Food and Drug Administration
Center for Biologics Evaluation and Research

139th Meeting of the Vaccines and Related Biological Products Advisory Committee

September 15, 2015

FDA White Oak Campus
Building 31, Great Room
Silver Spring, Maryland

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PROCEEDINGS (8:15 a.m.)

Agenda Item: Call to Order and Opening Remarks, Robert Daum, MD Chair

DR. DAUM: Good morning. We have a single agenda item today and I'm going to begin by asking the committee to introduce themselves and then we'll hear the Conflict of Interest Statement.

Dr. Tsai, could you begin by saying who you are and where you're from and maybe why you're here, and then we'll go around the table.

DR. TSAI: Sure. Good morning. My name is Ted Tsai. I'm with Takeda Vaccines and I'm the Pharma or industry representative to the committee.

DR. LONG: I'm Sarah Long, Chief of Infectious Diseases at St. Christopher's Hospital for Children and Professor of Pediatrics at Drexel University College of Medicine, and my interests are vaccines and vaccine-preventable diseases.

DR. GELLIN: I'm Bruce Gellin; I direct the National Vaccine Program Office at HHS.

DR. MC INNES: Good morning. I'm Pamela McInnes. I'm Deputy Director of the National Center for Advanced and Translational Sciences at the NIH.

DR. LEVY: Good morning. I'm Ofer Levy; I'm a

physician scientist at Boston Children's Hospital in Harvard Medical School. I'm a practicing clinician and I also lead a laboratory interested in vaccinology and immune ontogeny.

DR. PIEDRA: Good morning. My name is Pedro Piedra. I'm a pediatric infectious disease specialist by training. I'm at Baylor College of Medicine and I enjoy doing respiratory viral vaccine work.

DR. LEVANDOWSKI: I'm Roland Levandowski. I'm an independent infectious diseases and public health physician based here in Bethesda, and my background is research development, use and regulation of influenza vaccines.

DR. SAWYER: I'm Mark Sawyer. I'm a pediatric infectious disease physician from University of California San Diego at Rady Children's Hospital, and I also work with my local health department on the delivery of vaccines.

DR. ENGLUND: I'm Janet Englund, another pediatric infectious disease specialist at University of Washington and Seattle Children's Hospital. I also direct the Transplant Pediatric Infectious Disease Program at Fred Hutchinson Cancer Center, and I work a lot with vaccines.

DR. WHARTON: I'm Melinda Wharton. I trained in adult infectious diseases and am currently the Director of the Immunization Services Division at the Centers for

Disease Control and Prevention.

DR. DAUM: And now the FDA folks.

DR. WEIR: Jerry Weir, Director of the Division of Viral Products.

DR. GRUBER: My name is Marion Gruber. I'm the Director of the Office of Vaccines, Research and Review at CBER.

DR. BROWNE: Sarah Browne. I'm a medical officer in the Division of Vaccines and Related Product Applications.

DR. DAUM: Dr. Moore?

DR. MOORE: I'm Patrick Moore from the University of Pittsburg Cancer Institute. I'm the program leader in the cancer virology program. My training is in epidemiology and molecular biology.

DR. DAUM: Thank you. Dr. Pebsworth is our consumer representative and she is stuck in D.C. traffic and will be here a little bit later.

I am Robert Daum. I'm a pediatric infectious disease guy at University of Chicago.

I will now turn the floor over to Dr. Vijh, who will read the Conflict of Interest Statement.

Agenda Item: Conflict of Interest Statement, Sujata Vijh, Designated Federal Officer, VRBPAC

DR. VIJH: Thank you, Dr. Daum. I'm going to make a few administrative remarks and then read the Conflict of Interest Statement for the record.

Good morning, everyone. I am Sujata Vijh, the designated federal officer for today's Vaccines and Related Biological Products Advisory Committee meeting. Ms. Denise Royster is the committee management specialist for VRBPAC. She is being assisted by her colleague, Ms. Joanne Limkin, and they are both sitting probably outside.

