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Division / Office	DB/OBE
Committee Chair	Brenda Baldwin, Ph.D.
Clinical Reviewer(s)	Sarah Browne, MD
Project Manager	Theodore Garnett, Ph.D.
Priority Review	NO
Reviewer Name(s)	Ghideon Solomon, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Tsai-Lien Lin, Ph.D. Team Leader DB/VEB/VBT
	A. Dale Horne, Dr.PH, Branch Chief DB/VEB
	Estelle Russek-Cohen, Ph.D, Division Director OBE/DB
Applicant	Novartis Vaccines and Diagnostics
Established Name	
(Proposed) Trade Name	FLUAD 65
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Trivalent (surface antigen, formaldehyde- inactivated) influenza virus vaccine, adjuvanted with MF59C.1.
Dosage Form(s) and Route(s) of Administration	Suspension for injection supplied in 0.5 mL single- dose pre-filled syringes to be administered in an intramuscular injection.
Dosing Regimen	
Indication(s) and Intended Population(s)	FLUAD 65 is an inactivated influenza virus vaccine indicated for active immunization in persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

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GLOSSARY

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCDM	Biostatistics and Clinical Data Management
CHMP	Committee for Medicinal Products for Human Use
COPD	Chronic Obstructive Pulmonary Disease
eCRF	Electronic Case Report Form
EC	Ethics Committee
EDC	Electronic Data Capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio (of day X/day 1 GMTs within a vaccine group)
GMT	Geometric Mean Titer
HA	Hemagglutinin Antigen
HI	Hemagglutination Inhibition
HIPAA	Health Insurance Portability and Accountability Act
ICD-9	International Classification of Diseases Ninth Edition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ILI	Influenza-like Illness
IM	Intramuscular
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
PLT	Potentially Life Threatening
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TIV-ADJ	Adjuvanted Trivalent Influenza Vaccine
TIV-NONADJ	Non-adjuvanted Trivalent Influenza Vaccine
WHO	World Health Organization

1. Executive Summary

Novartis Vaccine submitted this BLA seeking licensure for an adjuvanted seasonal trivalent influenza virus vaccine (designated as FLUAD). The candidate vaccine includes a proprietary adjuvant, MF59C.1, and the influenza antigens are produced in eggs using the U.S.-licensed AGRIFLU manufacturing process.

The BLA includes immunogenicity and safety data from one pivotal clinical trial, V70_27 (conducted in the elderly ≥ 65 years of age), and several supportive studies (conducted in the elderly ≥ 65 years of age). Trial V70_27 was designed to provide the key supportive data for licensure.

Trial V70_27 was a randomized, active-controlled, observer blind, multicenter study that compared safety, immunogenicity, and effectiveness of an adjuvanted trivalent inactivated influenza subunit vaccine (TIV-ADJ) to Non-adjuvanted Trivalent Influenza Vaccine (TIV-NONADJ) (AGRIFLU) in subjects ≥ 65 years of age. Subjects were randomly allocated in a 1:1:1:3 ratio to receive one of three lots of TIV-ADJ (N = 3552) or control vaccine TIV-NONADJ (AGRIFLU) (N= 3552). The primary immunogenicity endpoints to be analyzed in a stepwise fashion included lot-to-lot consistency, non-inferiority, and then superiority of TIV-ADJ over TIV-NONADJ (AGRIFLU). Non-inferiority criteria were met if the lower bound of the 95% confidence interval for seroconversion rate (TIV-ADJ – TIV-NONADJ) and GMT ratios (TIV-ADJ: TIV-NONADJ) were $> -10\%$ and > 0.67 , respectively. Superiority criteria were met if the lower bound of the 95% confidence interval for seroconversion rate (TIV-ADJ – TIV-NONADJ) and GMT ratios (TIV-ADJ: TIV-NONADJ) were $>10\%$ and > 1.5 , respectively.

TIV-ADJ met its co-primary objective using the pre-specified criteria for lot-to-lot consistency and non-inferiority, but did not meet the pre-specified criteria for superiority.

The adjuvanted trivalent influenza vaccine (TIV-ADJ) was associated with higher incidence of local and systemic reactions, i.e. a higher percentage of subjects in the TIV-ADJ group than in the TIV-NONADJ (AGRIFLU) group reported any local or systemic reaction. But no imbalances in unsolicited AEs, deaths, SAEs, withdrawals due to AEs, or new onset chronic disease were reported.

2. Clinical and Regulatory Background

US development of this vaccine was conducted under BB-IND 14368, with an initial submission to the Agency on May 14, 2010.

TIV-ADJ is a trivalent seasonal influenza vaccine (surface antigen, inactivated, influenza vaccine based on AGRIFLU [licensed under STN 125297 in 2009]) adjuvanted with MF59C.1 and contains a total of 45 mcg per dose (15 mcg per strain) of purified HA antigen. MF59C.1 adjuvant, an oil-in-water emulsion, is composed of squalene as the oil

phase, stabilized with the surfactants polysorbate 80 and sorbitan trioleate, in citrate buffer.

The BLA includes immunogenicity and safety data from one pivotal clinical trial, V70_27 (conducted in the elderly ≥ 65 years of age), and several supportive studies (conducted in elderly ≥ 65 years of age). Trial V70_27 was designed to provide the key supportive data for licensure under accelerated approval. Under the accelerated approval regulations (21 CFR§601.41), licensure is based on a surrogate marker that is reasonably likely to predict clinical benefit. For evaluation of FLUAD, the surrogate marker is an antibody response as measured by a hemagglutination-inhibition (HAI) assay.

2.1 Disease or Health-Related Condition(s) Studied

Influenza Trivalent Vaccine, Adjuvanted, is a vaccine indicated for active immunization for the prevention of influenza disease caused by influenza subtypes A and B contained in the vaccine in persons 65 years of age and older.

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

FLUAD (TIV-ADJ) is indicated in Europe for active immunization against seasonal influenza in the elderly (individuals 65 years of age and older), especially those with an increased risk of associated complications (i.e., persons affected by underlying chronic diseases including cardiovascular or respiratory illness and diabetes). Several clinical studies have been performed in the elderly and in high-risk populations to assess and compare the immunogenicity of the MF59-adjuvanted vaccines with that of conventional non-adjuvanted vaccines.

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

Previous communications regarding TIV-ADJ (FLUAD) in the elderly include: a type B pre-IND meeting on March 3, 2010 and a type B pre-BLA meeting on December 16, 2011. An IND was filed on May 14, 2010 to evaluate the use of TIV-ADJ (FLUAD) in the elderly.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

Data sources including all materials reviewed (applicant's study reports, data sets analyzed, and literature referenced) were provided electronically and are available in the EDR on the following link:

(b) (4)

5.1 Review Strategy

The BLA is based on safety and immunogenicity data from a pivotal clinical trial, V70_27 (conducted in the elderly ≥ 65 years of age). Section 6 of this review discusses all the relevant statistical information of the study that reflects the indication sought by the applicant.

Other supportive studies, conducted in adults ≥ 65 years of age between 1992 and 2013 were also submitted to the BLA to provide additional safety data. These studies evaluated 4 different formulations of an MF59 adjuvanted product and were small and highly varied in design (e.g., uncontrolled, open-label, non-randomized, and/or using comparators that were not licensed in the US). Thus, the purpose of submitting these data was to provide a larger safety database. The applicant (Novartis) and CBER agreed prior to submission of the BLA that immunogenicity data from these studies would not be reviewed or included in labeling because antibody response may vary by strains included in the vaccine, there were differences in the assays used and the laboratory conducting the assays, and the assays were not adequately validated.

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

The basis for the statistical review is study V70_27 (reviewed below in Section 6 and summarized here in table 1). During the pre-BLA phase of product development it was agreed that this study would provide adequate immunogenicity, safety, and reactogenicity data to support licensure of FLUAD.

Table 1: Overview of trial serving as basis for licensure: study V70 27

Study ID	Design	Control	Total # Subjects	Age (years)	Country (number of sites)
V70_27	Randomized, observer-blind, multi-center	AGRIFLU	7082 (3545 in the TIV-ADJ group and 3537 in the AGRIFLU group)	65 years of age and older	United States (21) Philippines (11) Columbia (4) Panama (2)

Source: Reviewer's table created based on information in the CSR

5.4 Consultations

5.4.1 Advisory Committee Meeting

The Vaccines and Related Biological Products Advisory Committee (VRBPAC) was convened on September 15, 2015 to review and discuss the safety and immunogenicity data derived from trials conducted with FLUAD and submitted in the BLA.

The committee was asked to vote on whether the available safety and immunogenicity/efficacy data are adequate to support licensure of TIV-ADJ (FLUAD) for the proposed indication via the accelerated approval regulations. Committee members were also asked to discuss the safety and efficacy data required to show clinical benefit of TIV-ADJ (FLUAD) in pediatric populations as well as the appropriateness of the design of the confirmatory efficacy trial in elderly subjects.

The following table summarizes the votes by the advisory committee for each question

Table 2: Summary of votes by the advisory committee

Question	Yes	NO	Abstained
Are the immunogenicity data adequate to support the effectiveness of TIV-ADJ (FLUAD) under the accelerated approval regulation for the prevention of influenza disease in adults 65 years of age and older?	11	1	1
Are the available data adequate to support the safety of TIV-ADJ (FLUAD) when administered to adults 65 years of age and older?	10	2	1

Source: Reviewer's table created based on information from VRBPAC meeting on September 15, 2015

The committee also agreed to the use of adjuvanted quadrivalent inactivated influenza subunit vaccine (QIV-ADJ) for the confirmatory efficacy trial required to be conducted through the accelerated approval regulation.

5.5 Literature Reviewed

Holm, S. (1979). "A simple sequentially rejective multiple test procedure." *Scandinavian Journal of Statistics* 6 (2): 65–70

Dmitrienko, A (2013). Multiple Testing Procedures in Clinical Trials, IBS workshop ICH guideline (1998). *E-9 Statistical Principles for Clinical Trials*.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS: STUDY V70_27

The study was a phase 3, randomized, controlled, observer-blind, multicenter, parallel-group study to evaluate the safety, immunogenicity, and consistency of 3 consecutive lots of an MF59C.1-adjuvanted trivalent subunit influenza vaccine (FLUAD, referred to here in this memo as TIV-ADJ) in subjects ≥ 65 years of age. The primary objectives as described below in section 6.1 were to assess immunologic consistency among the TIV-ADJ lots and to compare the immune response to TIV-ADJ (using pooled immunogenicity data) with the response to a US-licensed non-adjuvanted trivalent subunit influenza vaccine (AGRIFLU™, referred here as TIV-NONADJ).

6.1 Study Objectives

Co-Primary Objectives

1. Lot-to-lot consistency: to evaluate immunologic equivalence of three consecutive production lots of TIV-ADJ, as measured by hemagglutination inhibition (HI) geometric mean titers (GMTs) at day 22 for each virus strain after a single 0.5-mL intramuscular (IM) injection.
2. Superiority of TIV-ADJ compared to TIV-NONADJ for homologous strains in all subjects: to evaluate the superiority of TIV-ADJ compared to TIV-NONADJ with regards to at least 2 homologous strains and to demonstrate the non-inferiority of TIV-ADJ compared to TIV-NONADJ with regards to all homologous strains in adults ≥ 65 years of age, as measured by GMT ratios and seroconversion rate differences at day 22.
3. To evaluate the immunogenicity of TIV-ADJ according to CHMP (Committee for Medicinal Products for Human Use) criteria.

Secondary Objectives

1. Superiority of TIV-ADJ compared to TIV-NONADJ for homologous strains in high risk subjects with predefined comorbidities: to evaluate the superiority of TIV-ADJ compared to TIV-NONADJ with regards to at least two homologous strains and to demonstrate the non-inferiority of TIV-ADJ compared to TIV-NONADJ with regards to all homologous strains in high-risk subjects with predefined comorbidities as measured by GMT ratios and seroconversion rate differences at day 22.
2. Superiority of TIV-ADJ compared to TIV-NONADJ for heterologous strains: to evaluate the superiority of TIV-ADJ compared to TIV-NONADJ with regards to at least two heterologous strains and to demonstrate the non-inferiority of TIV-ADJ compared to TIV-NONADJ with regards to all heterologous strains in adults ≥ 65 years and in high-risk subjects with predefined comorbidities, as measured by GMT ratios and seroconversion rate differences at day 22.
3. Clinical effectiveness of TIV-ADJ compared to TIV-NONADJ: to evaluate the clinical effectiveness of a single 0.5-mL IM injection of TIV-ADJ compared to a single 0.5-mL IM injection of TIV-NONADJ in adults ≥ 65 years of age.
4. Comparison of TIV-ADJ to TIV-NONADJ for homologous and heterologous strains in an antibody persistence subset of subjects: to assess the difference between TIV-ADJ and TIV-NONADJ with regards to homologous and heterologous strains in subjects included in the antibody persistence group, as measured by GMT ratios and seroconversion rate differences at day 181 and day 366.
5. To evaluate the immunogenicity of TIV-NONADJ according to CHMP criteria.

Safety Objectives

1. To describe safety and tolerability of TIV-ADJ compared to TIV-NONADJ in all subjects through day 8 following vaccination and all adverse events (AEs) and SAEs through day 22.

2. To describe SAEs, new onset of chronic diseases, and AEs resulting in withdrawal from the study through day 366.

6.2 Overall Trial Design

The study was designed as an observer-blind study; the study vaccines were administered by unblinded designated qualified healthcare personnel who had no subsequent contact with the subjects. The subjects and investigative site personnel involved in the monitoring or conduct of the study were blinded to the vaccine administered.

Subjects were randomized in a 1:1:1:3 ratio to receive either 1 of the 3 lots of TIV-ADJ (investigational vaccine; lots 1, 2, or 3) or TIV-NONADJ vaccine (active control), such that equal numbers of subjects received TIV-ADJ and TIV-NONADJ. Each subject received a single dose of TIV-ADJ or TIV-NONADJ; both vaccines contained 15 µg hemagglutinin antigen (HA) from each of the H1N1, H3N2, and B strains as active ingredients (45 µg HA total).

The overall study period was divided into a treatment phase (day 1 through day 22) and a follow-up phase (day 23 through study termination). TIV-ADJ and TIV-NONADJ vaccines were administered on day 1 after randomization. Immune response to the vaccines was evaluated on day 22. Blood samples (10 mL) for serology were drawn before vaccination on day 1 (baseline) and on day 22. In the antibody persistence group, 10-mL blood samples were also drawn on day 181 (6 months) and day 366 (1 year), and in the safety laboratory analysis subgroup, additional 10-mL blood samples were drawn on day 1 and day 8. Immunogenicity was assessed by HI assay, testing both homologous and heterologous H1N1, H3N2, and B strains. At randomization, subjects were stratified into two age cohorts, 65 to 75 years and >75 years.

