjects were randomized at a 2:1 ratio to receive either the TIVc or the TIVf in each age group.

6.2.3 Population

Healthy male and female children and adolescents 4 to ≤ 17 years of age were enrolled in this study.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Study vaccine TIVc: A 0.5 mL dose of Madin-Darby canine kidney (MDCK) cell culture-derived subunit influenza vaccine, including approximately 15µg of HA for each of the strains A/Brisbane/10/2010 (H1N1), A/Victoria/361/2011 (H3N2), B/Wisconsin/1/2010 (B), recommended for the 2013 influenza season in the Southern

Hemisphere. The Northern Hemisphere study vaccine TIVc was identical to the Southern Hemisphere formulation but contained different influenza strains A/Brisbane/10/2010 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachusetts/2/2012 (B) recommended by the WHO for use in the 2013/2014 Northern Hemisphere influenza season.

Control Vaccine TIVf (Fluvirin): A 0.5 mL dose of TIVf, containing approximately 15µg of HA of each of the three strains A/Christchurch/16/2010 (H1N1), A/Victoria/361/2011 (H3N2), and B/Hubei Wujiagang/158/2009 (B), recommended for the influenza season 2013 in the Southern Hemisphere. The Northern Hemisphere study vaccine TIVf was identical to the Southern Hemisphere formulation but contained different influenza strains A/Christchurch/16/2010 (H1N1), A/Texas/50/2012 (H3N2), and B/Massachusetts/02/2012 (B) recommended for the 2013/2014 Northern Hemisphere influenza season.

6.2.6 Sites and Centers

A total of 34 centers in 5 countries: 18 sites in the US, 6 sites in Australia, 2 sites in New Zealand, 5 sites in the Philippines, and 3 sites in Thailand.

6.2.7 Surveillance/Monitoring

N/A

6.2.8 Endpoints and Criteria for Study Success

Immunogenicity was not assessed in this study. Safety was assessed in accordance with available safety data typically collected for influenza vaccines.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The study was designed to extend the safety database of TIVc in the pediatric population 4 to ≤ 17 years of age, as requested by CBER, in order to reach a safety database of at least 3000 subjects vaccinated. In study V58P12, approximately 1900 subjects were treated with the TIVc. Hence, it was planned that about 1360 subjects were to be enrolled in the TIVc arm of the current study, accounting for a 20% drop out rate. The applicant expected that the current safety study would allow detecting an uncommon AE with an incidence rate of 0.2% with a probability of 93%; in the final database with 3000 subjects exposed to TIVc, an AE with a background incidence rate of 0.1% would be detected with a probability of 95%.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Populations for analyses were defined as follows:

- All Enrolled Set: All screened subjects who provided informed consent and demographic and/or other baseline screening measurements, regardless of the subject's randomization and treatment status in the trial and received a subject ID.
- Exposed Set: All subjects in the enrolled set who received a study vaccination.

- Safety Set (Overall): All subjects in the exposed set who had either post-vaccination safety data or solicited safety data.

Of 2055 total enrolled subjects, 2052 subjects received study vaccination and were included in the safety sets (1370 in TIVc group and 682 in TIVf group).

6.2.10.1.1 Demographics
Demographic characteristics were generally balanced between the TIVc and the TIVf groups for each age cohort. For each age cohort, the majority of the enrolled subjects were Asian (65% for ≥ 4 to ≤ 17 years; 58% for ≥ 4 to ≤ 8 years; 71% for ≥ 9 to ≤ 17 years) in both groups and a lower proportion were white (31% for ≥ 4 to ≤ 17 years; 37% for ≥ 4 to ≤ 8 years; 25%~26% for ≥ 9 to ≤ 17 years).

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
N/A

6.2.10.1.3 Subject Disposition
A total of 2055 subjects were enrolled in this study. Three subjects were enrolled in the study but did not receive study vaccination and were excluded from the safety set.
A total of 1359 subjects from the TIVc and 673 subjects from the TIVf group completed the study. Thirteen subjects (<1%) from the TIVc and 10 subjects (1%) from the TIVf group were prematurely withdrawn from the study. The most common reason of premature withdrawal from the study in both TIVc and TIVf groups was loss to follow-up. There were no withdrawals from the study due to AEs.