On behalf of the FDA, the Center for Biologics Evaluation and Research and VRBPAC, we would like to welcome you all to the 139th VRBPAC meeting. Dr. Robert Daum is the Chair of VRBPAC. Today's session has one topic that is open to the public in its entirety. The meeting topic is described in the Federal Register Notice of July 17, 2015.

The FDA, CBER, press and media contact, Ms. Sarah Petticord, is probably in the audience. She is right there. If the press would like to reach out to her, she is sitting on the side.

Mr. John Bowers is our transcriptionist, who is right here, and Dr. Vicky Pebsworth is a consumer

representative who is just stuck in traffic and is on her way. She is a temporary voting consumer representative for the meeting.

Just a few remarks about the microphones. Please press the microphones to speak and remember to switch them off when you have finished talking. I believe only four microphones at a time can be used. Please speak clearly and loudly into the microphone because the transcriptionist, members of the public, those listening via webcast, everybody would like to hear your discussion.

Please check your cell phones and pagers and make sure they are in silent mode. Also, if you would like to pre-order lunch, there's a kiosk outside so that you don't have to wait in line because we have a short break. I would now like to read the conflict of interest statement for the meeting into the public record.

The Food and Drug Administration is convening today, September 15, 2015, for a meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all participants of the committee are special government employees or regular federal employees from other agencies and are subject to the federal conflict

of interest laws and regulations.

The following information on the status of this advisory committee's compliance with federal ethics and conflict of interest laws including, but not limited to, 18 US Code, Section 208, is being provided to participants at this meeting and to the public.

The FDA has determined that all members of the advisory committee are in compliance with federal ethics and conflict of interest laws. Under 18 US Code, Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees where financial conflicts of interest exist when it is determined that the agency’s need for a particular individual’s service outweighs his or her potential financial conflict of interest.

Relating to the discussions at this meeting, members and consultants of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them including those of their spouse or minor children and, for the purposes of 18 US Code, Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, CRADAs, teaching, speaking, writing, patents and royalties and primary

employment.

For the topic today, September 15, 2015, the committee will discuss and make recommendations on the safety and immunogenicity of a seasonal trivalent influenza vaccine, surface antigen, inactivated, adjuvanted with MF59 (Fluad) manufactured by Novartis. This is a particular matter involving specific parties.

Based on the agenda and all financial interests reported by members, consultants and speakers, no conflict of interest waivers were issued under 18 US Code Section 208.

Dr. Theodore Tsai is the industry representative who acts on behalf of all related industry representatives, is not a special government employee, and industry representatives do not vote. There may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employers and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest.

This conflict of interest statement will be

available for review at the registration table.

We would like to remind members, consultants and participants that if their discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with any firms, its products and, if known, its direct competitors.

This concludes my reading of the conflict of interest statement for the record, and I hand over the meeting to Dr. Daum.

DR. DAUM: Thank you, Dr. Vijh. Dr. Hudgens has joined and I'll ask him if he wouldn't mind introducing himself.

DR. HUDGENS: Sorry I'm late. Michael Hudgens, Associate Professor of Vital Statistics, University of North Carolina.

DR. DAUM: Thank you, Dr. Hudgens.

Dr. Vijh has indicated what the topic is under discussion today, and I'm going to call on the first speaker, who is Brenda Baldwin. Dr. Baldwin is the primary

reviewer, Office of Vaccines Research and Review, Division of Vaccines and Related Product Applications, and she will perform the introduction and presentation of questions for the committee to deal with.

Agenda Item: Introduction and Presentation of Questions, Brenda Baldwin, PhD, Primary Reviewer OVRR/DVRPA

DR. BALDWIN: Thank you for the introduction. Today's meeting will be about Fluad, which is an influenza vaccine that's adjuvanted with MF59C.1. The applicant is Novartis Vaccines and Diagnostics.

In terms of today's agenda, I will introduce the topic and then present the questions. This will be followed by presentations by Novartis and their representatives, and then FDA presentation of clinical data by Dr. Sarah Browne. This will be followed by an open public hearing and then committee discussion and vote.