6.3 Study Population

Approximately 7000 subjects were planned for enrollment in this study. The statistical considerations require approximately 3150 evaluable subjects for each vaccine group (TIV-ADJ and TIV-NONADJ). Assuming a dropout rate of 10%, an overall enrollment of approximately 7000 subjects was planned. Homologous influenza virus strain antibody testing was to be performed in all 7000 subjects, and heterologous influenza strain antibody testing on 1750 subjects, at visits 1 (day 1) and 3 (day 22). Subjects whose blood samples were planned for heterologous strain antibody testing were randomly selected according to the original 1:1:1:3 randomization ratio.

About 700 subjects at 14 sites in the United States were to be included in an antibody persistence group, with additional serology assessments at visit 5 (day 181) and visit 7 (day 366). Initially, samples from about 400 subjects with complete sets of samples (i.e., from days 1, 22, 181, and 366) were to be tested for antibody persistence, for both homologous and heterologous strains, and the remaining samples were to be stored for future evaluation of immune response. Of the 700 subjects in the antibody persistence

group, 200 subjects were further designated as a laboratory safety analysis subgroup, with these assessments on day 1 and day 8.

6.4 Selection of Trial Population

Inclusion Criteria

1. Males and females of age ≥ 65 years on the day of vaccination.
2. Individuals who had given written consent after the nature of the study was explained according to local regulatory requirements.
3. Individuals able to attend all scheduled visits and to comply with all study procedures.
4. Individuals with access to a working telephone and able to receive periodic telephone calls.

Exclusion Criteria

1. Individuals with behavioral or cognitive impairment or a psychiatric condition that, in the opinion of the investigator, may interfere with the subject's ability to participate in the study.
2. Individuals who were not able to comprehend and/or follow all required study procedures for the whole period of the study.
3. Individuals with history of any illness that, in the opinion of the investigator, might pose additional risk to the subjects due to participation in the study.
4. Known or suspected impairment/alteration of immune function, including:
 - a. Receipt of immune stimulants within 60 days prior to visit 1.
 - b. Receipt of corticosteroids, defined as:
 - i. Continuous use with a dosage equivalent to >15 mg/day of oral prednisone for 90 days preceding vaccination.
 - ii. Sporadic use with a dosage equivalent to >40 mg/day of oral prednisone for >14 consecutive days in the 90 days preceding vaccination.
 - iii. Use of topical or inhalant corticosteroids is acceptable.
 - c. Receipt of parenteral immunoglobulin preparation, blood products, and/or plasma derivatives within 3 months prior to visit 1 or planned during the duration of the study.
 - d. Receipt of anti-cancer chemotherapy or radiation therapy within the past 12 months.
 - e. Acquired immunodeficiency.
 - f. HIV infection or HIV-related disease.
 - g. Heritable immunodeficiency.
 - h. Abnormalities of splenic or thymic function.
5. Individuals with a known bleeding diathesis, or any other condition that may be associated with prolonged bleeding.
6. History of Guillain-Barré syndrome.
7. Individuals with history of allergy to vaccine components and/or a history of any anaphylaxis, serious vaccine reactions or hypersensitivity to influenza viral proteins,

- egg proteins (including ovalbumin), polymyxin, neomycin, betapropiolactone, thimerosal/ sodium ethylmercuriothiosalicylate/ mercury and nonylphenol ethoxylate/ nonoxynol-9 (spermicide).
8. Receipt of another investigational agent within 30 days prior to enrollment in the study or before completion of the safety follow-up period in another study, whichever is longer, prior to enrollment and unwilling to refuse participation in another clinical study through the end of the study.
(NOTE: Concomitant participation in an observational trial (not involving drugs, vaccines, or medical devices) is acceptable).
 9. Individuals who received any other vaccines within 2 weeks for inactivated vaccines or 4 weeks for live vaccines prior to enrollment in this study or who were planning to receive any vaccine within 3 weeks from the study vaccine.
 10. Individuals who received vaccination against seasonal influenza in the previous 6 months.
 11. Research staff directly involved with the clinical study or family/household members of research staff. Research staff is individuals with direct or indirect contact with study subjects, or study site personnel who have access to any study documents containing subject information. This would include receptionists, persons scheduling appointments or making screening calls, regulatory specialists, laboratory technicians, etc.
 12. Individuals with oral temperature $\geq 38.0^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$) on day of study vaccination.
NOTE: Vaccinations were not to be administered to any subject with a clinically significant active infection (as assessed by the investigator) or measured oral (sublingual) temperature $\geq 38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ within 3 days of the intended date of vaccination. If either of these is observed or reported, vaccination should have been postponed until the subject's temperature remained below $38.0^{\circ}\text{C}/100.4^{\circ}\text{F}$ for at least 3 days or until the investigator felt that the subject's acute illness had stabilized, as appropriate.
 13. Individuals with history of substance or alcohol abuse within the past 2 years.
 14. Individuals providing consent who do not consent to the retention of their serum samples after study completion.
 15. Elective surgery or hospitalization planned prior to enrollment to occur during the treatment phase.
 16. Elective surgery or hospitalization planned prior to enrollment to occur during the follow-up phase that, according to the opinion of the investigator, might pose additional risk to the subject.
 17. Subjects deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized without his/her consent.
 18. Subjects from whom blood cannot be drawn at visit 1.

6.5 Study Treatments Dose and Mode Administration

Randomization/Treatment Allocation Procedures

A subject who fulfilled all the inclusion/exclusion criteria was given a subject number by the investigator or delegated study staff personnel. A web-based system that automates the random assignment of treatment arms in the specified ratio was to be used. Upon entry of the subject number and basic demographic information, a randomization number

was produced by the electronic data capture (EDC) randomization system. This number corresponded to a vaccination group in the randomization list produced by the Biostatistics and Clinical Data Management department (BCDM) at Novartis. Only the qualified unblinded health care professional at the site was to have access to the randomization list, prior to administering the assigned vaccine to the subject.

6.6 Study Centers and Duration of Study

This study was conducted by multiple investigators at multiple study centers (21 sites in US, 4 sites in Colombia, 2 sites in Panama, and 11 sites in Philippines). Date of first enrollment was August 13, 2010 and date of last visit was November 16, 2011.

6.8 Endpoints and Assessment Methods

6.8.1 Primary endpoints

Immunogenicity

Immunogenicity was assessed by hemagglutination inhibition (HI) assay, for titrating antibodies against homologous strains A/California/7/2009-like (H1N1), A/Perth/16/2009-like (H3N2), and B/Brisbane/60/2008-like and heterologous strains A/Brisbane/10/2007-like (H3N2), A/Wisconsin/67/2005-like (H3N2), and B/Malaysia/2506/2004-like. The heterologous strains were selected from historical strains and had a sufficient pool of virus material required for all testing required for the study.

The immunogenicity endpoints based on the HI titer were comparisons between pairs of TIV-ADJ lots and comparisons of the TIV-ADJ with the TIV-NONADJ vaccines for:

- GMT
- GMR of day X/day 1 HI titers (where day X is day 22, day 181, or day 366)
- Percentage of subjects achieving seroconversion
- Percentage of subjects achieving HI titer ≥ 40 .

Seroconversion was defined as negative pre-vaccination HI serum titer (<10) and a post-vaccination titer ≥ 40 or at least a 4-fold increase in HI serum titer from a nonnegative pre-vaccination serum (≥ 10).

Co-primary endpoints were evaluated at day 1 and day 22, and secondary endpoints were evaluated at day 1, day 22, day 181, and day 366.

Immunogenicity data collected at day 181 and day 366 were used to assess homologous and heterologous antibody persistence following vaccination.

Clinical effectiveness endpoints: The clinical effectiveness of TIV-ADJ was evaluated in comparison with TIV-NONADJ. This evaluation included comparing influenza-like illness (ILI), exacerbation of preexisting chronic disease, health care utilization (emergency room visits, unscheduled physician visits, hospitalizations for specific

conditions), and all-cause mortality except injury (intentional and unintentional) in each of the vaccination groups.

- a. ILI: Defined as a fever of $\geq 37.2^{\circ}\text{C}$ (99.0°F) or feverishness (defined as the subject's subjective report of fever or a chill) and at least 2 of the following symptoms: headache, myalgia, cough, or sore throat;
- b. Exacerbation of chronic disease: Defined as an emergency room visit, unscheduled physician visit, or hospitalization for the following preexisting chronic diseases:
 - Congestive heart failure
 - Chronic obstructive pulmonary disease
 - Asthma
 - Hepatic disease
 - Renal insufficiency
 - Neurological/neuromuscular or metabolic disorders including diabetes mellitus;
- c. Health care utilization: Defined as an emergency room visit, an unscheduled physician visit, or hospitalizations for:
 - Community-acquired influenza or pneumonia
 - Cardiopulmonary disease
 - Cardiac disease
 - Respiratory or pulmonary disease;
- d. All-cause mortality except injury (intentional or unintentional).

Safety

Safety was evaluated by assessing:

- Local and systemic reactions occurring within 1 week after administration of the study vaccine, assessed at 30 minutes post-vaccination and for the intervals 6 hours through day 3, days 4 through 7, and 6 hours through day 7 post-vaccination
- All AEs occurring within 1 year of vaccination, assessed for the periods days 1 through 21, days 22 through 180, and days 181 through day 366
- All SAEs and other significant AEs reported throughout the study (through day 366, divided into the periods days 1 through 28, days 29 through 180, and days 181 through 366) and
- Changes in serum chemistry and hematology as assessed by clinical laboratory tests.

For the subgroups of subjects 65 through 75 years of age and >75 years of age, safety analyses were confined to:

- A summary of subjects with at least 1 reactogenicity sign
- A summary of SAEs with onset from days 1 through 21 post-vaccination
- A summary of all AEs by system organ class with onset from days 1 through 21 after Vaccination.

6.9 Statistical Considerations & Statistical Analysis Plan

Definition of populations to be analyzed:

All Enrolled Population: All subjects who signed the ICF, completed screening procedures, and provided demographic data.

All Randomized Subjects: All randomized subjects.

Full Analysis Set (FAS), Immunogenicity Day 22: All randomized subjects who received a study vaccination and provided evaluable serum samples both at day 1 and at day 22. In the event that the administered vaccine was not assigned according to randomization, subjects were to be analyzed as randomized in the FAS. In the event that subjects were randomized in the wrong age cohort, subjects were to be analyzed in the age cohort they were randomized to.

Per Protocol Set (PPS), Immunogenicity Day 22: All subjects in the FAS who received the correct vaccine, provided evaluable serum samples on both at day 1 and at day 22, and had no major protocol deviation prior to unblinding.

6.9.1 Hypotheses and Statistical Methods for Primary Endpoints

6.9.1.1 Primary Response Variables:

Lot-to-lot consistency:

For lot-to-lot consistency, the following equivalence hypotheses were to be tested simultaneously for each of the 3 vaccine strains:

$$H_0: (\mu_{\text{lot } 1} - \mu_{\text{lot } 2}) \leq -0.176 \text{ or } (\mu_{\text{lot } 1} - \mu_{\text{lot } 2}) \geq 0.176 \text{ or} \\ (\mu_{\text{lot } 1} - \mu_{\text{lot } 3}) \leq -0.176 \text{ or } (\mu_{\text{lot } 1} - \mu_{\text{lot } 3}) \geq 0.176 \text{ or} \\ (\mu_{\text{lot } 2} - \mu_{\text{lot } 3}) \leq -0.176 \text{ or } (\mu_{\text{lot } 2} - \mu_{\text{lot } 3}) \geq 0.176$$

vs.

$$H_1: (\mu_{\text{lot } 1} - \mu_{\text{lot } 2}) > -0.176 \text{ and } (\mu_{\text{lot } 1} - \mu_{\text{lot } 2}) < 0.176 \text{ and} \\ (\mu_{\text{lot } 1} - \mu_{\text{lot } 3}) > -0.176 \text{ and } (\mu_{\text{lot } 1} - \mu_{\text{lot } 3}) < 0.176 \text{ and} \\ (\mu_{\text{lot } 2} - \mu_{\text{lot } 3}) > -0.176 \text{ and } (\mu_{\text{lot } 2} - \mu_{\text{lot } 3}) < 0.176$$

H_1 refers to the alternative hypothesis of pairwise equivalence (consistency) transformed to the log10 scale. Accordingly, $\mu_{\text{lot } 1}$, $\mu_{\text{lot } 2}$, and $\mu_{\text{lot } 3}$ denote the means of log-transformed day 22 titers of the corresponding lot groups. The lot-to-lot consistency was claimed if the 2-sided 95% CIs of all the 3 pairwise comparisons were within the equivalence ranges. Significance level of all these tests was $\alpha = 2.5\%$ (1-sided), which needed no adjustment for multiplicity as all hypotheses had to be rejected (intersection-union test).

Lot-to-lot consistency was to be tested on the PPS. For each of the 3 influenza strains (A/H1N1, A/H3N2, and B), an analysis of covariance (ANCOVA) model with a qualitative factor for vaccine group (i.e., 3 parallel groups), country of residence, and age cohort, and a quantitative factor for log-transformed pre-vaccination antibody titer was used. GMTs, GMT ratios, and corresponding confidence intervals were to be calculated based on these models. Summary statistics were to be completed by providing minimum, maximum, and median titers for each of the vaccine groups. Ratios of GMTs and their

95% CIs were to be calculated for each pair of lots, separately for each influenza strain. To assess equivalence, the lower bounds of the CIs were to be compared with the pre-specified thresholds.

Non-inferiority:

For assessing the non-inferior immunogenicity of TIV-ADJ (pooling the 3 lot groups) versus TIV-NONADJ, the following (1-sided) hypotheses were to be tested for each of the 3 homologous strains, resulting in a total of 6 hypotheses:

$$HA_0: \mu_{(TIV-ADJ)} - \mu_{(TIV-NONADJ)} < -0.176 \text{ or } \pi_{(TIV-ADJ)} - \pi_{(TIV-NONADJ)} < -0.10$$

vs.

$$HA_1: \mu_{(TIV-ADJ)} - \mu_{(TIV-NONADJ)} \geq -0.176 \text{ and } \pi_{(TIV-ADJ)} - \pi_{(TIV-NONADJ)} \geq -0.10$$

where, HA_1 refers to the alternative hypothesis of non-inferiority. Accordingly, $\mu_{(TIV-ADJ)}$ and $\mu_{(TIV-NONADJ)}$ denote the means of log-transformed day 22 titers of the TIV-ADJ and TIV-NONADJ vaccine group, respectively. Similarly, $\pi_{(TIV-ADJ)}$ and $\pi_{(TIV-NONADJ)}$ denote the seroconversion rates at day 22 of the TIV-ADJ and TIV-NONADJ vaccine groups, respectively. Non-inferiority was to be claimed if the lower bound of the 2-sided 95% CI for GMT ratios and seroconversion rates was higher than or equal to the specified ranges. Significance level was $\alpha = 2.5\%$ (1-sided), which needs no further adjustment for multiplicity (intersection-union test).

Non-inferiority analyses were to be performed on the PPS. Analyses on GMTs (lognormal distributed data) were to be done for each of the 3 influenza strains separately using ANCOVA models, with a qualitative factor for vaccine group (i.e., 2 parallel groups), country, and age cohort, and a quantitative factor for log-transformed pre-vaccination antibody titer. Point estimates and 2-sided 95% CIs for ratios of GMTs were to be based on these models.