6.2.11 Efficacy Analyses

N/A

6.2.12 Safety Analyses

6.2.12.1 Methods
Evaluation of the safety endpoints was descriptive without pre-specified criteria.

6.2.12.3 Deaths
No deaths were reported in this study.

6.2.12.4 Nonfatal Serious Adverse Events
There were 40 subjects (24 (2%) from TIVc group and 16 (2%) from TIVf group) who reported 46 SAEs throughout the study period. All the SAEs were judged by the investigator as unrelated to the study vaccine. A total of 3 pregnancies were confirmed during the course of the study: 1 is ongoing, 1 resulted in a spontaneous abortion, and 1 resulted in still birth. Neither of the two adverse outcomes was judged by the investigator to be related to study vaccine.

6.2.12.5 Adverse Events of Special Interest (AESI)

N/A

6.2.12.6 Clinical Test Results

N/A

6.2.12.7 Dropouts and/or Discontinuations

Please refer to section 6.2.10.1.3.

7. INTEGRATED OVERVIEW OF EFFICACY

The applicant provided an Integrated Summary of Efficacy (ISE) in this submission. The ISE contains immunogenicity results from a single study V58P12; there is no additional efficacy analysis based on data pooling from multiple studies. In the ISE, the immunogenicity data for subjects 4 to < 18 years of age from this study were evaluated using the non-inferiority criteria for GMT and seroconversion rate, and the CBER criteria for seroconversion rate and the percentage of subjects achieving HI ≥ 1:40.

According to the protocol of study V58P12, the primary objective of the study was to establish the non-inferiority of TIVc versus a comparator, TIVf, for all three strains after 2 doses administered 4 weeks apart to children 4 to < 9 years of age. The study had a secondary objective that was to evaluate immunogenicity, measured by seroprotection (HI ≥ 1:40), and by the percentage of subjects achieving seroconversion, of two vaccinations of either TIVc or TIVf administered 4 weeks apart to children 4 to < 9 years of age. As described in section 6.1, the primary endpoint analysis indicated that non-inferiority of TIVc versus TIVf was not met; non-inferiority was demonstrated for 4 of 6 non-inferiority endpoints; and two non-inferiority criteria were not met for the A/H3N2 strain. However, the secondary endpoint analysis showed that 5 of 6 alternative immunogenicity criteria were met; both alternative criteria were met for A/H1N1 and A/H3N2 strains while only seroconversion criterion was met for the B strain. In the ISE, the applicant appears to use both the primary and secondary endpoint analyses to provide statistical evidence for efficacy. For instance, it is stated in the ISE and Clinical Overview that "noninferiority criteria were not met for the A/H3N2 strain, but for this strain both CBER criteria were met" (ISE page 23, Clinical Overview page 21). Here CBER criteria refer to the alternative immunogenicity criteria.

Reviewer Comment*: In the V58P12 protocol, the primary objective was defined based on the non-inferiority criteria, and the secondary endpoint analyses were based on the alternative immunogenicity criteria. While the secondary endpoint analysis can provide useful information, it is not the pre-specified primary endpoint to support Flucelvax's efficacy in the pediatric population. The ISE analysis results indicated that the primary objective of establishing non-inferiority between TIVc and TIVf was not met for the A/H3N2 strain. However, the CBER criteria, which are the secondary objective in the protocol, were met for this strain. The reviewer defers to the other members of the review team for further consideration based on the totality of evidence submitted.*

8. INTEGRATED OVERVIEW OF SAFETY

Integrated safety analysis was conducted on the combined clinical safety data from studies V58_31 and V58P12 to demonstrate the safety and tolerability of TIVc in children and adolescents 4 to < 18 years of age. These two studies are post-marketing commitments under STN-125408 and were conducted under IND 11580. Both studies had similar study populations, were similarly designed, and had similar safety and tolerability endpoints. The two studies differ slightly in terms of baseline requirements for influenza vaccination. Children 4 to < 9 years of age enrolled into V58P12 were expected not to have been fully vaccinated against influenza in the past. By contrast, children 4 to < 9 years of age enrolled into V58_31 were randomized according to whether or not they were regarded as "previously vaccinated" (against influenza) versus "not previously vaccinated." All children 9 to < 18 years of age were regarded as "previously vaccinated" in both studies. The applicant suggested that the differences in previous influenza vaccination status are not expected to impact the interpretation of the analysis of the data because children in the current US population represent a blend of those who are regarded as "previously vaccinated" and "not previously vaccinated."