As for background, I will discuss the currently licensed influenza vaccines for use in adults 65 years of age and older. I will provide a description of Fluad, an overview of the Fluad BLA, a regulatory perspective on inclusion of an adjuvant in vaccine formulations, what is present in the clinical package for Fluad, and then the questions to the committee.

In the United States, there are currently 12

licensed influenza vaccines for use in adults 65 years of age and older. Nine of these are trivalent influenza vaccines and three are quadrivalent influenza vaccines. The three quadrivalent influenza vaccines are egg-derived and inactivated. Of the nine trivalent vaccines, eight are inactivated and one is a recombinant HA vaccine. Three of these vaccines are manufactured by Novartis, and we will hear a little bit more about Agriflu in upcoming slides.

Fluad is the vaccine under discussion today. It is a trivalent inactivated subunit influenza vaccine, and it's manufactured using the same process as Agriflu. It is combined with MF59C.1, which is an oil-in-water emulsion adjuvant, and, of note, this adjuvant is not contained in any currently licensed U.S. vaccine. The proposed indication is for active immunization of adults 65 years of age and older against influenza disease caused by influenza subtypes A and type B contained in the vaccine.

Each 0.5 ml vaccine dose contains 45 micrograms of hemagglutinin, and this is egg-derived, and also contains MF59C.1 oil-in-water emulsion adjuvant. The adjuvant consists of squalene, polysorbate 80, sorbitan trioleate, sodium citrate dihydrate, citric acid monohydrate. It is supplied in a 0.5 ml single-dose prefilled syringe and is administered as one dose

intramuscularly.

Of note before I move on, I want to also highlight that Agriflu and Fluad have equivalent amounts of the HA protein at 45 micrograms.

The BLA that Novartis submitted was submitted on November 25, 2014 under the accelerated approval regulation, which is 21 CFR 601.41. Under the accelerated approval regulation, licensure is based on a surrogate marker that is reasonably likely to predict clinical benefit. For Fluad, this surrogate immune marker is the 22-day post-vaccination antibody response as measured by a hemagglutination inhibition assay, or HAI. Of course, demonstration of safety is required.

A confirmatory efficacy trial is also required to verify and describe the clinical benefits. Novartis will be performing this efficacy trial in the future.

The next couple of slides will provide the regulatory perspective on inclusion of an adjuvant in vaccine formulations. The Code of Federal Regulations defines adjuvants as constituent materials -- that's under 21 CFR 610.15. These regulations state, "All ingredients shall meet generally accepted standards of purity and quality…" and states further, "An adjuvant shall not be introduced into a product unless there is satisfactory

evidence that it does not adversely affect the safety or potency of the product." In other words, we are looking for, as with all vaccines, a positive benefit-risk profile.

An adjuvant is licensed in combination with an antigen; it is not licensed separately.

While the added benefit should be demonstrated in early clinical trials or animal studies, there is no requirement to demonstrate the added benefit in comparative Phase 3 clinical trials using the adjuvanted and unadjuvanted vaccine formulations. However, Phase 3 trials demonstrating the added benefit may be requested by the agency on a case-by-case basis; for example, if an applicant is planning to make a claim of superiority of their adjuvanted vaccine over their unadjuvanted vaccine in the package insert.

The clinical data that was provided in the BLA for Fluad included immunogenicity and safety data from one Phase 3 trial, and that was V70_27. This was a randomized, observer-blinded, multicenter trial with 7,104 total subjects who received either one of three lots of Fluad or Agriflu. One dose was administered intramuscularly to healthy adults 65 years of age and older. The primary immunogenicity objectives were to evaluate lot-to-lot consistency, non-inferiority and then superiority. The

primary safety objectives were to look at solicited adverse events, unsolicited adverse events, serious adverse events, new onset of chronic disease, other significant adverse events and adverse events leading to trial withdrawal.

There was additional supportive safety data from adults over 65 years of age that were performed between 1992 and 2013, and this consists of almost 28,000 subjects.

In summary, this VRBPAC is being convened to review and discuss Fluad safety and immunogenicity data. The committee will be asked to vote on whether the available data are adequate to support the safety and effectiveness of Fluad for use in adults 65 years of age and older.