Analyses addressing seroconversion rates (binary data) were to be done using log-linear models, with a qualitative factor for vaccine group, country of residence, and age cohort. Vaccination group differences along with 95% CIs were based on this model. The pre-vaccination titer was not used as an additional covariate in the model because the applicant indicated that the definition of seroconversion implicitly accounted for variation in baseline titer.

Reviewer's comment: While the definition of seroconversion provides partial control for variability in baseline titers, it does not fully account for such variation. However, using pre-vaccination titer as an additional covariate in the model considered may not be straightforward to implement.

Superiority:

According to the stepwise achievement of objectives, the following superiority test(s) were only conducted if all above non-inferiority hypotheses were rejected.

The superiority of TIV-ADJ (pooling the 3 lot groups) to TIV-NONADJ was to be shown for at least 2 of 3 (homologous) strains with regard to both GMTs and seroconversion rates. The following (1-sided) hypotheses were to be tested for each strain, resulting in a total of 6 hypotheses:

$$HB_0: \mu_{(TIV-ADJ)} - \mu_{(TIV-NONADJ)} \leq 0.176 \quad \text{vs.} \quad HB_1: \mu_{(TIV-ADJ)} - \mu_{(TIV-NONADJ)} > 0.176$$

$$HC_0: \pi_{(TIV-ADJ)} - \pi_{(TIV-NONADJ)} \leq 0.15 \quad \text{vs.} \quad HC_1: \pi_{(TIV-ADJ)} - \pi_{(TIV-NONADJ)} > 0.15$$

where $\mu_{(TIV-ADJ)}$ and $\mu_{(TIV-NONADJ)}$ denote the means of log-transformed day 22 titers of the TIV-ADJ and TIV-NONADJ vaccine group, respectively, and $\pi_{(TIV-ADJ)}$ and $\pi_{(TIV-NONADJ)}$ the seroconversion rates at day 22 of the TIV-ADJ and TIV-NONADJ vaccine group.

Each of the 6 superiority hypotheses was to be tested applying a multiple test procedure that keeps the family-wise error rate at 1-sided $\alpha=2.5\%$.

Superiority was to be tested on the FAS. Analyses on GMTs (log-normal distributed data) were to be done for each of the 3 influenza strains separately using ANCOVA models with a qualitative factor for vaccine group (i.e., 2 parallel groups), country of residence, and age cohort, and a quantitative factor for log-transformed pre-vaccination antibody titer. Point estimates and 2-sided 95% CIs, unadjusted for multiplicity, for ratios of GMTs were based on these models.

Analyses on seroconversion rates (binary data) were to be done using log-linear models with a qualitative factor for vaccine group, country, and age cohort. Vaccination group differences along with unadjusted 95% CIs were to be based on this model. Unlike the specification in Protocol Amendment 3, pre-vaccination titer was not to be used as an additional covariate in the model because the applicant suggested that the definition of seroconversion implicitly accounted for variability in baseline titer.

Reviewer's comment: Again, the definition of seroconversion does not totally control for baseline titer variability, but using pre-vaccination titer as an additional covariate may be challenging to implement in the model considered.

To assess superiority of TIV-ADJ versus TIV-NONADJ, the lower bound of the 95% CI was to be compared with the pre-specified thresholds.

6.9.1.2 Secondary Response Variables (Superiority, Antibody Persistence, and Clinical Effectiveness):

Superiority of TIV-ADJ versus TIV-NONADJ for homologous strains in subpopulations: GMTs, day 22/day 1 GMRs, seroconversion, and percentages of subjects with HI titer ≥ 40 , as defined above, were to be analyzed also in the subsets of

subjects with predefined comorbidities, in order to evaluate the superiority of TIV-ADJ versus TIV-NONADJ in these subpopulations.

Superiority of TIV-ADJ versus TIV-NONADJ for heterologous strains: was to be analyzed by assessing non-inferiority followed by superiority as described above for homologous strains. These analyses were to be done on a subset of 1750 subjects from overall population as well as restricted to the subjects with predefined underlying comorbid conditions.

Antibody persistence: Homologous and heterologous antibodies were evaluated at day 181 and day 366 in a subset of subjects. GMTs, day 181/day 1 and day 366/day 1 GMRs, seroconversion, and percentages of subjects with HI titer ≥ 40 were to be compared between TIV-ADJ and TIV-NONADJ at both day 181 and day 366. Point estimates and 2-sided 95% CIs were to be calculated applying the models described above.

Clinical Effectiveness of TIV-ADJ versus TIV-NONADJ: To evaluate the clinical effectiveness of TIV-ADJ versus TIV-NONADJ, the incidence of subjects with ILI, the incidence of subjects reporting exacerbation of preexisting chronic diseases, the incidence of subjects with health care utilization (emergency room visits, unscheduled physician visits, hospitalizations for specific conditions), and all-cause mortality were to be compared. These data were to be collected during the follow-up phase only.

Additionally, for subjects enrolled in the United States, the follow-up time windows for ILI were defined as:

- A narrow time window as all adjacent weeks with a high influenza rate, i.e., as close as possible to the epidemic peaks;
- An intermediate time window with all adjacent weeks with a medium influenza rate; and
- The broadest time window covering the regular 1-year follow-up time.

Relative vaccine effectiveness (VE) was to be calculated as $1 - RR$, where RR is the relative risk of effectiveness endpoint (e.g., ILI, exacerbation of preexisting chronic disease, and at least one health care utilization [emergency room visits, unscheduled physician visits, and hospitalizations for specific conditions]) in the TIV-ADJ group versus the TIV-NONADJ group. This relative risk statistic was calculated using a Poisson Regression Model, including country of residence as covariate. Additional analyses by Log Binomial modeling and the Cochran-Mantel-Haenszel (CMH) approach were to be considered to evaluate robustness.

Analysis of Safety and Tolerability Endpoints

All randomized subjects who were vaccinated and provided post-vaccination safety data were included in the safety analyses. The safety of the study vaccines was to be assessed in terms of number of subjects exposed to study vaccines with reported local and systemic reactions, as well as the number of all subjects with reported SAEs and/or AEs (as specified for each time period) per vaccine group. The safety analyses also included data from the physical assessment, laboratory testing and any reactions or AEs observed

by study personnel following vaccination. All SAEs and AEs (including onset of chronic illness) were judged by the investigator as probably related, possibly related, or not related to vaccine and were to be tabulated. All SAEs and AEs resulting in withdrawal from the study were to be summarized.

Solicited local reactions included tenderness at injection site, erythema, induration, swelling and pain at injection site; solicited systemic reactions included chills, myalgia, arthralgia, headache, fatigue, nausea, vomiting, diarrhea and fever (measured body temperature).

Unsolicited reactions included all AEs, including SAEs and AEs that lead to subject's withdrawal, from day 1 through day 22. All SAEs, new onset of chronic diseases, and AEs leading to withdrawal, were to be collected throughout the study (through day 366).

Analysis of Extent of Exposure: The numbers of subjects receiving vaccination were to be summarized by vaccine group and age cohort.

Analysis of Local and Systemic Reactions: Frequencies and percentages of subjects experiencing each reaction were to be presented by symptom severity. Summary tables showing the occurrence of any local or systemic reaction at each time point were also to be presented.

Post-vaccination reactions reported from day 1 through day 7 were to be summarized by maximal severity and by vaccine group. The severity of local reactions, including injection site erythema, induration and swelling were to be categorized as 0 (none), 1 to <25 mm (considered none per CBER criterion), 25 to ≤50 mm (mild), 51 to ≤100 mm (moderate), >100 mm (severe), potentially life threatening (PLT, required emergency room consultation or required hospitalization).

The severity of tenderness, pain and systemic reactions (i.e., chills, myalgia, arthralgia, headache, fatigue, nausea, vomiting) occurring up to 7 days after each vaccination were to be categorized as none, mild (transient with no limitation in normal daily activity), moderate (some limitation in normal daily activity), severe (unable to perform normal daily activity), or potentially life threatening (PLT, caused a specific severe reaction, required emergency room visit, or required hospitalization). The severity of diarrhea occurring up to 7 days after vaccination was to be categorized as none, mild (2 to 3 loose stools a day), moderate (4 to 5 stools a day), severe (6 or more watery stools a day), or potentially life threatening (PLT, required emergency room visit, or required hospitalization).

Each local and systemic reaction was also to be categorized as none versus any. Oral temperature was to be categorized as <38°C (no fever), 38-38.4°C (mild), 38.5-38.9°C (moderate), 39-40°C (severe), and >40°C (potentially life threatening, PLT).

6.9.2 Populations Analyzed

See section 6.9 above.

6.9.3 Handling of Missing Data and Outliers

Missing data resulting from dropouts were considered missing completely at random (i.e., non-informative). Therefore, subjects with missing data were excluded without any imputation technique.

6.9.4 Determination of Sample Size and Power Calculation

A sample size adequate to demonstrate that the ratios of post-vaccination (day 22) GMTs between all pairs of the 3 TIV-ADJ lots are equivalent (i.e., lot 1 to lot 2; lot 2 to lot 3; lot 1 to lot 3), with the lower and upper bounds of the 2-sided 95% CI within the range of 0.67 to 1.5 (between -0.176 and 0.176 on a log10 scale) for each vaccine strain, was required. Provided a standard deviation of 0.6 for the log10 antibody titers (for each vaccine lot and for each strain), approximate pairwise equivalence of factor 1.1 (0.0414 on a log10 scale), and independence of the 3 lot-to-lot pairwise comparisons, a single equivalence test with 1050 evaluable subjects per lot group would have power of 99.9%. However, because the total number of comparisons is 9 (i.e., 3 pairwise comparisons for each of 3 strains), power is reduced to 99.1%. To account for an estimated dropout rate of 10%, a sample size of n=3500 (i.e., 1167 subjects per lot group) was to be recruited into the TIV-ADJ group and 3500 into the TIV-NONADJ group.

Due to the planned stepwise testing procedure, power for the lot-to-lot consistency analysis was maximized to maintain adequate power for all subsequent analyses as designated in the objectives. To demonstrate this, sample size calculations for other study objectives were calculated.

6.9.5 Changes in the Conduct of the Study or Planned Analyses

Changes to the Statistical Analysis Plan: The original statistical analysis plan (SAP) was issued on August 12, 2010; Amendments 1 and 2 were issued on August 2nd 2011 and November 25 2011, respectively. These amendments include changes to the statistical analyses that reflect the amendments to the study protocol described above. Moreover, technical details of the statistical analyses were added to the protocol amendments. Following completion of analyses specified in the SAP and its amendments, additional *ad hoc* analyses were specified, and an Addendum 1 to the SAP was issued to incorporate these analyses.

In October 2013, it was found that the company's statistical standard program to analyze lot-to-lot consistency data was used in an inappropriate way to calculate the GMT and the 2-sided 95% confidence intervals for the ratios of GMT in study V70_27; an Addendum 2 to the SAP was issued to address this issue.

Based on a request from CBER for a correction of HAI titer and subsequent re-calculation of all immunogenicity results presented in the CSR, the update of the titers was performed by dividing the original titer results by 2. An Addendum 3 to the SAP was issued on April 21, 2015 to incorporate the reanalysis. Statistical analyses of all immunogenicity results were rerun based on the re-calculations; data were replaced, and results and conclusions were updated accordingly in the CSR on May 5, 2015.

6.10 Study Population and Disposition

6.10.1 Disposition of Subjects

Overall 7109 subjects were enrolled into the study. Five of these subjects were not randomized to vaccine groups due to insufficient randomization numbers allocated to the sites. These 5 subjects did not receive study vaccinations and were discontinued from the study. In addition, 22 of the 7104 randomized subjects (11 in each vaccine group) did not receive study vaccinations.

Of the 7109 enrolled subjects, 7082 were randomized and vaccinated, and 6717 of the 7109 subjects (94%) completed the study (95% of the vaccinated subjects completed). Major reasons for premature withdrawal included loss to follow-up (2%), death (1%), and withdrawal of consent (1%).

Of the 7082 randomized and vaccinated subjects, 14 subjects (7 in each vaccine group) were administered a vaccine different from the vaccine assigned at randomization. Among subjects randomized to the TIV-ADJ group, 3 were vaccinated with TIVNONADJ and 4 with TIV-ADJ from a lot different from their assigned lot; 7 subjects randomized to the TIV-NONADJ group were vaccinated with TIV-ADJ. Table 3 presents a summary of study completions as randomized.

Table 3: Summary of Study Completion: As Randomized

	TIV-ADJ	TIV-NONADJ	Not Randomized	Total
Enrolled Population	3552	3552	5	7109
Exposed (Vaccinated) ^a	3541 (100%)	3541 (100%)	0	7082 (100%)
Completed Study	3361 (95%)	3356 (94%)	0	6717 (94%)
Missing Primary Reason	1 (<1%)	0	0	1 (<1%)
Premature Withdrawals	190 (5%)	196 (6%)	5 (100%)	391 (6%)
Reasons:				
Death ^b	51 (1%)	46 (1%)	0	97 (1%)
AE	3 (<1%)	2 (<1%)	0	5 (<1%)
Withdrew consent	52 (1%)	43 (1%)	0	95 (1%)
Lost to follow-up	73 (2%)	91 (3%)	2 (40%)	166 (2%)
Inappropriate enrollment	5 (<1%)	4 (<1%)	2 (40%)	11 (<1%)
Administrative reason	1 (<1%)	1 (<1%)	0	2 (<1%)
Protocol deviation	2 (<1%)	2 (<1%)	0	4 (<1%)
Unable to classify	3 (<1%)	7 (<1%)	1 (20%)	11 (<1%)

^a Percentages of exposed subjects are defined as 100% here, however, all other percentages in the table are calculated using the enrolled population as the denominator (i.e., defined as 100%).

^b One subject (320/090) withdrew after developing an AE (lung neoplasm) that subsequently led to death; the death is not included in this table because an AE, rather than death, was the cause of the withdrawal.

Source: Adapted from Clinical study report for study V70_27 BLA 125510 Page 109

Of the 5 AEs leading to premature withdrawal, 1 was considered related to the study vaccination. This subject (311/034) received the TIV-NONADJ vaccine and was subsequently diagnosed with Guillain-Barré syndrome; the subject died during the study due to Guillain-Barré syndrome. None of the other 97 deaths recorded during the study were thought by the investigator to be related to study vaccine. Premature withdrawals due to other reasons such as inappropriate enrollment or protocol deviation occurred in <1% of subjects. The total number and reasons for premature withdrawals were similar between the TIV-ADJ and TIV-NONADJ vaccine groups.

6.10.2 Protocol Deviations

Nineteen percent (19%) and 18% of subjects had at least 1 protocol deviation in the TIV-ADJ and TIV-NONADJ groups, respectively. A major protocol deviation was defined as a deviation with the potential to have a significant impact on the immunogenicity results of a given subject. These deviations were identified through data listing reviews and review of monitoring reports; both were conducted prior to unblinding of the study.