8.1 Safety Assessment Methods

TIVc and the comparator vaccine were assessed for reactogenicity (solicited AEs) and general safety (unsolicited AEs). The integrated data for each vaccine group included an assessment of both overall incidence rates and weighted risk ratio analyses for solicited AEs. As the sample sizes and randomization schemes varied between the two studies, a pooled Mantel-Haenszel type estimator for the risk ratio adjusted for the study was calculated. A weighted risk ratio of 1 indicates that both vaccine groups have similar risk; a number > 1 indicates that the risk of an event is greater for subjects exposed to TIVc and a number < 1 indicates that the risk of an event is greater for subjects exposed to TIVf.

Note that since safety evaluation is usually exploratory, confidence intervals are interpreted as descriptive flagging devices rather than as hypothesis tests. If the 95% confidence interval (CI) includes 1, there is no evidence of different risks of developing an event, although this finding could be due to insufficient sample size. On the other hand, a CI that excludes the value 1 may or may not suggest an effect that warrants further investigation.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The integrated safety database includes studies V58P12 and V58_31.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The integrated analysis of safety included all subjects who had been randomized in studies V58P12 and V58_31, who were exposed to at least one dose of vaccine, and who had safety data. The integrated safety set comprised 3346 subjects 4 to < 18 years of age exposed to TIVc and 1829 subjects 4 to < 18 years of age exposed to TIVf. Of the

3346 subjects treated with TIVc, 2012 subjects were 4 to < 9 years of age and 1334 were 9 to < 18 years of age. Of the 1829 subjects treated with TIVf, 1172 were 4 to < 9 years of age and 657 were 9 to < 18 years of age. Subjects 9 to < 18 years of age as well as subjects 4 to < 9 years of age who were previously vaccinated were enrolled to receive one dose of vaccine. Subjects 4 to < 9 years of age who were not previously vaccinated were enrolled to receive two doses of vaccine.

Overall, 49% of subjects were female in the TIVc group and 50% were female in the TIVf group. Subjects were predominantly Caucasian (59% in the TIVc group and 61% in the TIVf group) and Asian (27% in the TIVc group and 24% in the TIVf group). The majority of subjects were not vaccinated in the previous year (87% in the TIVc group and 88% in the TIVf group).

8.3 Caveats Introduced by Pooling of Data across Studies/Clinical Trials

None

8.4 Safety Results

8.4.1 Deaths

There were no deaths reported in the integrated safety set.

8.4.2 Nonfatal Serious Adverse Events

Fewer than 1% of subjects in each vaccine group had an SAE during the treatment period (8 subjects in the TIVc group and 5 subjects in the TIVf group overall); none of these was considered vaccine related. The number of subjects with SAEs during the follow-up period was larger than that of the treatment period (31 [1%] subjects and 18 [1%] subjects in the TIVc and TIVf groups overall, respectively).

8.4.3 Study Dropouts/Discontinuations

Across the combined age groups, the percentage of subjects who did not complete the study was ≤ 5%. The most common reason for study withdrawal was the subject being lost to follow-up (4% in both vaccine groups) followed by withdrawal by the subject (< 1% in both vaccine groups). Notably, a greater proportion of subjects in the younger age group withdrew than in the older age group (7% in both vaccine groups in the 4 to < 9 years age group and < 1% in both vaccine groups in the 9 to < 18 years age group).

8.4.4 Common Adverse Events

Please refer to section 8.4.6, 8.4.7 and 8.5.

8.4.5 Clinical Test Results

N/A

8.4.6 Systemic Adverse Events

Among solicited systemic AEs reported after any vaccination in children 4 to < 18 years of age, the most common AEs (occurring in > 10% of subjects) were myalgia (TIVc 16%; TIVf 14%), headache (15% in both vaccine groups), fatigue (TIVc 13%; TIVf 15%), and malaise (12% in both vaccine groups). Among these events, only the difference in the rate of fatigue between TIVc and TIVf was notable (TIVc/TIVf 95% CI of weighted risk ratio 0.7471 – 0.9886). For the less common solicited systemic AEs (occurring in < 10% of subjects), subjects in the TIVc group were at higher risk for reporting loss of appetite (9% and 5% of subjects in the TIVc and TIVf groups, respectively; risk ratio 1.6011 [95% CI 1.1200 - 2.2887]) and arthralgia (5% and 4% of subjects in the TIVc and TIVf groups, respectively; risk ratio 1.3911 [95% CI 1.0613 - 1.8233]) than subjects in the TIVf group. The majority of events of loss of appetite and arthralgia were mild in severity and the duration of event reporting was similar between the 2 vaccine groups.