Questions to the committee. One, are the immunogenicity data adequate to support the effectiveness of Fluad under the accelerated approval regulation for the prevention of influenza disease in adults 65 years of age and older? Please vote yes or no.

Number two, are the available data adequate to support the safety of Fluad when administered to adults 65 years of age and older? Please vote yes or no.

Thank you.

DR. DAUM: Are there any clarifying questions on Dr. Baldwin’s presentation from the committee?

DR. PIEDRA: Just one. In the conduct of the efficacy trial does the outcome matter, or is just that an efficacy trial has to be performed?

DR. BALDWIN: Obviously, they would have to prove that there was efficacy with this vaccine.

DR. DAUM: I see no further questions and we can move on to the Novartis presentation. Novartis is now going to present a series of talks. They have asked, and I reluctantly agreed, to present all of their talks and have clarifying questions from the committee at the end of their presentations. We discussed this and this is what we decided to do.

The first talk will be the introduction by Dr. Mansi, then the disease burden by Dr. Talbot, who is an Assistant Professor of Medicine at Vanderbilt. Then the mechanism of action of this vaccine by Dr. Singh, the immunogenicity of this vaccine by Dr. Heijnen, then the safety of the vaccine by Dr. Lindert and, finally, the benefit-risk performance of the vaccine by Dr. Van Buynder, staff specialist in public health, GCHHS, and an adjunct professor at Simon Fraser University.

We will hold clarifying questions until all of these Novartis presentations have been given. It’s only an hour and a quarter, according to Novartis folks.

Sponsor Presentations – Novartis Vaccines and Diagnostics, Inc.

Agenda Item: Introduction, James Mansi, PhD, Novartis

DR. MANSI: Good morning, Mr. Chairman, Members of the Vaccines and Related Biological Products Advisory Committee, and Members of the Food and Drug Administration. My name is James Mansi, head of Medical Affairs at Novartis Influenza Vaccines. I'd like to thank you for this opportunity to present the data supporting our adjuvanted trivalent influenza vaccine known as aTIV.

aTIV represents an important option in the fight against seasonal influenza in people 65 years of age and older. aTIV met non-inferiority in the pivotal study and demonstrated an enhanced immune response compared to TIV while maintaining an acceptable safety profile.

Influenza is a highly communicable acute respiratory disease that is recognized as an important cause of hospitalization and death, especially in older adults. For the last 35 years, in each influenza season, 5 percent to 20 percent of the United States population is typically infected. The resulting burden is significant. Between 3,300 to more than 48,000 people die from an illness related to the flu each year. Approximately 90

percent of these deaths occur in those over 65 years.

Additionally, about 226,000 individuals are hospitalized each year due to influenza, and 63 percent of them are older adults. Importantly, once an older patient is hospitalized, there is a rapid decline in their health status and quality of life.

This burden of influenza in the elderly is largely driven by immunosenescence, the age-related decline of the immune system. With respect to this burden of illness, one subtype, H3N2, is particularly problematic in older adults. When H3N2 predominates, either alone or along with another strain, we see higher seasonal surges in mortality. This graph shows the number of influenza-associated deaths from 1976 through 2007 with the dominant strains highlighted by year. H3N2 predominated in more than 70 percent of the seasons, as shown in red or blue. Additionally, we see the highest mortality rates in seasons where H3N2 alone predominated.

The importance of influenza vaccination in the prevention of seasonal influenza is well recognized. However, standard influenza vaccines produce a sub-optimal immune response in older adults. One way to enhance the immune response to influenza vaccines is through the addition of an adjuvant. MF59 is the proprietary oil-in-

water emulsion adjuvant component in aTIV. Essentially, MF59 enhances the magnitude, breadth and duration of the immune response. Each 0.5 ml dose of aTIV contains 15 micrograms of influenza virus hemagglutinin surface antigens from each of the three virus strains and MF59.

aTIV is supported by an extensive clinical development program spanning 39 clinical trials that have enrolled over 27,000 adults age 65 years and older. Sixteen of these are open-label studies and 23 are randomized clinical trials comparing aTIV to TIV. In today's presentation we will review data from the 23 randomized control trials with a primary focus on data from our pivotal trial.