Major protocol deviations leading to exclusion from the day 22 PPS were recorded for 325 subjects (9%) in the TIV-ADJ group and 293 subjects (8%) in the TIV-NONADJ group. The most commonly reported major protocol deviations were collection of visit 3 (day 22) blood samples out of the visit window (6% and 5%, TIV-ADJ and TIVNONADJ groups, respectively) and missing visit 3 entirely (2% in both groups). All other major protocol deviations occurred in <1% of subjects. Specifically, 38 subjects were enrolled who did not fulfill the study entry criteria (of note, 2 of these were never randomized due to insufficient randomization numbers and were subsequently withdrawn from the study). Other less common but major deviations included use of exclusionary concomitant medications (n=43) and presence of exclusionary medical conditions (n=12). Fifteen enrolled subjects developed withdrawal criteria and were removed from the per protocol analysis.

Fourteen subjects did not receive the correct study vaccine according to the vaccine group to which they were randomized, and were reallocated to the group for the vaccine they actually received but were excluded from the per protocol analysis.

The applicant provided a detailed by-subject listing of all protocol deviations, major and minor as an appendix to the CSR.

6.11 Immunogenicity and Efficacy Results

6.11.1 Data Sets Analyzed

Over 99% of enrolled subjects were randomized to 1 of the 4 vaccine groups (receiving either 1 of the 3 lots of TIV-ADJ or TIV-NONADJ). Per protocol, 1768 subjects (25% of randomized subjects across vaccine groups) were randomly selected for inclusion in the day 22 FAS for immunogenicity analysis using heterologous strains. The majority of these subjects were retained for the day 22 PPS for heterologous testing (1649 subjects; 23% of all randomized subjects).

Subjects with chronic medical conditions (referred to as “high-risk” subjects) were allowed to enroll in this study. About 36% (n=2573) of all randomized subjects in the day 22 FAS were high-risk; most of these subjects were included in the day 22 PPS (34% of randomized subjects; n=2385).

Effectiveness of the study vaccines was estimated by comparing the percentages of subjects with ILI, exacerbation of pre-existing chronic disease, healthcare utilization (emergency room visits, unscheduled physician visits, and hospitalizations for specific conditions), and all-cause mortality between the two vaccine groups. These analyses were performed using the FAS and, for ILI, also the mFAS. The mFAS excluded any events that occurred after receipt of non-study influenza vaccine.

Tables 4 and 5 summarize the populations analyzed: all subjects and high risk subjects, respectively.

Table 4: Overview of Populations Analyzed: All Subjects

	TIV-ADJ	TIV-NONADJ	Not Randomize d	Total
Enrolled Population:	3552 (100%)	3552 (100%)	5 (100%)	7109 (100%)
Randomized Population:				
Not vaccinated	11 (<1%)	11 (<1%)	5 (100%)	27 (<1%)
Vaccinated	3541 (100%)	3541 (100%)	0	7082 (100%)
Day 22 FAS				
Homologous	3479 (98%)	3482 (98%)	0	6961 (98%)
Heterologous subset	887 (25%)	881 (25%)	0	1768 (25%)
Day 22 PPS				
Homologous	3227 (91%)	3259 (92%)	0	6486 (91%)
Heterologous subset	834 (23%)	815 (23%)	0	1649 (23%)
Day 366 PPS (Persistence subset)	189 (5%)	191 (5%)	0	380 (5%)
Clinical Effectiveness ^a	3541 (100%)	3541 (100%)	0	7082 (100%)
ILI-FAS	3497 (98%)	3499 (99%)	0	6996 (98%)
Healthcare utilization - FAS	3499 (99%)	3502 (99%)	0	7001 (98%)

^a Data for ILI are from day 22 through day 366; data for exacerbation of chronic disease and healthcare utilization are from day 1 through day 366.

Source: Adapted from Clinical study report for study V70_27 BLA 125510 Page 118

Table 5: Overview of Populations Analyzed: High-Risk Subjects

	TIV-ADJ (N=1300)	TIV-NONADJ (N=1273)	Not Randomized	Total (N=2573)
Day 22 FAS	1300 (37%)	1273 (36%)	0	2573 (36%)
Homologous				
Heterologous subset	330 (9%)	333 (9%)	0	663 (9%)
Day 22 PPS	1195 (34%)	1190 (34%)	0	2385 (34%)
Homologous				
Heterologous subset	302 (9%)	307 (9%)	0	609 (9%)
Clinical effectiveness – FAS ^a				
ILI	1306 (37%)	1279 (36%)	0	2585 (36%)
Exacerbation of chronic disease	1307 (37%)	1281 (36%)	0	2588 (36%)
Healthcare utilization	1307 (37%)	1281 (36%)	0	2588 (36%)

^a Data for ILI are from day 22 through day 366; data for exacerbation of chronic disease and healthcare utilization are from day 1 through day 366.

Source: Adapted from Clinical study report for study V70_27 BLA 125510 Page 118

6.11.2 Demographic and Baseline Characteristics

The demographic and baseline characteristics of the FAS are provided in table 6.

Table 6: Demographic and Other Baseline Characteristics: Day 22 FAS

	TIV-ADJ N=3479	TIV-NONADJ N=3482	Total N=6961
Age (Mean ± SD; years)	71.9±5.3	71.8±5.3	71.9±5.3
Gender:			
Male	1252 (36%)	1178 (34%)	2430 (35%)
Female	2227 (64%)	2304 (66%)	4531 (65%)
Age Cohorts:			
65-75 years	2504 (72%)	2531 (73%)	5035 (72%)
>75 years	975 (28%)	951 (27%)	1926 (28%)
Country:			
Colombia	503 (14%)	495 (14%)	998 (14%)
Panama	108 (3%)	102 (3%)	210 (3%)
Philippines	1832 (53%)	1830 (53%)	3662 (53%)
United States	1036 (30%)	1055 (30%)	2091 (30%)
Ethnic Origin:			
Asian	1837 (53%)	1840 (53%)	3677 (53%)
Black	44 (1%)	39 (1%)	83 (1%)
Caucasian	969 (28%)	971 (28%)	1940 (28%)
Hispanic	616 (18%)	613 (18%)	1229 (18%)
Other	11 (<1%)	16 (<1%)	27 (<1%)
Native American/Alaskan	1 (<1%)	3 (<1%)	4 (<1%)
Pacific/Hawaii	1 (<1%)	0	1 (<1%)

Source: Adapted from Clinical study report for study V70_27 BLA 125510 Page 120

The baseline and demographic characteristics of subjects in the day 22 FAS were closely matched between the two vaccine groups.

6.11.3 Immunogenicity Analysis Results

6.11.3.1 Lot-to-Lot Consistency of TIV-ADJ

The first co-primary immunogenicity objective was to evaluate immunologic equivalence of 3 consecutive production lots of TIV-ADJ (lots 1, 2, and 3), as measured by HI GMTs at day 22 for each virus strain after a single 0.5 mL IM injection.

The results of lot-to-lot consistency analysis for the 3 consecutive TIV-ADJ lots and the changes made in the TIV-ADJ ratios and 95% CIs based on the model with 3 parallel groups are presented in table 7.

Table 7: Geometric Mean HI Titers and Lot-to-Lot Ratios Against Homologous Strains (Lot-to-Lot Consistency): Day 22 PPS

Strain		Lot 1	Lot 2	Lot 3	Lot 1:Lot 2	Lot 1:Lot 3	Lot 2:Lot 3
A/California/7/2009-like (H1N1)	N	1072	1078	1075			
	Day 1	7.19	7.84	8.04	0.92	0.89	0.98
	(95% CI)	(6.55-7.89)	(7.15-8.6)	(7.33-8.82)	(0.83-1.01)	(0.81-0.99)	(0.88-1.08)
	Day 22*	105	94	99	1.12	1.06	0.95
	(95% CI)	(95-116)	(85-103)	(90-110)	(1.03-1.24)	(0.95-1.17)	(0.85-1.05)
A/Perth/16/2009-like (H3N2)	N	1072	1078	1075			
	Day 1	24	26	25	0.93	0.97	1.05
	(95% CI)	(22-28)	(23-30)	(22-28)	(0.82-1.06)	(0.85-1.11)	(0.92-1.2)
	Day 22*	274	271	278	1.01	0.99	0.98
	(95% CI)	(251-299)	(249-296)	(255-303)	(0.92-1.11)	(0.91-1.08)	(0.89-1.07)
B/Brisbane/60/2008-like	N	1073	1078	1076			
	Day 1	6.04	6.22	6.26	0.97	0.97	0.99
	(95% CI)	(5.62-6.49)	(5.79-6.68)	(5.83-6.72)	(0.90-1.05)	(0.89-1.04)	(0.92-1.07)
	Day 22*	28	28	29	1.00	0.96	0.96
	(95% CI)	(26-31)	(26-31)	(27-32)	(0.91-1.1)	(0.87-1.05)	(0.87-1.05)

*Day 22 GMTs and vaccine group GMT ratios are adjusted for baseline titer, country, and age cohort

Bold: Result satisfied the pre-specified success criteria.

Source: Reviewer's analysis results based on the submitted data

After a single IM dose of TIV-ADJ, the adjusted day 22 GMTs showed increased titers against each of the 3 homologous strains among subjects vaccinated with all 3 TIV-ADJ lots. The 95% CIs of GMT ratios for the pairwise lot-to-lot group comparisons all fell within the equivalence range of 0.67 to 1.5, satisfying the predefined success criteria for consistency of the product from the 3 different lots.

After the pre-specified criteria for consistency of the lots were met, data from subjects receiving vaccine from any of the 3 lots were pooled into a single TIV-ADJ group for comparison with the TIV-NONADJ group.

6.11.3.2 Non-inferiority (NI) of TIV-ADJ to TIV-NONADJ

TIV-ADJ and TIV-NONADJ immunogenicity data were used to demonstrate the NI of TIV-ADJ compared with TIV-NONADJ with regards to all homologous strains in subjects ≥ 65 years of age, as measured by GMT ratios and seroconversion rate differences at day 22.

Tables 8 and 9 present the NI comparison results based on the GMT ratios and seroconversion rates, respectively.

Table 8: Non-inferiority of TIV-ADJ vs TIV-NONADJ using GMT

Strain		TIV-ADJ	TIV-NONADJ	TIV-ADJ:TIV-NONADJ
A/California/7/2009-like (H1N1)	N	3225	3257	
	Day 1	7.64	7.68	0.99
	(95% CI)	(7.22-8.10)	(7.23-8.16)	(0.94-1.05)
	Day 22	99	70	1.41
	(95% CI)	(93-106)	(66-75)	(1.32-1.49)
A/Perth/16/2009-like (H3N2)	N	3225	3256	
	Day 1	27	26	1.04
	(95% CI)	(25-29)	(24-28)	(0.94-1.12)
	Day 22	272	169	1.61
	(95% CI)	(257-288)	(159-179)	(1.52-1.73)
B/Brisbane/60/2008-like	N	3227	3259	
	Day 1	6.14	6.12	1.00
	(95% CI)	(5.88-6.43)	(5.85-6.44)	(0.96-1.05)
	Day 22	28	24	1.15
	(95% CI)	(26-29)	(23-26)	(1.08-1.21)

* Day 22 GMTs and vaccine group GMT ratios are adjusted for baseline titer, country, and age cohort

Bold: Result satisfied the pre-specified success criteria.

Source: Reviewer's analysis results based on the submitted data

The lower bound of the 95% CI for the day 22 vaccine group GMT ratios (TIV-ADJ: TIV-NONADJ) for all 3 homologous strains was > 0.67 , the pre-specified criterion for a lower bound, thereby establishing non-inferiority of TIV-ADJ to TIV-NONADJ against homologous strains. The highest difference was observed in the A/H3N2 strain.

Table 9: Non-inferiority of TIV-ADJ vs TIV-NONADJ using Seroconversion rate

Strain	TIV-ADJ	TIV-NONADJ	TIV-ADJ – TIV-NONADJ*
A/California/7/2009-like (H1N1)	N=3225	N=3257	
	69%	58%	9.9%
	(67%-70%)	(57%-60%)	(7.56%-12.1%)
A/Perth/16/2009-like (H3N2)	3225	3256	
	73%	58%	13.9%
	(71%-74%)	(56%-60%)	(11.7%-16.1%)
B/Brisbane/60/2008-like	3227	3259	
	33%	29%	3.2%
	(31%-35%)	(28%-31%)	(1.1-5.3%)

* Day 22 vaccine group differences are adjusted for country and age cohort

Bold: Result satisfied the pre-specified success criteria.

Source: Reviewer's analysis results based on the submitted data

The lower bounds of the 95% CI for day 22 differences in seroconversion rates for all 3 homologous strains were $\geq -10\%$, thus meeting the pre-specified criterion to demonstrate non-inferiority of TIV-ADJ to TIV-NONADJ by seroconversion.

6.11.3.3 Superiority of TIV-ADJ to TIV-NONADJ

The superiority co-primary objective was to evaluate the superiority of TIV-ADJ compared with TIV-NONADJ with regards to at least 2 homologous strains in subjects ≥ 65 years of age, using pre-specified success criteria measured by GMT ratios and seroconversion rate differences at day 22 using the FAS.

The multiplicity introduced by the superiority objective was taken into account using the Bonferroni-Holm multiple testing correction of the alpha. Adjusted p-values were calculated using the method described by Dmitrienko et al.

Superiority analysis results based on GMT and seroconversion rates using the day 22 FAS are presented in tables 10 and 11, respectively.

Table 10: Superiority comparison of TIV-ADJ vs TIV-NONADJ using GMT: GMT (95% CI) and vaccine group ratios against homologous strains (Day 22 FAS)

Strain		TIV-ADJ	TIV-NONADJ	TIV-ADJ:TIV-NONADJ	Unadjusted p-value	Multiplicity Adjusted P-value
A/California/7/2009-like (H1N1)	N	3477	3480		0.998	1.00
	Day 1	7.82	7.76	1.01		
	(95% CI)	(7.35-8.22)	(7.33-8.21)	(0.94-1.05)		
	Day 22	98	71	1.36		
	(95% CI)	(92-104)	(67-76)	(1.28-1.47)		
A/Perth/16/2009-like (H3N2)	N	3477	3479		0.011	0.055
	Day 1	27	26	1.04		
	(95% CI)	(25-29)	(24-28)	(0.94-1.12)		
	Day 22	267	167	1.61		
	(95% CI)	(253-282)	(158-176)	(1.51-1.68)		
B/Brisbane/60/2008-like	N	3479	3482		1.00	1.00
	Day 1	6.19	6.14	1.01		
	(95% CI)	(5.94-6.46)	(5.89-6.41)	(0.97-1.05)		
	Day 22	27	24	1.14		
	(95% CI)	(26-29)	(23-25)	(1.08-1.21)		

P-value=1-sided p-value used to test superiority, i.e., whether TIV-ADJ/TIV-NONADJ ratio is >1.5 .

Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ:TIV-NONADJ) are adjusted for day 1 titer, country, and age cohort.

Bold: Result satisfied the pre-specified success criteria.

Source: Reviewer's analysis results based on the submitted data

The pre-specified superiority criteria for TIV-ADJ to TIV-NONADJ in terms of GMT ratio against homologous strains was not achieved, as the lower limit of the 95% CI for at least two of the three strains did not meet the criterion. Although the 95% CI for the day 22 GMT ratio for the A/H3N2 strain on day 22 had a lower bound >1.5 , with an unadjusted p-value for superiority of 0.011, after adjusting for multiple comparisons the p-value was 0.055.

The GMT ratios were >1 for each of the 3 homologous strains, indicating the adjusted day 22 GMTs against each of the 3 homologous strains in the TIV-ADJ group were statistically significantly higher than those of the TIV-NONADJ group.

Table 11: Superiority comparison of TIV-ADJ vs TIV-NONADJ using Seroconversion: Percentage (95%CI) of Subjects with Seroconversion* and Vaccine Group Differences Against Homologous Strains (Day 22 FAS)

Strain	TIV-ADJ	TIV-NONADJ	(TIV-ADJ) – (TIV-NONADJ)**	Unadjusted p-value	Multiplicity Adjusted P-value
A/California/7/2009-like (H1N1)	N=3477 69% (67%-70%)	N=3480 60% (57%-60%)	9.5% (7.4%-11.5%)	0.664	1.00
A/Perth/16/2009-like (H3N2)	N=3477 72.6% (71%-74%)	N=3479 58.3% (56%-60%)	13.4% (11%-16%)	<0.001	0.002
B/Brisbane/60/2008-like	N=3479 38% (32%-34%)	N=3482 30.5% (28.7%-31.6%)	3% (1%-5%)	1.00	1.00

* Seroconversion defined as pre-vaccination HI titer <10 and post-vaccination HI titer ≥40 or an increase in HI titer of at least 4-fold from a pre-vaccination HI titer of ≥10.

P-value= multiplicity-adjusted 1-sided p-value used to test whether the adjusted TIV-ADJ minus TIV-NONADJ difference exceeds 10%.

** Day 22 vaccine group difference are adjusted for country and age cohort.

Bold: Result satisfied the pre-specified success criteria.

Source: Reviewer's analysis results based on the submitted data

The lower bound of the 95% CI for the TIV-ADJ minus TIV-NONADJ difference in day 22 seroconversion rates for the A/H3N2 strain was >10%, with an unadjusted p-value for superiority of 0.0004, after adjusting for multiple comparisons the p-value was 0.002. Thus, the pre-specified superiority criterion was met, and hence superiority was achieved for this strain.

The lower bound of the 95% CI for the TIV-ADJ minus TIV-NONADJ difference in day 22 seroconversion rates for both A/H1N1 and B homologous strains is not >10%. Thus, superiority for these two strains was not achieved.

Therefore, the 2-strain requirement for establishing superiority by difference in seroconversion rates for homologous strains was not achieved. But the multiplicity-adjusted difference in percentage of subjects who seroconverted by day 22 was statistically significantly higher (lower bound of the 95% CI >0, i.e., statistical superiority was met) in the TIV-ADJ group than in the TIV-NONADJ group for each of the homologous strains tested.

6.11.3.4 Secondary Immunogenicity Objectives

6.11.3.4.1 Secondary Objective 1: Superiority of TIV-ADJ compared with TIV-NONADJ for homologous strains in high-risk elderly subjects

The first of the secondary immunogenicity objectives was to demonstrate the non-inferiority of TIV-ADJ versus TIV-NONADJ for all 3 homologous strains in high-risk subjects with predefined comorbidities, and to evaluate the superiority of TIV-ADJ compared with TIV-NONADJ for at least 2 homologous strains, as assessed by GMT vaccine group ratios and seroconversion rate differences at day 22.

a. Non-inferiority of TIV-ADJ versus TIV-NONADJ against Homologous Strains among High-Risk Subjects

Tables 12 and 13 summarize the NI comparison results of TIV-ADJ to TIV-NONADJ against homologous strains among high-risk subjects, based on GMT ratio and seroconversion rates, respectively.

Table 12: GMT (95% CI) and Vaccine Group Ratios in High-Risk Subjects Against Homologous Strains: Day 22 PPS

Strain		TIV-ADJ	TIV-NONADJ	TIV-ADJ:TIV-NONADJ
A/California/7/2009-like (H1N1)	N	1194	1190	
	Day 1	8.04	8.48	0.95
	(95% CI)	(7.32-8.84)	(7.72-9.33)	(0.85-1.05)
	Day 22	110	80	1.38
	(95% CI)	(100-122)	(73-88)	(1.25-1.52)
A/Perth/16/2009-like (H3N2)	N	1194	1190	
	Day 1	28	27	1.04
	(95% CI)	(25-31)	(24-30)	(0.92-1.17)
	Day 22	260	165	1.57
	(95% CI)	(238-283)	(152-180)	(1.44-1.72)
B/Brisbane/60/2008-like	N	1195	1190	
	Day 1	6.33	6.54	0.97
	(95% CI)	(5.88-6.79)	(6.09-7.02)	(0.90-1.04)
	Day 22	30	27	1.12
	(95% CI)	(28-33)	(25-29)	(1.03-1.22)

Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ: TIV-NONADJ) are adjusted for baseline titer, country, and age cohort.

Bold: Result satisfied the pre-specified success criteria.

Source: Reviewer's analysis results based on the submitted data

The lower bound of the 95% CIs around the TIV-ADJ:TIV-NONADJ ratios for each of the 3 strains was >0.67, thus establishing non-inferiority of TIV-ADJ to TIV-NONADJ with regards to GMT ratio against homologous strains among high-risk subjects.

Table 13: Percentage (95% CI) of Subjects with Seroconversion and Vaccine Group Differences in High-Risk Subjects against Homologous Strains

Strain	TIV-ADJ	TIV-NONADJ	TIV-ADJ – TIV-NONADJ*
A/California/7/2009-like (H1N1)	N=1194 65% (63%-68%)	N=1190 54% (51%-57%)	10.9% (7.1%-14.7%)
A/Perth/16/2009-like (H3N2)	N=1194 67% (64%-69%)	N=1190 52% (49%-55%)	14% (10.2%-17.7%)
B/Brisbane/60/2008-like	N=1195 27% (25%-30%)	N=1190 25% (23%-28%)	2.2% (-1.0%-5.4%)

Seroconversion defined as HI titer <10 pre-vaccination and ≥40 post-vaccination or at least a 4-fold increase in HI from pre-vaccination HI titer ≥10.

*Differences in the day 22 seroconversion rates are adjusted for country and age cohort and therefore do not equal the difference between the two columns to the left.

Bold: Result satisfied the pre-specified success criteria.

Source: Reviewer's analysis results based on the submitted data

The lower bounds of the 95% CIs around the differences in seroconversion rates were higher than the pre-specified cutoff of -10% for each of the 3 strains. Non-inferiority of TIV-ADJ to TIV-NONADJ was thus established with regard to difference in seroconversion rates against homologous strains among high-risk subjects.

b. Superiority of TIV-ADJ versus TIV-NONADJ against Homologous Strains among High-Risk Subjects

The lower bounds of the 95% CIs for the day 22 vaccine group GMT ratios (TIVADJ: TIV-NONADJ) were <1.5 for each of the 3 homologous strains tested. Therefore, the requirement for establishing superiority of TIV-ADJ to TIV-NONADJ in terms of GMT ratio against homologous strains in high-risk subjects was not achieved.

None of the 3 strains met the criterion for superiority; even without adjustment for multiplicity, p-values for testing the TIV-ADJ minus TIV-NONADJ difference were above the cutoff. Therefore, the 2-strain requirement for establishing superiority by difference in seroconversion rates for homologous strains among high-risk subjects was not achieved.

6.11.3.4.2 Secondary Objective 2: Superiority and Non-inferiority of TIV-ADJ compared with TIV-NONADJ for heterologous strains.

The second of the secondary immunogenicity objectives was to evaluate the superiority of TIV-ADJ compared with TIV-NONADJ for at least 2 of 3 heterologous strains, and to demonstrate the non-inferiority of TIV-ADJ compared with TIV-NONADJ for all 3 strains, in all subjects and in the subset of high-risk subjects (all subjects were ≥65 years of age) with predefined comorbidities, as measured by vaccine group GMT ratios and seroconversion rate differences at day 22. No adjustments for multiplicity were made in the analyses of this objective.

a. Non-inferiority of TIV-ADJ versus TIV-NONADJ (Heterologous Strains)

Table 14: GMT (95% CI) and Vaccine Group Ratios against Homologous Strains

Strain		TIV-ADJ	TIV-NONADJ	TIV-ADJ:TIV-NONADJ
A/Brisbane/10/2007-like (H3N2)	N	834	814	
	Day 1	33	33	0.98
	(95% CI)	(28-38)	(29-39)	(0.84-1.14)
	Day 22	185	128	1.45
A/Wisconsin/67/2005-like (H3N2)	N	834	815	
	Day 1	105	109	0.96
	(95% CI)	(90-121)	(94-127)	(0.82-1.12)
	Day 22	518	382	1.36
B/Malaysia/2506/2004-like	N	834	814	
	Day 1	8.72	8.82	0.99
	(95% CI)	(8.1-9.5)	(8.08-9.64)	(0.90-1.08)
	Day 22	44	41	1.09
	(95% CI)	(40-49)	(37-45)	(0.98-1.21)

Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ: TIV-NONADJ) are adjusted for baseline titer, country, and age cohort.

Bold: Result satisfied the pre-specified success criteria.

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.148

The lower bound of the 95% CI for the day 22 vaccine group GMT ratios (TIV-ADJ: TIVNONADJ) for all 3 heterologous strains tested was >0.67, thus establishing non-inferiority of TIV-ADJ to TIV-NONADJ with regard to GMT against heterologous strains.

Table 15: Percentage (95% CI) of subjects with seroconversion and vaccine group differences against heterologous strains

Strain	TIV-ADJ	TIV-NONADJ	TIV-ADJ – TIV-NONADJ*
A/Brisbane/10/2007-like (H3N2)	N=834 57% (54%-61%)	N=814 46% (43%-50%)	11.9% (7.3%-16.5%)
A/Wisconsin/67/2005-like (H3N2)	N=834 56% (52%-59%)	N=815 45% (42%-49%)	11.5% (6.9%-16.2%)
B/Malaysia/2506/2004-like	N=834 40% (37%-44%)	N=814 37% (34%-41%)	3.9% (0%-8.3%)

*Difference in the day 22 seroconversion rates are adjusted for country and age cohort

Bold: Result satisfied the pre-specified success criteria.

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.149

The lower bound of the 95% CI of the adjusted difference in seroconversion rates between the vaccine groups was >-10% for all 3 strains, thus establishing non-inferiority of TIV-ADJ to TIV-NONADJ with regard to seroconversion rates against heterologous strains.

b. Non-inferiority of TIV-ADJ versus TIV-NONADJ among High Risk subjects (Heterologous Strains)

Table 16: GMT (95% CI) and vaccine group ratios in high risk subjects against Heterologous Strains

Strain		TIV-ADJ	TIV-NONADJ	TIV-ADJ:TIV-NONADJ
A/Brisbane/10/2007-like (H3N2)	N	302	307	
	Day 1	34	33	1.04
	(95% CI)	(28-43)	(26-41)	(0.81-1.32)
	Day 22	188	140	1.35
	(95% CI)	(159-223)	(118-165)	(1.13-1.61)
A/Wisconsin/67/2005-like (H3N2)	N	302	307	
	Day 1	100	100	1
	(95% CI)	(79-127)	(79-127)	(0.78-1.27)
	Day 22	483	375	1.29
	(95% CI)	(415-561)	(323-436)	(1.12-1.51)
B/Malaysia/2506/2004-like	N	302	307	
	Day 1	9.14	9.57	0.95
	(95% CI)	(7.87-11)	(8.24-11)	(0.82-1.12)
	Day 22	58	53	1.11
	(95% CI)	(50-68)	(45-61)	(0.95-1.32)

Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ: TIV-NONADJ) are adjusted for baseline titer, country, and age cohort.

Bold: Result satisfied the pre-specified success criteria.

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.150

The lower bound of the 95% CI for the day 22 vaccine group GMT ratios (TIV-ADJ: TIV-NONADJ) for all 3 heterologous strains tested was >0.67. Therefore, non-inferiority of TIV-ADJ to TIV-NONADJ with regard to GMT was achieved against heterologous strains among high-risk subjects.

Table 17: Percentage (95% CI) of subjects with seroconversion and vaccine group differences in high risk subjects against heterologous strains (day 22 PPS)

Strain	TIV-ADJ	TIV-NONADJ	(TIV-ADJ) – (TIV-NONADJ)*
A/Brisbane/10/2007-like (H3N2)	N=302 52% (46%-57%)	N=307 39% (34%-45%)	12.6% (5.1%-20%)
A/Wisconsin/67/2005-like (H3N2)	N=302 51% (45%-56%)	N=307 38% (33%-44%)	12.1% (4.6%-19.7%)
B/Malaysia/2506/2004-like	N=302 35% (30%-41%)	N=307 33% (27%-38%)	3.7% (-3%-10.5%)

*Difference in the day 22 seroconversion rates are adjusted for country and age cohort

Bold: Result satisfied the pre-specified success criteria.

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.151

The lower bounds of the 95% CIs for the difference in seroconversion rates were >-10% for all 3 strains. Therefore, non-inferiority of TIV-ADJ to TIV-NONADJ with regard to seroconversion rates against heterologous strains among high-risk subjects was achieved.

c. Superiority of TIV-ADJ versus TIV-NONADJ against Heterologous Strains

Table 18: GMT (95% CI) and Vaccine Group Ratios against Heterologous Strains

Strain		TIV-ADJ	TIV-NONADJ	TIV-ADJ:TIV-NONADJ
A/Brisbane/10/2007-like (H3N2)	N	887	880	
	Day 1	33	33	1
	(95% CI)	(29-38)	(29-38)	(0.86-1.16)
	Day 22	181	122	1.49
	(95% CI)	(162-202)	(109-136)	(1.33-1.67)
A/Wisconsin/67/2005-like (H3N2)	N	887	881	
	Day 1	106	109	0.98
	(95% CI)	(92-122)	(95-126)	(0.84-1.13)
	Day 22	508	369	1.38
	(95% CI)	(463-557)	(336-405)	(1.25-1.52)
B/Malaysia/2506/2004-like	N	887	880	
	Day 1	9.0	9.0	1
	(95% CI)	(8.33-9.76)	(8.32-9.77)	(0.92-1.09)
	Day 22	44	40	1.09
	(95% CI)	(40-48)	(36-44)	(0.99-1.21)

Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ: TIV-NONADJ) are adjusted for baseline titer, country, and age cohort.

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.148

The lower bound of the 95% CI for the day 22 vaccine group GMT ratio against each of the 3 heterologous strains was <1.5. Therefore, TIVADJ did not achieve superiority compared with TIV-NONADJ with regards to GMT.