The most common solicited systemic AEs in the 4 to < 9 years age group were myalgia (TIVc 15%; TIVf 13%), headache (TIVc 14%: TIVf 15%), fatigue (TIVc 13%; TIVf 15%), and malaise (12% in both vaccine groups). Although the frequency of reporting differed between the two vaccine groups for some events, no difference appeared noteworthy. The most common solicited systemic AEs in the 9 to < 18 years age group were myalgia (TIVc 17%; TIVf 16%), headache (TIVc 17%; TIVf 16%), fatigue (TIVc 12% and TIVf 15%), and malaise (12% in both vaccine groups). With the exception of loss of appetite, the rate of reporting in the 9 to < 18 years age group for any individual solicited systemic AE was not higher for the TIVc group than the TIVf vaccine group. The incidences of individual solicited systemic AEs were generally similar between age subgroups, with the exception of nausea, loss of appetite, and fever, which occurred in a slightly higher proportion of subjects 4 to < 9 years of age compared to subjects 9 to < 18 years of age.

8.4.7 Local Reactogenicity

Among solicited local AEs reported after any vaccination in children 4 to < 18 years of age, pain at the injection site was the most common solicited local AE and was reported slightly more frequently in the TIVc group (48% of subjects) than in the TIVf group (45% of subjects). This difference was also observed for both age groups (49% versus 46% for subjects 4 to < 9 years of age and 45% versus 42% for subjects 9 to < 18 years of age, for TIVc and TIVf groups, respectively). Pain at the injection site was classified predominantly as mild in severity (38% of subjects in the TIVc group and 35% of subjects in the TIVf group overall), with events classified as severe reported in 1% of subjects. Other commonly reported solicited local AEs included erythema and induration reported for 18% and 10% (in both vaccine groups) in subjects 4 to < 18 years of age, respectively. The rate of reporting for any individual solicited local AE was not notably different between TIVc and TIVf groups.

Percentages of subjects reporting each solicited local AE after any vaccination were generally higher in both vaccine groups in the 4 to < 9 years age group than the 9 to < 18 years age group. The most common solicited local AEs in the 4 to < 9 years of age group

were pain at the injection site (TIVc 49%; TIVf 46%) and injection site erythema (TIVc 21%; TIVf 20%). The frequency of reporting of some solicited local AEs was higher in the TIVc group than in the TIVf group, but the difference was small. For subjects in this age group who received two doses of the vaccine, solicited local AE reporting decreased with the second vaccination. The most common solicited local AEs in the 9 to < 18 years of age group were pain at the injection site (TIVc 45%; TIVf 42%) and injection site erythema (13% in both vaccine groups). As with subjects 4 to < 9 years of age, differences in the incidence of solicited local AE reporting between vaccine groups were sometimes observed but were not noteworthy.

8.4.8 Adverse Events of Special Interest

N/A

8.5 Additional Safety Evaluations

During the treatment period, the incidence of unsolicited AEs was generally similar for the two vaccine groups overall and within age subgroups. The majority of the events were classified as mild or moderate in severity. A higher percentage of unsolicited AEs occurred in subjects 4 to < 9 years of age than in subjects 9 to < 18 years of age (40% and 43% of subjects in the TIVc and TIVf groups, respectively, for the 4 to < 9 years age group and 19% and 21% of subjects in the TIVc and TIVf groups, respectively, for the 9 to < 18 years of age group). Unsolicited AEs occurred less frequently in all groups during the follow-up period than during the treatment period (13% and 12% of subjects in the TIVc and TIVf groups, respectively, for the 4 to < 9 years age group and 13% and 16% of subjects in the TIVc and TIVf groups, respectively, in the 9 to < 18 years age group). Unsolicited SAEs occurring during the treatment period were infrequent (occurring in < 1% of subjects in both vaccine groups overall and by age group) and remained infrequent through the follow-up period. The most common all-causality unsolicited AEs were cough (5% overall in each vaccine group), upper respiratory tract infection (5% overall in each vaccine group), and pyrexia and nasopharyngitis (each in 2% and 3% of subjects overall in the TIVc and TIVf groups, respectively).

8.6 Safety Conclusions

TIVc showed a safety profile similar to that of TIVf in children and adolescents 4 to < 18 years of age.