We will also describe 16 first-dose randomized control trials which include the pivotal trial and seven revaccination studies. Also included in the presentation are data from two large observational studies that provide insight into the potential effectiveness of aTIV.

The 17 years of post-marketing experience represents a robust global safety database. Taken together, we will show that the data demonstrate a positive benefit-risk profile supporting accelerated approval of aTIV.

The clinical program supporting aTIV spans more

than 20 years with the first clinical trials having begun in 1992. Since then, aTIV has been reviewed and approved by many health authorities. It was approved for use in Europe for people 65 years of age and older in 1997. In 2011, aTIV was approved in Canada for the same indication, and then in 2015 it was approved in Canada for pediatrics. aTIV is currently approved in more than 30 countries worldwide with more than 76 million doses distributed across the various countries.

Accelerated approval requires a surrogate endpoint reasonably likely to predict clinical benefit. Our pivotal study followed the CBER criteria for an adequately-powered non-inferiority immunogenicity trial of HI antibody responses as compared to a U.S.-licensed seasonal influenza vaccine. We are also committed to conducting a confirmatory study to demonstrate clinical benefit in patients. The proposed indication for aTIV is for active immunization in persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B.

With this information in mind, let’s look at the agenda for today’s presentation. First, we have Dr. Keipp Talbot, Assistant Professor of Medicine from Vanderbilt University. Having widely published on the burden of

respiratory illness, vaccine efficacy and correlates of immunity in older adults, Dr. Talbot will discuss the current unmet medical need for enhanced influenza vaccines.

Dr. Manmohan Singh will then describe the mechanism of action of MF59. Dr. Esther Heijnin will describe the immunogenicity data of aTIV followed by Dr. Lindert who will discuss the safety data. Lastly, we have Dr. Paul Van Buynder with us today who has extensive public health experience with aTIV in seasonal programs in Canada. He will provide the clinical context of aTIV and talk about its benefit-risk. We also have Martin Roessner, biostatistician, and Diana Noah, serology expert, to address your questions.

All external experts have been compensated for their time and travel to today's meeting. I would now like to invite Dr. Talbot to the lectern.

Agenda Item: Disease Burden, H. Keipp Talbot, MD, MPH, Vanderbilt University School of Medicine

DR. TALBOT: Good morning. I'm delighted to be here because I like to talk about influenza a lot, especially in older adults, and the types of vaccines we need to address this issue and this disease.

Influenza is one of the top ten causes of death in people over 65 years of age and is a leading cause of

morbidity in older adults. Influenza-associated deaths remain high, and this is in part due to immunosenescence or the aging of the immune system, or the dysregulation of the immune system. Immunosenescence not only increases the incidence and severity of infections but also reduces a patient's ability to respond to immunization. These two issues create a particular unmet need in the older population.

It may not be currently known, but our current influenza vaccine was designed for young military recruits. As a result, influenza immunization does help reduce the risk of severe disease due to influenza, but the current options are suboptimal in the level of protection provided. So what would an ideal vaccine look like in this population? Well, an ideal vaccine would provide a strong immune response. It would offer a wide breadth of protection not only to homologous but also to heterologous strains, and would provide protection for the duration of the influenza season.

Compared to younger adults, immune response for older adults to standard vaccine is low. This figure highlights the much lower antibody responses to influenza vaccine in older adults, which are shown in yellow, compared to younger adults, shown in blue. There is

certainly a need to elicit higher antibody responses in older adults as higher antibodies correlate to better seasonal protection.

In addition, it’s essential that influenza vaccines not only elicit a strong immune response, but that the stronger immune response covers each of the individual vaccine strains. Although efficacy against all strains is suboptimal, these data illustrate that efficacy has been particularly low for H3N2. This was especially problematic during this past season. Among patients over 65 years of age we had the highest influenza-associated hospitalization rate in a decade.

One remaining issue is the importance of persistence. Influenza immunization often occurs early in the fall with many older adults lining up as soon as the vaccine is available in August or September. However, the period of influenza circulation varies yearly and sometimes lasts as late as April, which leaves a very large time period between immunization and possible exposure to influenza. This means antibodies need to persist over a long period of time.