Table 19: Percentage (95% CI) of subjects with seroconversion and vaccine group differences against heterologous strains (day 22 FAS)

Strain	TIV-ADJ	TIV-NONADJ	(TIV-ADJ) – (TIV-NONADJ)*
A/Brisbane/10/2007-like (H3N2)	N=887 58% (54%-61%)	N=880 46% (42%-49%)	12.8% (8.4%-17.2%)
A/Wisconsin/67/2005-like (H3N2)	N=887 56% (53%-60%)	N=881 45% (41%-48%)	12.5% (8.1%-17.1%)
B/Malaysia/2506/2004-like	N=887 41% (38%-44%)	N=880 38% (35%-41%)	4.2% (0%-8.4%)

*Difference in the day 22 seroconversion rates are adjusted for country and age cohort

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.153

The lower bounds of the 95% CIs of these differences against all 3 heterologous strains were <10%. Therefore, the requirement for establishing superiority with regard to seroconversion against heterologous strains was not achieved.

d. Superiority of TIV-ADJ versus TIV-NONADJ in High risk subjects against Heterologous Strains

Table 20: GMT (95% CI) and Vaccine Group Ratios in high risk subjects against Heterologous Strains (day 22 FAS)

Strain		TIV-ADJ	TIV-NONADJ	TIV-ADJ:TIV-NONADJ
A/Brisbane/10/2007-like (H3N2)	N	330	333	
	Day 1	35	32	1.08
	(95% CI)	(28-43)	(26-40)	(0.82-1.32)
	Day 22	182	134	1.28
A/Wisconsin/67/2005-like (H3N2)	N	330	333	
	Day 1	103	99	1.04
	(95% CI)	(83-129)	(80-123)	(0.82-1.32)
	Day 22	463	362	1.28
B/Malaysia/2506/2004-like	N	330	333	
	Day 1	9.7	9.92	0.98
	(95% CI)	(8.44-11)	(8.64-11)	(0.84-1.13)
	Day 22	56	50	1.13
	(95% CI)	(49-64)	(43-57)	(0.97-1.31)

Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ: TIV-NONADJ) are adjusted for baseline titer, country, and age cohort.

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.154

The lower bounds of the 95% CIs for the day 22 vaccine group GMT ratios (TIV-ADJ: TIV-NONADJ) were <1.5 for each of the 3 heterologous strains tested. Therefore, the requirement for establishing superiority of TIV-ADJ to TIV-NONADJ with regards to GMT against heterologous strains was not achieved.

Table 21: Percentage (95% CI) of subjects with seroconversion and vaccine group differences in high risk subjects against heterologous strains (day 22 FAS)

Strain	TIV-ADJ	TIV-NONADJ	(TIV-ADJ) – (TIV-NONADJ)*
A/Brisbane/10/2007-like (H3N2)	N=330	N=333	
	52% (46%-57%)	39% (34%-45%)	12.4% (5.2%-19.5%)
A/Wisconsin/67/2005-like (H3N2)	N=330	N=333	
	51% (45%-56%)	38% (33%-43%)	12.6% (5.4%-19.8%)
B/Malaysia/2506/2004-like	N=330	N=333	
	36% (31%-41%)	33% (28%-39%)	3.4% (-3.1%-10%)

*Difference in the day 22 seroconversion rates are adjusted for country and age cohort

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.155

The 95% CI lower bounds for the difference in seroconversion rates for each of the 3 heterologous strains were <10%. Therefore, the 2-strain requirement for establishing superiority of TIV-ADJ to TIV-NONADJ with regards to seroconversion rates among high-risk subjects was not achieved.

6.11.3.4.3 Secondary Objective 3: Clinical Effectiveness of TIV-ADJ compared with TIV-NONADJ

The third of the secondary objectives was to evaluate the clinical effectiveness of a single 0.5-mL IM injection of TIV-ADJ compared with that of a single 0.5-mL IM injection of TIV-NONADJ in subjects ≥ 65 years of age from day 22 through day 366. Effectiveness of the study vaccines was assessed in terms of incidence of subjects with influenza-like illness (ILI) as defined in section 6.8.1 above.

a. Incidence of subjects with ILI:- Overall study population

Table 22 summarizes the ILI across vaccine groups for the interval day 22 through day 366 for both full analysis set and modified analysis set.

Table 22: Influenza-Like Illnesses across vaccine groups: FAS and mFAS, Day 22 through Day 366

		Risk Ratio (95% CI)
FAS	Subjects with ≥ 1 ILI	1.02 (0.87 - 1.19)
	Total Reported ILIS	1.02 (0.88 - 1.17)
mFAS	Subjects with ≥ 1 ILI	1.01 (0.86 - 1.18)
	Total Reported ILIS	1.01 (0.87 - 1.16)

Risk ratios (TIV-ADJ : TIV-NONADJ) and confidence intervals are adjusted for country.

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.157

No significant difference was noted between vaccine groups in incidence of ILI from day 22 through day 366 (Risk Ratio: 1.02 [95% CI: 0.87- 1.19]). In addition, total numbers of ILIs reported for each vaccine group were compared in order to account for multiple ILIs in some subjects; no significant difference was observed (Risk Ratio: 1.02 [95% CI: 0.88- 1.17]).

The percentage of subjects with ILI varied when assessed by country. Table 23 presents the ILI across vaccine groups by country.

Table 23: Influenza-Like Illnesses across vaccine groups by Country (All Subjects FAS Day 22 through Day 366)

Country	TIV-ADJ n (%)	TIV-NONADJ n (%)	Risk Ratio (95% CI)
Colombia	127 (24.6%)	104 (20.6%)	1.19 (0.92 - 1.54)
Panama	20 (18.5%)	21 (20.6%)	0.90 (0.49 - 1.68)
Philippines	103 (5.6%)	113 (6.2%)	0.91 (0.70 - 1.19)
United States	72 (6.9%)	76 (7.2%)	0.96 (0.70 - 1.33)

n= number of subjects with ILI. %= percentage of subjects with ILI

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.158

b. Incidence of subjects with ILI: - High risk subjects

No significant difference was noted between TIV-ADJ and TIV-NONADJ vaccine groups with regard to the incidence of total ILI events in high-risk subjects (Risk Ratio: 0.91 [95% CI: 0.71-1.16]); this was also true for the day 22 through day 181 interval.

The percentages of high-risk subjects with ILI by country were similar to those in the overall FAS. No significant difference was noted between vaccine groups in individual countries for the day 22 through day 366 interval or for the day 22 through day 181 interval.

c. Incidence of ILI in the US during time windows encompassing peak and intermediate influenza transmission

For subjects enrolled in study sites in the US, additional analyses were performed to evaluate the incidence of ILI during time windows chosen to encompass peak influenza transmission in the community. This allowed increased specificity, and thus more reliable estimates, for risk ratio and vaccine effectiveness.

Table 24: Incidence of Influenza-Like Illness in the United States During Peak and Intermediate Activity Windows: FAS

Population	Activity Window	TIV-ADJ	TIV-NONADJ	Risk Ratio (95% CI)
All Subjects (FAS)	Intermediate	34 (3.3%)	34 (3.2%)	1.02 (0.63-1.64)
	Peak	16 (1.6%)	14 (1.3%)	1.16 (0.57-2.38)
High-Risk Subjects	Intermediate	26 (3.9%)	18 (2.7%)	1.46 (0.80-2.65)
	Peak	11 (1.7%)	7 (1.0%)	1.59 (0.62-4.09)

Source: Adapted from Tables 14.2.1.8.7; 14.2.1.8.8; 14.2.1.8.17 and 14.2.1.8.18 of Clinical Study Report V70_27 (BLA 125510)

The incidence of ILI was similar in both vaccine groups during the peak and intermediate activity windows. Moreover, no significant difference in vaccine effectiveness was noted between vaccine groups.

d. Exacerbation of preexisting chronic disease

The effectiveness of the study vaccines was assessed in terms of the percentage of subjects reporting an exacerbation of preexisting chronic conditions (i.e., congestive heart failure, COPD, asthma, hepatic disease, renal insufficiency, and neurological/neuromuscular or metabolic disorders including diabetes mellitus) during the study's follow-up period. Exacerbation of preexisting chronic disease was defined as an emergency room visit, unscheduled physician visit, or hospitalization.

Among high-risk subjects (i.e., subjects with preexisting chronic disease), 4% in each vaccine group had exacerbations of that disease during the follow-up period, based on the Effectiveness FAS (Risk Ratio: 1.35; 95% CI: 0.80 - 2.26). The percentages of subjects with exacerbation of chronic disease, analyzed by disease, ranged from 2% to 11% in the TIV-ADJ group and 0 to 13% in the TIV-NONADJ group. In the TIV-ADJ group, subjects with preexisting COPD had the highest rate of exacerbation (11%) among the analyzed diseases, while in the TIV-NONADJ group; subjects with preexisting congestive heart failure had the highest rate (13%) and those with COPD the same rate as in the TIVADJ group. There was no significant difference between vaccine groups in the percentages of subjects reporting exacerbation of any of the above mentioned conditions, i.e., the 95% CIs include 1 in all cases.

e. Healthcare utilization

The percentage of subjects with emergency room visits, unscheduled physician visits, and hospitalizations due to community acquired influenza or pneumonia, cardiopulmonary disease, cardiac disease, respiratory or pulmonary disease were recorded throughout the follow-up phase.

Overall study population: A low percentage of subjects (8%) in both vaccine groups reported use of health care services overall. There were no significant differences between vaccine groups by type of visit, i.e., the 95% CIs include 1 in all cases.

High-risk subjects: In both vaccine groups, the percentage of high-risk subjects reporting emergency room visits, unscheduled physician visits, and hospitalization was higher than in the overall study population (13% and 14% for TIV-ADJ and TIV-NONADJ, respectively, vs. ~8% for both vaccine groups in all subjects. As with the overall FAS, most of these reports of healthcare utilization were due to respiratory or pulmonary disease (8% to 10%). There was no significant difference between vaccine groups in percentage of subjects reporting any healthcare utilization or healthcare utilization for a specified diagnosis.

f. Mortality

Overall study population: The all-cause mortality rate (excluding injury) in the FAS overall, by country, is presented in table 25.

Table 25: Comparison of all-cause mortality (excluding injury) by country: FAS (Effectiveness), Day 1 through Day 366.

Country	TIV-ADJ	TIV-NONADJ	TIV-ADJ/TIV-NONADJ Hazard Ratio (95% CI)
Colombia	7/519 (1.4%)	7/509 (1.4%)	1.13 (0.76 - 1.68)
Panama	0/109 (0%)	0/105 (0%)	
Philippines	39/1873 (2.1%)	34/1867(1.8%)	
United States	6/1039 (0.6%)	5/1060 (0.5%)	

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, p.158

The Philippines had the highest mortality rate and Panama had the lowest rate, with no deaths in either vaccine group. When analyzed by duration of survival, no significant difference in all-cause mortality was noted between the vaccine groups (Hazard Ratio: 1.13 [95% CI: 0.76-1.68]).

High-risk subjects: The point estimates for all-cause mortality rate (excluding injury) in high-risk subjects by country were similar in both vaccine groups and displayed a pattern similar to that seen in the FAS overall. The highest percentage of deaths among high-risk subjects was in the Philippines and the lowest in Panama. When analyzed by duration of survival, there was no significant difference between vaccine groups among the high-risk subjects (Hazard Ratio: 0.98 [95% CI 0.53-1.81]).

6.11.3.4.4 Secondary Objective 4: Comparison of TIV-ADJ with TIV-NONADJ for homologous and heterologous strains in antibody persistence subset

The fourth secondary objective was to assess the difference between TIV-ADJ and TIV-NONADJ in persistence of antibodies against homologous and heterologous strains in a subset of subjects. Antibody persistence was assessed by GMT and seroconversion rates in serum samples from day 181 (6 months) and day 366 (1 year) post-vaccination. These assessments indicate numerical differences only, because the study was not powered to allow demonstration of significant differences in persistence. Also, no adjustments for baseline, country, or age were made in this subset due to its relatively small size.

a. Homologous strains (FAS, persistence subset)

GMT: By day 181, GMTs for all strains and both vaccine groups had declined compared with day 22. Table 26 presents the GMT comparison on day 181 and day 366 for both vaccine groups.

Table 26: GMT (95% CI) and vaccine group ratios against homologous strains: FAS (Persistence)

Strain		TIV-ADJ	TIV-NONADJ	TIV-ADJ:TIV-NONADJ
A/California/7/2009-like (H1N1)	N	189	191	
	Day 181	35 (30-42)	34(29-40)	1.05(0.82-1.33)
	Day 366	25(21-30)	26(22-31)	0.94(0.73-1.22)
A/Perth/16/2009-like (H3N2)	N	189	191	
	Day 181	62(52-73)	46(39-54)	1.35(1.06-1.71)
	Day 366	35(29-42)	27(23-32)	1.3(1.01-1.67)
B/Brisbane/60/2008-like	N	189	191	
	Day 181	12(11-15)	11(9.51-13)	1.12(0.9-1.39)
	Day 366	10(8.84-12)	9.96(8.58-12)	1.03(0.83-1.27)

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, table 14.2.1.7.1

Overall the GMT in both vaccine groups were similar. However, GMTs against the homologous A/H3N2 strain at day 181 and day 366 were higher in the TIV-ADJ group than in the TIVNONADJ group.

Seroconversion: Overall, the seroconversion rates were similar in both vaccine groups at day 181 and day 366. The highest difference 11.9% (32% for TIV-ADJ, and 20.1% for TIV-NONADJ) was observed for the homologous A/H3N2 strain at day 181, between the TIV-ADJ and TIV-NONADJ groups. By day 366 the difference decreased to 3.8%.

b. Heterologous strains

GMT: By day 181, antibody levels against heterologous strains had declined in both vaccine group subsets (N=189 and N=191, respectively, for TIV-ADJ and TIV-NONADJ), with no significant difference between them in GMTs at day 181 or day 366 against the heterologous strains tested.

Seroconversion: The percentages of subjects with seroconversion against both heterologous A/H3N2 strains were slightly higher in the TIV-ADJ than in the TIV-NONADJ group at both day 181 and day 366, but the differences were not statistically

significant. For the heterologous B strain, there was no significant difference between vaccine groups from day 22 on, though a numerically higher percentage of subjects showed seroconversion in the TIV-ADJ than in the TIV-NONADJ group at day 22 (difference: 4.4%; 95% CI lower bound: -3.8%).

6.11.4 Immunogenicity Subgroup Analysis

Subgroup analyses were conducted to assess the effects of age, underlying chronic conditions, previous pandemic H1N1 vaccination, and baseline serology status on the immune response to the study vaccines in terms of GMT, seroconversion rate (including ≥ 4 -fold increases in titer), and percentages of subjects achieving HI titer ≥ 40 . In addition, immunogenicity was also assessed by stratifying subjects based on country, race, and gender.