9. ADDITIONAL STATISTICAL ISSUES

N/A

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The primary objective of study V58P12 was to establish the non-inferiority of TIVc versus a comparator, TIVf, for all three strains after 2 doses administrated 4 weeks apart to children 4 to < 9 years of age. Non-inferiority was demonstrated for the A/H1N1 and B

strains by GMTs and the percentages of subjects achieving seroconversion at day 50. However, non-inferiority criteria were not met for the A/H3N2 strain. Therefore, the primary objective of establishing non-inferiority for all three strains was not met.

In the primary endpoint analysis with subjects 3 to < 4 years of age included, reported in the original BLA (STN 125408/0), the lower bound of the two-sided 95% CI on the difference between the day 50 seroconversion rates (TIVc - TIVf) for strain A/H3N2 was > -10%. The applicant suggested that reduction of sample size may have led to the difference in outcome. The reviewer's analysis on subjects 3 to < 4 years of age indicated that the point estimates of seroconversion rate difference (TIVc-TIVf) and GMT ratio (TIVc/TIVf) were substantially higher than those of subjects 4 to < 9 years of age. The point estimate of difference in seroconversion rate was 5% for the 3 to < 4 years age group, and -7% for the 4 to < 9 years age group; the point estimate of GMT ratio was 0.89 for the 3 to < 4 years age group, and 0.56 for the 4 to < 9 years age group. Because of the small size of the 3 to < 4 years age group, the 95% CIs were rather wide. Nevertheless, the substantial differences in point estimates may suggest potential difference in immune response to the vaccines between subjects 3 to < 4 years and subjects 4 to < 9 years of age. It is possible that different immune responses to the vaccines between subjects 3 to < 4 years and subjects 4 to < 9 years old may also contribute to the observed outcome difference.

In the V58P12 protocol, the primary objective was defined based on the non-inferiority criteria, and the secondary endpoint analyses were based on the alternative immunogenicity criteria. The ISE results showed that the pre-specified primary objective of establishing non-inferiority between TIVc and TIVf was not met for strain A/H3N2. However, the analysis based on the CBER criteria, which was not planned as the primary objective in the protocol, showed that TIVc induces satisfactory immune response in terms of seroconversion rate and percentage of subjects achieving an HI antibody titer ≥ 1:40 for strain A/H3N2. The CBER criterion with respect to percentage of subjects achieving a titer ≥ 1:40 was not met for strain B, which is commonly seen in influenza vaccine trials due to lower assay sensitivity for strain B. The reviewer defers to the other members of the review team for further considerations based on the totality of evidence submitted.

10.2 Conclusions and Recommendations

The primary objective of establishing non-inferiority of Flucelvax (TIVc) compared to Fluvirin (TIVf) for all three strains in subjects 4 to < 9 years of age was not met. Ratio of GMTs (Flucelvax/Fluvirin) and 95% CI were 0.89 (0.76 to 1.04) for the strain A/H1N1, 0.56 (0.47-0.67) for the strain A/H3N2, and 0.85 (0.68-1.06) for the strain B. Difference in seroconversion rate (Flucelvax – Fluvirin) and 95% CI were 0% (-3% to 2%) for the strain A/H1N1, -7% (-12% to -2%) for the strain A/H3N2, and 0% (-6% to 7%) for the strain B. Non-inferiority was demonstrated for the A/H1N1 and B strains by GMTs (CI lower limits exceeded 0.67) and the percentages of subjects achieving seroconversion at day 50 (CI lower limits exceeded -10%); however, the noninferiority criteria were not met for the A/H3N2 strain.

Although the primary objective was not met, the applicant suggested that relevant immune response was observed following vaccination with TIVc in the 4 to < 9 years age group based on a secondary endpoint analysis that showed five out of six alternative immunogenicity criteria were met. The secondary endpoint analyses on the age group 4 to < 9 years showed that the lower limit of the two-sided 95% CI for percentage of subjects achieving an HI antibody titer ≥ 1:40 was greater than 70% (the non-inferiority criterion) for strains A/H1N1 and A/H3N2; however, TIVc did not meet the criterion for strain B, with the lower limit of the two-sided 95% CI for percentage of subjects achieving an HI antibody titer ≥ 1:40 being 60%. The lower limit of the two-sided 95% CI for seroconversion rate was greater than 40% (the non-inferiority criterion) for all three strains. For subjects 9 to <18 years of age, the alternative immunogenicity criteria were met for all three strains. The reviewer defers to the other members of the review team for further considerations based on the totality of evidence submitted.

The integrated safety analysis showed comparable safety profiles between TIVc and TIVf in children and adolescents 4 to < 18 years of age. There appear to be no major safety concerns from a statistical perspective.