The current options in seasonal influenza vaccine for older adults are limited. It is well recognized that the conventional vaccines produce suboptimal responses for

this population. The only current vaccine that directly addresses immunosenescence is the high-dose inactivated vaccine. This vaccine uses four times the dose of traditional vaccine in order to overcome immunosenescence. The higher antibody titers correlate with higher efficacy compared to conventional vaccine. It's imperative that we have enough vaccine to ensure adequate supply to this high-risk population.

In view of the limitations of current vaccines, there has been increasing recognition of the need for new-generation influenza vaccines. Ideally, these new vaccines will provide more consistent and broader coverage across all seasonal virus subtypes and variants. Enhanced vaccines are needed.

I want to thank you for your time and introduce Dr. Singh, who will discuss the mechanism of action for aTIV.

Agenda Item: Mechanism of Action, Manmohan Singh, Novartis

DR. SINGH: Thank you. I am Manmohan Singh, Head of Translational Research at Novartis Vaccines. I would like to briefly review the mechanism of action of aTIV with particular attention to the adjuvant component of this vaccine.

As Dr. Talbot mentioned, more immunogenic vaccines are needed for the older population, and adjuvants enhance this immune response. Aluminum salts have been included in licensed vaccines as an adjuvant for nearly 100 years and have an excellent safety profile. However, aluminum salts are not effective adjuvants for flu vaccines; therefore, we sought an alternative.

MF59, the adjuvant in aTIV, enhances the immune response and has an acceptable safety profile. MF59 is an oil-in-water emulsion in which droplets of squalene and surfactants are suspended in a citric buffer. It's this droplet structure that is critical for the adjuvant effect. No single component of MF59 enhances immunogenicity.

When selecting an adjuvant for use in a vaccine we look for certain attributes that enhance the immune response without any immediate or long-term side effects. The adjuvant must also be biocompatible, rapidly eliminated and demonstrate long-term stability. Oddly, it should also have the potential to improve efficacy with the same or lower amounts of antigen.

When developing MF59 we sought to achieve these key attributes. To achieve these we comprehensively evaluated each component of MF59. The final composition represents a balance that optimizes immunogenicity, safety

and formulation stability. Squalene is a natural component of the human body and is eliminated from the injection site within hours. The surfactants are commonly used in other approved parenteral products as well. The small and controlled droplet size keeps viscosity low for ease of injection and allows for sterile filtration. MF59 does not act as an antigen depot, and antigen binding to the droplet is not necessary for the adjuvant effect.

MF59 provides additional advantages when combined with the flu vaccine which may translate into improved efficacy for older adults. According to preclinical data, MF59 acts primarily locally and it improves the titer, breadth and duration of antibody responses to flu vaccines. It also enhances T-cell and memory responses. Additionally, MF59 adjuvant can be manufactured consistently and has a shelf life of several years, contributing to a reliable vaccine supply.

MF59 adjuvanted vaccines elicit greater CD4-positive T-cell responses in mice. The higher antigen-specific T-cell response is important because CD4-positive T-cells help produce long-lasting B-cell membrane and high titer neutralizing antibodies. Therefore, the effect of MF59 on T-cell responses may in part explain the improved antibody responses observed in clinical trials.

Let me present our current understanding of how MF59 works. Based on data from animal studies, we know that MF59 acts predominantly at the injection site creating a local influx of immune cells within the muscle. It then increases antigen presentation in the draining lymph nodes. Importantly, the adjuvant effect is localized to the injection site and draining lymph node.

MF59's mechanism of action can be described in three basic steps. First, MF59 recruits immune cells at the site of injection. The cells that are recruited are primarily monocytes, macrophages, neutrophils and dendritic cells. Second, MF59 differentiates recruited immune cells into antigen-presenting cells. With the MF59 adjuvanted vaccine, more antigen is transported from the injection site to the draining lymph node. Third, within the lymph node, MF59 leads to T-cell activation and an increased B-cell expansion.