All subgroup analyses were performed on the day 22 FAS for both homologous and heterologous strains, and for the analysis by age cohort. Statistical significance was assumed if the 95% CI of a given vaccine group GMT ratio was >1 or if the 95% CI of a vaccine group difference for seroconversion (or ≥ 4 -fold increase in HI titer) and percentage of subjects with HI titer ≥ 40 was >0 .

6.11.4.1 Age cohort subgroup analysis (FAS; homologous and heterologous strains)

a. Homologous strains

GMT: At day 22, the adjusted GMT ratios indicated a statistically significantly higher response in the TIV-ADJ group than in the TIV-NONADJ group against all 3 homologous strains in both age cohorts (see table 25 below).

Seroconversion: Rates of seroconversion (including increases of ≥ 4 -fold in titer) on day 22 were significantly higher in the TIV-ADJ group than in the TIV-NONADJ group against the A/H1N1 and A/H3N2 homologous strains in both age cohorts. There was a numerically, though not significantly, higher rate of seroconversion against the homologous B strain in both age cohorts in the TIV-ADJ group than in the TIV-NONADJ group; the point estimate for the difference was 2.9% for the 65 to 75 years age cohort and 4.1% in the >75 years age cohort.

Table 27: Analysis by Age cohort of GMTs and vaccine group GMT ratios (95% CIs) against Homologous strains: Day 22 FAS

		65 to 75 Years			>75 Years		
		TIV-ADJ	TIV-NONADJ	TIV-ADJ: TIV-NONADJ	TIV-ADJ	TIV-NONADJ	TIV-ADJ: TIV-NONADJ
A/California/7/2009 - like (H1N1)		N=2502	N=2529		N=975	N=951	
	Day 1	6.43 (6.12-6.76)	6.42 (6.11-6.74)	1 (0.94-1.07)	7.9 (7.26-8.59)	7.92 (7.27-8.63)	1 (0.88-1.12)
	Day 22 ^a	95 (90-100)	70 (66-73)	1.37 (1.27-1.47)	95 (88-104)	68 (62-74)	1.41 (1.25-1.59)
	Day 22 to Day 1	15 (14-16)	11 (10-11)	1.37 (1.26-1.49)	12 (11-13)	8.54 (7.74-9.42)	1.41 (1.23-1.62)
A/Perth/16/2009-like (H3N2)		N=2502	N=2528		N=975	N=951	
	Day 1	24 (23-26)	23 (22-25)	1.03 (0.95-1.13)	26 (24-29)	26 (23-28)	1.02 (0.89-1.17)
	Day 22 ^a	304 (290-319)	189 (180-198)	1.61 (1.5-1.72)	272 (251-293)	171 (158-185)	1.59 (1.43-1.78)
	Day 22 to Day 1	13 (12-14)	8.1 (7.58-8.65)	1.57 (1.43-1.73)	10 (9.39-11)	6.61 (5.96-7.32)	1.57 (1.36-1.82)
B/Brisbane/60/2008 - like		N=2504	N=2531		N=975	N=951	
	Day 1	4.79 (4.62-4.97)	4.71 (4.53-4.88)	1.02 (0.97-1.07)	6.92 (6.46-7.41)	7.13 (6.65-7.64)	0.97 (0.88-1.07)
	Day 22 ^a	22 (21-23)	19 (18-20)	1.14 (1.07-1.22)	32 (30-35)	28 (26-30)	1.15 (1.04-1.28)
	Day 22/1	4.63 (4.41-4.86)	4.09 (3.9-4.29)	1.13 (1.06-1.21)	4.66 (4.28-5.06)	3.98 (3.65-4.33)	1.17 (1.04-1.32)

^a Day 22 GMTs and vaccine group GMT ratios (TIV-ADJ:TIV-NONADJ) are adjusted for baseline titer.

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, table 14.2.1.5.1

b. Heterologous strains

GMT: Baseline titers were higher for the >75 years age cohort than for the 65-75 years age cohort for all heterologous strains, but no significance testing was done for this relationship. The day 22 vaccine group GMT ratios (TIV-ADJ: TIVNONADJ) indicated a statistically significantly higher response to TIV-ADJ versus TIVNONADJ for both heterologous A/H3N2 strains (A/Wisconsin/67/2005-like and A/Brisbane/10/2007-like) only in the 65 to 75 years cohort (vaccine group GMT ratios of 1.5 [95% CI lower bound: 1.33] and 1.66 [95% CI lower bound: 1.44], respectively), although TIV-ADJ induced numerically higher responses in the >75 years cohort. Against the heterologous B strain, neither age cohort had a statistically significant difference between TIV-ADJ and TIVNONADJ.

Seroconversion: TIV-ADJ induced statistically significantly higher responses than TIV-NONADJ to both heterologous A/H3N2 strains in both age cohorts. For the heterologous B strain, there was a numerically higher response to TIV-ADJ than to TIV-NONADJ in the both age cohorts, but this was not statistically significant.

6.11.4.2 Underlying chronic condition subgroup analysis (FAS; homologous strains)

Among enrolled subjects, 36% in both vaccine groups had at least 1 predefined chronic condition classifying them as high-risk subjects and were included in the high-risk FAS subset for immunogenicity analyses (refer to table 3 and table 4 in section 6.11.1 above). Immune responses were assessed in terms of GMT, seroconversion rate (including ≥ 4 -fold increase in titer), and percentage of subjects achieving HI titer ≥ 40 by underlying chronic condition. Note that numbers of subjects with each chronic condition varied from N=26 for hepatic disease to N=2121 for the neurological/neuromuscular and metabolic disorders. This latter group encompassed a wide range of diseases with unknown effects on immune function, with diagnoses ranging from epilepsy to diabetes mellitus.

GMT: The adjusted day 22 vaccine group GMT ratios (TIV-ADJ:TIV-NONADJ) indicate numerically higher antibody responses against all homologous strains in the TIV-ADJ group than in the TIV-NONADJ group (table 28), but this difference was statistically significant only in some conditions for the A/H1N1 and A/H3N2 strains. For the A/H1N1 and A/H3N2 strains, significantly higher responses in the TIV-ADJ group were seen among subjects with neurological/neuromuscular or metabolic disorders, and for the A/H3N2 strain, significantly higher responses were also seen for subjects with CHF, COPD, and renal insufficiency, despite the small sample sizes.

Table 28: Analysis by Underlying Condition of GMT Vaccine Group Ratio (95% CI) against Homologous Strains

		Asthma	CHF	COPD	Hepatic Disease	Neurologic/Metabolic ^a	Renal Insufficiency
		TIV-ADJ [N=162]: TIV-NONADJ [N=155]	TIV-ADJ [N=77]: TIV-NONADJ [N=79]	TIV-ADJ [N=171]: TIV-NONADJ [N=174]	TIV-ADJ [N=13]: TIV-NONADJ [N=13]	TIV-ADJ [N=1075]: TIV-NONADJ [N=1045]	TIV-ADJ [N=49]: TIV-NONADJ[N=57]
A/California/7/2009 -like (H1N1)	Day 1	1 (0.74 – 1.34)	0.76 (0.5 – 1.14)	0.64 (0.48 – 0.87)	1.13 (0.44 – 2.91)	0.99 (0.88 – 1.11)	0.82 (0.51 – 1.31)
	Day 22 ^b	1.09 (0.83 – 1.43)	1.24 (0.83 – 1.86)	1.18 (0.91 – 1.54)	1.81 (0.57 – 5.76)	1.35 (1.21 – 1.5)	1.44 (0.84 – 2.49)
A/Perth/16/2009 - like (H3N2)	Day 1	1.02 (0.73 – 1.44)	1.4 (0.9 – 2.19)	0.78 (0.58 – 1.07)	1.74 (0.54 – 5.57)	1.1 (0.98 – 1.25)	1.18 (0.69 – 2.02)
	Day 22 ^b	1.3 (1 – 1.71)	1.9 (1.28 – 2.81)	1.49 (1.17 – 1.89)	2.21 (0.85 – 5.7)	1.54 (1.39 – 1.71)	1.73 (1.07 – 2.8)
B/Brisbane/60/2008 -like	Day 1	1.11 (0.87 – 1.41)	0.77 (0.55 – 1.08)	0.89 (0.71 – 1.12)	1.06 (0.47 – 2.37)	[TIV – ADJ N=1076] 0.98 (0.9 – 1.08)	0.99 (0.65 – 1.5)
	Day 22 ^b	1.03 (0.81 – 1.32)	1.29 (0.9 – 1.86)	1.14 (0.91 – 1.42)	1.34 (0.63 – 2.82)	1.09 (1 – 1.19)	1.26 (0.85 – 1.89)

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease

Bold: Day 22 Vaccine group GMT ratio significant with a 95% CI lower bound of >1.

^a Neurological/neuromuscular or metabolic disorders including diabetes mellitus.

^b Day 22 GMTs, GMT ratios, and confidence intervals are adjusted for baseline titer.

Source: Adapted from - BLA 125510; Clinical Study Report V70_27

Seroconversion: Across all subgroups with underlying chronic conditions, a higher percentage of subjects in the TIV-ADJ group than in the TIV-NONADJ group seroconverted by day 22. Statistically significantly higher responses in several chronic-condition subgroups were seen for the homologous A/H3N2 strain and in the neurological/neuromuscular or metabolic disorders subgroup were seen for both A/H1N1 and A/H3N2 strains.

6.11.4.3 Previous pandemic H1N1 vaccination subgroup analysis (FAS; homologous strains)

Approximately 2% of subjects in either vaccine group had received H1N1 pandemic vaccination in the 6 months preceding vaccination (79 subjects and 74 subjects, respectively, in the TIV-ADJ and TIV-NONADJ groups).

In all analyses (GMT ratios, seroconversion, and percentage of subjects with HI titer ≥ 40), TIV-ADJ induced a greater response than TIVNONADJ against all 3 homologous strains, but no statistical significance testing comparing vaccine groups among previously-vaccinated subjects was carried out because of the small sample sizes.

6.11.4.4 Baseline serology status subgroup analysis (FAS; homologous strains)

At baseline, approximately half of subjects across vaccine groups in the FAS had a HI titer ≥ 10 against homologous B (49% in each vaccine group) and A/H1N1 strains (52% and 50% in the TIV-ADJ and TIV-NONADJ groups, respectively), while a majority of subjects had a HI titer ≥ 10 at baseline against the A/H3N2 strain (86% in each vaccine group).

GMT: Regardless of baseline serostatus, TIV-ADJ induced statistically significantly higher antibody responses at day 22 than did TIV-NONADJ against all 3 homologous strains.

Seroconversion: In both subgroups (baseline titer < 10 or ≥ 10), the TIV-ADJ group showed higher percentages of seroconversion rates (including ≥ 4 -fold increase in titers) than the TIV-NONADJ group against all homologous strains at day 22 with all differences being significant except for that of the group with HI titer < 10 against the homologous B strain.

6.11.4.5 Immunogenicity subgroup analysis by country (Homologous Strains)

The study enrolled subjects ≥ 65 years of age from 4 countries: Colombia (14%), Panama (3%), the Philippines (53%), and the USA (30%). Immunogenicity was assessed based on country of enrollment.

In all countries, the homologous A/H3N2 strain had the highest percentage of subjects who were positive (e.g., HI titer > 10) at baseline. The US had the highest percentages of subjects with baseline titers > 10 (A/H1N1: 62% to 65%; A/H3N2: 78% to 79%; and B-strain: 57% to 58% for TIV-ADJ and TIV-NONADJ, respectively). The country with the lowest percentages of subjects with HI titer > 10 at baseline was the Philippines (A/H1N1:

21% to 20%; A/H3N2: 73% to 71% for TIV-ADJ and TIV-NONADJ, respectively; and B-strain: 13% [both vaccine groups]).

GMT: After adjustment of day 22 GMTs for baseline titer, subjects in all countries had statistically significantly higher responses to TIV-ADJ compared with TIV-NONADJ against all 3 homologous strains, with the exception of the response to the B strain in Panama and the A/H1N1 and B homologous strains in the Philippines. The most salient difference among countries was against the A/H3N2 strain, where the day 22 GMT ratio was 2 among subjects in Panama, with ratios of 1.47 to 1.78 in the other countries. Differences in response to the A/H1N1 strain were within the range (for day 22 GMT ratio) of 1.35 through 1.47 across countries. The difference in response to TIV-ADJ versus TIV-NONADJ was less pronounced for the B strain, with day 22 GMT ratios of 1.08 to 1.3 across countries.

Seroconversion:

In all countries except Panama, there was a significantly higher percentage of subjects in the TIV-ADJ group than in the TIV-NONADJ group who seroconverted against all 3 homologous strains. In Panama, while that relationship held true for all 3 strains, it was statistically significant only for the A/H3N2 strain.

With respect to comparison of subjects from the Philippines with subjects from the US, the differences between vaccine groups were markedly greater among US subjects; this was true for all 3 strains. Specifically, against the A/H1N1 and A/H3N2 strains, the difference in percentages of subjects who seroconverted (TIV-ADJ minus TIV-NONADJ) was 14.3% and 18.8%, respectively, in the US and 7.6% and 10%, respectively, in the Philippines.

6.11.4.5 Immunogenicity subgroup analysis by race (FAS; Homologous Strains)

The racial and ethnic makeup of participating subjects reflected the composition of the general population of their respective countries (e.g., all Filipino's were Asian; most Americans were Caucasian). In fact, the predominance of a single race/ethnic group in participating countries resulted in a high correlation between "country" and "race," making it difficult to statistically separate the potential effects of these two variables. Nevertheless, an analysis stratified by race/ethnicity was conducted. The results were similar to the by-country stratified analysis in section 6.11.4.4 above.

6.11.4.5 Immunogenicity subgroup analysis by Sex (FAS; Homologous Strains)

Additional immunogenicity assessments were performed by gender. There were more women than men in each vaccine group (in both the FAS and the PPS: TIV-ADJ 64% female and TIV-NONADJ 66%).

There were no apparent differences between male and female subjects in differential responses to the TIV-ADJ versus the TIV-NONADJ vaccines. That is, in both genders, there was a statistically significantly higher response in the TIV-ADJ group than in the

TIV-NONADJ group against all 3 homologous strains with regards to day 22 GMT, against both A homologous strains for both genders, and the B strain for males only with regard to seroconversion rates, and percentages of subjects with HI titer ≥ 40 .

6.11.7 Immunogenicity Conclusion

Primary Immunogenicity Objectives:

Lot-to-lot Consistency: Lot-to-lot consistency for the 3 consecutive TIV-ADJ lots was demonstrated.

Non-inferiority and Superiority comparisons, homologous strains:

- TIV-ADJ was non-inferior to TIV-NONADJ against all 3 homologous strains using the predefined requirements (i.e., the day 22 GMT ratio had a 95% CI with a lower bound >0.67 and the day 22 seroconversion rate had a 95% CI with a lower bound $>-10\%$ for the PPS).
- Superiority of TIV-ADJ to TIV-NONADJ in terms of GMT ratio and seroconversion rate against homologous strains was not achieved, as the lower limit of the 95% CI for at least two of the three strains did not meet the pre-specified superiority criteria.
- Statistically significantly higher GMTs (ratio >1) and seroconversion rates (difference >0) for TIV-ADJ compared with TIV-NONADJ were demonstrated for all homologous strains.