Let's look at how this mechanism translates into response in the clinical setting. We initially performed animal studies to examine increased breadth of response. These results were confirmed in an earlier study published by Ansaldi, et al, which showed that aTIV improved the immune response in older adults. In this study, pre and post-vaccination sera from older adults was collected.

Investigators examined antibody responses using conventional measurements against three drifted H3N2 strains. H3N2 strain was chosen because it has the greatest antigenic variability or the shortest number of years compared to the generally more consistent H1N1 and B strains.

The data show sera protection and seroconversion percentages for both aTIV and TIV-vaccinated groups. In the first two columns, you can see the responses to A/Wyoming, the vaccine strain. The person's seroconversion against the vaccine strain was significantly enhanced in those receiving aTIV. The immune response was also improved with aTIV against strains that were antigenically distinct from the vaccine strain. The strains chosen represent some of those that could have been co-circulating during the season. This is important because this increased immune response could improve protection against drifted strains.

In summary, the mechanism of action of MF59 is well characterized and supports observed clinical safety profile. Its enhancement of antigen presentation at the injection site and interactions in the draining lymph node follow well-established immune pathways. MF59 enhances the magnitude, breadth and durability of the immune response.

Thank you. I will now turn the presentation over to Dr. Heijnen to review the immunogenicity results of aTIV.

Agenda Item: Immunogenicity, Esther Heijnen, Novartis

DR. HEIJNEN: Thank you. I am Esther Heijnen, Head of the Global Clinical Program, and I will now present immunogenicity data supporting adjuvanted TIV for accelerated approval.

Data from our clinical development program demonstrate that aTIV is non-inferior to the comparator and generated higher antibody titers against homologous and heterologous influenza A and B strains. Additionally, the data show higher antibody titers up to 12 months after vaccination for H3N2.

Let me begin with an overview of the clinical development program supporting the benefit of aTIV in older adults. First I will describe our pivotal study V70_27, and then I will describe the supportive data including 15 additional first-dose randomized controlled trials to show consistency in response in subjects. In these trials, aTIV was compared to a non-adjuvanted influenza vaccine.

I will also touch on our seven revaccination trials. These provide information regarding repeat

vaccination with up to three doses in consecutive seasons. Now let me walk you through the pivotal V70_27 study design.

The pivotal study was designed to evaluate immunogenicity and safety of aTIV. Our pivotal study was randomized, controlled, observer-blinded and multi-centered. 7,104 study participants were randomized in this trial in a 1-1-1-3 ratio and they were allocated to one of three lots of adjuvanted TIV or to a non-adjuvanted seasonable influenza vaccine, shown here as TIV. The TIV was a U.S.-licensed comparator that had the same antigen content as the test vaccine and is approved for use in older adults.

Individuals received a single dose of vaccine on day 1, and this is the start of the treatment phase. The treatment phase lasted until day 22 when the co-primary objectives were evaluated. Participants were followed for safety until one year after vaccination. Additional blood samples were taken at day 181 and day 366 to evaluate persistence of the vaccine.

Our pivotal study included men and women aged 65 years and older, and both healthy individuals and those with comorbidities were included in the trial. Comorbidities included chronic but stable underlying health

conditions. Excluded from the trial were individuals with known or suspected impairment of immune function, a history of allergy to vaccine and those who had received vaccination against seasonal influenza in the previous 6 months.

Let's now look at the study objectives. The initial immunogenicity objective was to evaluate the immunologic equivalence of three consecutive lots of aTIV. This was measured by GMT at day 22 for each virus strain. The 95 percent confidence intervals of GMT ratios all fell within the pre-specified equivalent rate of 0.67 to 1.5. Therefore, we achieved the first immunogenicity objective of lot equivalence.

The next step was to pool data from those receiving vaccine from any of the three lots into a single aTIV group, and this allowed us to compare those receiving aTIV with the non-adjuvanted TIV.

The second co-primary objective was to assess the non-inferior immunogenicity of aTIV compared to TIV. This was based on hemagglutination antibody responses for the homologous influenza strains. Homologous strains refers to influenza strains recommended by the WHO for use in the vaccine.