Secondary Immunogenicity Objectives:

Non-inferiority and superiority of TIV-ADJ compared with TIV-NONADJ for homologous strains in high risk subjects with predefined comorbidities:

- TIV-ADJ was non-inferior to TIV-NONADJ among high-risk subjects against all 3 homologous strains using the predefined requirements, i.e., the day 22 GMT ratio had a 95% CI with a lower bound >0.67 and the day 22 seroconversion rate had a 95% CI with a lower bound $>-10\%$ for the PPS.
- Superiority of TIV-ADJ to TIV-NONADJ in terms of GMT ratio and seroconversion rate against homologous strains among high-risk subjects was not achieved, as the lower limit of the 95% CI did not meet the pre-specified superiority criteria.
- Statistically significantly higher GMTs (ratio >1) and seroconversion rates (difference >0) for TIV-ADJ against the 2 homologous A strains compared with TIV-NONADJ were demonstrated among high-risk subjects.

Non-inferiority of TIV-ADJ compared with TIV-NONADJ for all 3 heterologous strains and Superiority of TIV-ADJ compared with TIV-NONADJ for at least 2 of 3 heterologous strains in all subjects and in high-risk subjects with predefined comorbidities:

- TIV-ADJ was non-inferior to TIV-NONADJ against heterologous strains using the predefined requirements for all subjects and subjects in the high-risk subgroup (i.e., with specified underlying chronic conditions).

- TIV-ADJ was not superior to TIV-NONADJ against heterologous strains among all subjects or among the high-risk subgroup.

Clinical effectiveness:

- There was no significant difference in the clinical effectiveness observed between vaccine groups after a single dose, in terms of the incidence of ILI, exacerbation of preexisting chronic conditions, healthcare utilization, or mortality in the 12-month follow-up period.
- There was also no significant difference between vaccine groups when clinical effectiveness was evaluated in the high-risk subgroup.

6.12 Safety Results and Evaluation

6.12.1 Extent of Exposure

Almost all (>99%) enrolled subjects received 1 of 2 study vaccines; 27 subjects did not receive a study vaccine. All randomized subjects who received a study vaccine and provided post-vaccination safety data were included in the safety set. The reasons for exclusion from the safety set were that subjects had not received a vaccination or had not provided safety data. Safety laboratory tests were performed on a subset of subjects from the antibody persistence group and included 3% of enrolled subjects.

6.12.2 Adverse Events

An overview of solicited local and systemic reactions from 6 hours through 7 days post-vaccination is provided in table 28. Higher percentages of subjects in the TIV-ADJ group than in the TIV-NONADJ group reported such reactions.

Table 29: Number (%) of subjects overall with solicited reactions

	TIV-ADJ N=3505	TIV-NONADJ N=3495
Any	1619 (46%)	1164 (33%)
Local ^a	1137 (32%)	593 (17%)
Systemic	1120 (32%)	902 (26%)
Other ^b	210 (6%)	165 (5%)

^a Erythema, induration, and swelling were assessed by measuring with a ruler; continuous data were categorized as <25 mm, 25 to ≤50 mm, 51 to ≤100 mm, and >100 mm. For the purpose of this table, any measurement of <25 mm was considered no reaction and is not included.

^b 'Other' refers to remaining at home due to any post-vaccination reaction or use of analgesic/antipyretic medication.

Source: Adapted from - BLA 125510; Clinical Study Report V70_27, tables 12.2.1.1-1, 14.3.1.2.1 and 14.3.1.2.4.

When analyzed by age cohort, subjects over 75 years of age reported fewer reactions than subjects 65 through 75 years for both local and systemic reactions, irrespective of vaccine group. Within the TIV-ADJ group, 34% of younger subjects reported local reactions, while 27% of older subjects did so; likewise, systemic reactions were reported by 33% and 29%, respectively, of younger and older subjects in the TIV-ADJ group (no statistical testing was done for these comparisons).

6.12.2.1 Immediate Adverse Events

Ten percent (10%) of subjects receiving TIV-ADJ and 8% of those receiving TIV-NONADJ had a solicited AE within 30 minutes of vaccination. The most common AE was pain, with 5% and 4% for TIV-ADJ and TIV-NONADJ, respectively. The majority of AEs, including injection site pain, tenderness, erythema, and induration as well as fever, chills, myalgia, arthralgia, headache, nausea, vomiting, and diarrhea, were mild with $\leq 1\%$ reported as moderate in severity. Grade 3 (severe) AEs in the TIV-ADJ group included pain (2 subjects), headache (1 subject), myalgia (1 subject), and diarrhea (1 subject). One subject in the TIV-NONADJ group reported grade 3 myalgia. There were no anaphylactic episodes reported.

6.12.2.2 Solicited adverse events within 7 days of vaccination

In the time frame of 6 hours through 7 days after receiving either TIV-ADJ or TIV-NONADJ, 46% versus 33% had at least one reactogenicity sign, respectively. Local reactions were reported by 32% and 17% of recipients, respectively. The most commonly reported local reactions were injection site pain (TIV-ADJ, 25% vs. TIV-NONADJ, 12%) and tenderness (TIV-ADJ, 21% vs. TIV-NONADJ, 11%). Erythema, induration, and swelling (>25 mm in diameter) were reported by $\leq 1\%$ of subjects in both groups during that period. Systemic reactions were reported by 32% and 26% of subjects, in the TIV-ADJ and TIV-NONADJ groups, respectively. The most commonly reported systemic reactions were myalgia (15% TIV-ADJ vs. 10% TIV-NONADJ), headache (13% vs. 11%), and fatigue (13% vs. 10%). Less commonly reported systemic reactions were arthralgia (8% in each group), chills (7% and 5%), and diarrhea (5% each); others were reported by 1% to 4% of subjects in each vaccine group.

Severe reactions were balanced for both solicited local and systemic reactions and comprised $\leq 1\%$ of subjects in each group across all categories.

6.12.2.3 Unsolicited adverse events

During the period from day 1 through day 21, 16% of subjects in each of the vaccine groups reported at least 1 unsolicited AE. Unsolicited AEs considered by the investigator to be possibly or probably related to the study vaccination were reported by 4% and 5% of subjects in those groups, respectively. Nasopharyngitis (1% in both groups) and headache ($<1\%$ in both groups) were also the most common related AEs. Most of these AEs were solicited reactions that persisted beyond day 7.

The percentages of subjects with other categories of AE or who died were the same for both vaccine groups: SAE, 7%; AE leading to premature withdrawal, 1%; new onset of chronic disease, 6%; and death, 1%.

6.12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths occurred within 21 days of vaccination. Review of SAEs, deaths, and AEs leading to study withdrawal did not reveal imbalances by system organ class or evidence of relation to the vaccine (Table 29). The applicant captured new-onset chronic diseases and other AEs of special interest for one year following vaccine administration, whether

or not they met criteria for an SAE; review and analyses of these events did not reveal any new signals or imbalances.

Table 30: Overview of Deaths, SAEs, AEs Leading to Trial Withdrawal, or New-Onset Chronic Disease

Parameter	TIV-ADJ n (%)	TIV-NONADJ n (%)
SAEs (total)	264 (7%)	243 (7%)
SAEs (day 1-21)	19 (1%)	20 (1%)
Deaths (day 1-21)	0	0
Deaths (total)	52 (1.5%)	46 (1.3%)
AEs leading to study withdrawal (total)	52 (1%)	49 (1%)
AEs leading to study withdrawal (day 1-21)	4 (<1%)	2 (<1%)
New Onset Chronic Disease (total)	227 (6%)	223 (6%)
New Onset Chronic Disease (day 1-21)	18 (1%)	17 (<1%)

n: number of subjects with specified event

Source: Adapted from BLA 125510/0.0 Clinical Study Report Tables

6.12.3.1 Deaths

A total of 98 subjects (1.4%) died during the study; 52 deaths occurred in the TIV-ADJ group (1.5%) while 46 deaths occurred in the TIV-NONADJ group (1.3%; table 30 above). One subject (311/034) who received TIV-NONADJ died of Guillain-Barré syndrome; this AE was considered by the investigator to be related to study vaccine. A narrative for this event is provided in the CSR.

Four of the 98 subjects who died had verbatim causes of death that were different from the AE preferred term with outcome of death; 3 of these subjects had “unknown” listed as the verbatim cause of death but had at least 1 AE with death as an outcome. The remaining subject had a “cardiorespiratory arrest” as the verbatim cause of death but no AE with death listed as an outcome.

6.12.3.2 Nonfatal Serious Adverse Events

In both vaccine groups, 39 subjects (1% of the safety set) developed SAEs from day 1 through day 21 (table 30). Most SAEs were moderate to severe in intensity, the system organ class (SOC) with the largest number of subjects reporting an SAE was “infections and infestations,” with 7 subjects in the TIV-ADJ group and 4 subjects in the TIV-NONADJ group, respectively, reporting such an event. The only AE within that SOC to be reported by more than 1 subject was pneumonia, in 3 subjects.

In addition, 2 subjects and 3 subjects in the TIV-ADJ and TIV-NONADJ groups, respectively, reported SAEs in the SOC “cardiac disorders” and “respiratory, thoracic, and mediastinal disorders.”

6.12.3.3 New onset of chronic disease

In both vaccine groups, approximately 6% of subjects reported onset of new chronic disease during the study (table 30). The most commonly reported classes of these events (those reported by at least 50 subjects total in a given SOC) were “vascular disorders” (50 subjects and 51 subjects in the TIV-ADJ and TIV-NONADJ groups, respectively),

”metabolism/nutrition disorders (44 and 33 subjects),” ”musculoskeletal/connective tissue/bone disorders” (38 and 27 subjects, and ”cardiac disorders” (25 and 31 subjects). All of these AEs were moderate to severe in intensity and all but 2 were considered by the investigator to be unrelated to study vaccination. There were no notable differences between the vaccine groups in the proportion of subjects with new onset of chronic diseases.

6.12.4 Safety Conclusion

The adjuvanted trivalent influenza vaccine (TIV-ADJ) was more reactogenic than TIV-NONADJ; it was associated with higher incidences of local and systemic reactions. Within the 7-day post-vaccination period, a higher percentage of subjects in the TIV-ADJ group than in the TIV-NONADJ group reported any local or systemic reaction (46% vs. 33%, respectively).

Unsolicited AEs, including SAEs and AEs leading to withdrawal or new onset chronic disease were reported in similar percentages of the TIV-ADJ and TIVNONADJ groups. Most SAEs and other significant AEs were considered by the investigator to be not related to the study vaccination.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

V70_27 was a randomized, controlled, observer-blind study to assess the immunogenicity and safety of MF59C.1-adjuvanted trivalent influenza vaccine (TIV-ADJ) in comparison with a licensed, non-adjuvanted, trivalent influenza vaccine (TIV-NONADJ) in subjects 65 years of age and older in Colombia, Panama, the Philippines, and the United States. The majority of subjects, 53%, were in the Philippines; 30% were in the United States.

The co-primary study objectives:

- Three weeks after vaccination (at day 22), the 95% CIs of the vaccine group GMT ratios for each of the pairwise lot-to-lot group comparisons fell within the pre-specified equivalence range of 0.67 to 1.5. Therefore, immunological equivalence of the 3 TIVADJ lots was demonstrated against all homologous strains.
- The day 22 GMT ratio (TIV-ADJ: TIV-NONADJ) had a 95% CI with a lower bound >0.67 , and the day 22 seroconversion rate had a 95% CI with a lower bound $>-10\%$ for the PPS, satisfying the predefined requirements for non-inferiority. Hence, TIV-ADJ was demonstrated to be non-inferior to TIV-NONADJ against all 3 homologous strains.
- Superiority of TIV-ADJ to TIV-NONADJ in terms of GMT ratio and seroconversion rates against homologous strains was not achieved, as the lower limit of the 95% CI for at least two of the three strains did not meet the pre-defined superiority criteria. For the A/H1N1 and B strains, the vaccine group

- GMT ratios (table 10) were 1.36 (lower bound of 95% CI: 1.28) and 1.14 (lower bound of 95% CI: 1.08), respectively; for the A/H3N2 strain, the ratio was 1.61 (lower bound of 95% CI: 1.51). In terms of seroconversion difference (table 11); for the A/H1N1 and B strains, the differences were 9.5% (lower bound of 95% CI: 7.4%) and 3% (lower bound of 95% CI: 1%), respectively; for the A/H3N2 strain, the difference was 13.4% (lower bound of 95% CI: 11%).
- - Statistically significantly higher GMTs and seroconversion rates for TIV-ADJ compared with TIV-NONADJ were demonstrated for all homologous strains.

The non-inferiority comparisons of all secondary objectives met the pre-specified criteria and, hence, TIV-ADJ was demonstrated to be non-inferior to TIV-NONADJ for homologous strains in high-risk subjects with predefined comorbidities, and for the three selected heterologous strains in all subjects and in high-risk subjects with predefined comorbidities.

The pre-defined success criteria for superiority were not met for all superiority secondary objectives hence clinical superiority was not achieved for homologous strains in high-risk subjects with predefined comorbidities and for the three selected heterologous strains in all subjects and in high-risk subjects with predefined comorbidities.

Statistically significantly higher GMTs and seroconversion rates for TIV-ADJ against the two homologous A strains compared with TIV-NONADJ were demonstrated among high-risk subjects. Both day 22 GMTs and day 22 seroconversion rates were also significantly higher for TIV-ADJ than for TIV-NONADJ against both heterologous A strains.

Analysis of subgroups defined by various factors: age (65-75 vs. >75 years of age), presence of underlying chronic conditions, previous pandemic H1N1 vaccination, baseline serostatus, country, and gender – showed that immune response to TIV-ADJ was generally higher than that to TIV-NONADJ.

The adjuvanted trivalent influenza vaccine (TIV-ADJ) was associated with higher incidences of local and systemic reactions, i.e. a higher percentage of subjects in the TIV-ADJ group than in the TIV-NONADJ group reported any local or systemic reaction. But no imbalances in unsolicited AEs, deaths, SAEs, withdrawals due to AEs, or new onset chronic disease were reported.

10.2 Conclusions and Recommendations

Although the adjuvanted trivalent influenza vaccine (TIV-ADJ) was associated with higher incidences of local and systemic reactions, it elicited statistically significantly higher immune response than TIV-NONADJ in subjects ≥ 65 years of age, including subjects with chronic conditions who were at higher risk for influenza-related complications.

All the findings in the study indicate a statistically significant increase in immune response using the TIV-ADJ over TIV-NONADJ. I defer to the medical reviewers regarding whether the observed increase in immune response, although not sufficient to meet the pre-defined superiority criteria, may suggest benefit to the elderly population for whom high immune response is difficult to achieve.

No statistical reasons have been found to preclude approval of TIV-ADJ (FLUAD 65) as an inactivated influenza virus vaccine indicated for active immunization in persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.