As you have heard, achieving non-inferiority is a

criterion for accelerated approval per the 2007 CEBR guidance. The objective was met if non-inferiority was shown for both GMT and seroconversion for all three influenza strains. To show non-inferiority, the lower bound of the 95 percent confidence interval of the GMT ratio had to be equal to or larger than 0.67, and the lower bound for seroconversion rate differences had to be equal to or larger than -10 percent.

Once non-inferiority was established, results were analyzed for superiority. The superiority objective required demonstration of superiority by GMT ratio and seroconversion for at least two out of three influenza strains. To show superiority, the lower bound of the 95 percent confidence interval of GMT ratios had to be larger than 1.5, and the differences in the seroconversion rate had to be larger than 10 percent.

The secondary objective included evaluating immunogenicity in older adults with pre-specified underlying conditions -- the comorbidity subset. In addition, we evaluated HI responses to heterologous influenza strains. These strains are variants of the same type included in the vaccine that are not included in the vaccine composition. To assess HI antibody persistence following vaccination we analyzed antibody titer 6 and 12

months after vaccination.

Now turning to the results, starting with the populations used for the analysis, 3,552 individuals were randomized to aTIV. And of those, more than 99 percent went on to receive vaccination. We tested the superiority objective on the full analysis set, or FAS, and non-inferiority was tested on the per protocol set, or PPS. The PPS included all subjects in the FAS who had no major protocol deviation. Approximately 8 percent of individuals in both treatment arms had major protocol deviations and were excluded from the PPS.

We also evaluated the subset of 887 subjects exposed to aTIV for heterologous strains and a subset of 189 subjects exposed to aTIV for persistence. Here you see the baseline demographics from the full analysis set. Groups were well-balanced between aTIV and TIV. The mean age was 72 years, and two-thirds were female. Thirty percent of study participants were enrolled from centers in the U.S., 53 percent of participants were Asian, 28 percent were Caucasian, and 18 percent were Hispanic. The percentage of individuals in each ethnic group was similar between study arms, and the baseline demographics were similar for the per protocol set.

Thirty-seven percent of those enrolled in both

treatment arms had comorbidities. In addition, we evaluated sero-positivity, meaning an HI titer of greater than or equal to 10 at baseline. Approximately 50 percent were seropositive for H1N1 and for B, and 86 percent of individuals were seropositive at baseline for H3N2.

The non-inferiority objective comparing aTIV to a U.S.-licensed comparator was met in the pivotal study. For all three strains included in the vaccine, the lower bound of the 95 percent confidence interval for GMT ratios for homologous strains was above 0.67, and the lower bound of the 95 percent confidence interval for seroconversion was above -10 percent for all three strains.

The superiority objective was not met in the pivotal study. Of note, aTIV met the superiority threshold for difference in seroconversion against the H3N2 strain. The day 22 GMTs against each of the three homologous strains in the aTIV group exceeded 1. This indicates higher titers in the aTIV group compared to the TIV group for all three influenza strains. In addition, the differences for seroconversion exceeded 0, indicating higher seroconversion rates for aTIV.

We also conducted an analysis on individual subgroups. Subgroups evaluated were gender, race, age, country and sero-positivity status at baseline. For

brevity, this slide shows the results of the H3N2 strain. Non-inferiority was demonstrated across all subgroups for all three strains, and the results for the U.S. are consistent with the results for the other countries.

Now turning to the results of the secondary objective in the pivotal study, aTIV met non-inferiority criteria within a subset of subjects with underlying comorbidities based on the GMT ratios. The lower bound of the 95 percent confidence intervals well exceeded the 0.67 non-inferiority margin for all three strains. GMT ratios also exceeded 1, indicating higher titers in the aTIV group. aTIV also achieved non-inferiority in individuals with comorbidities for sero-conversion.

aTIV also met non-inferiority criteria in regard to GMT ratios for heterologous strains. These included two H3N2 strains and one B strain. The lower bound against both of the heterologous H3N2 strains exceeded 1. Again, this indicates a higher response for aTIV compared to TIV. Results for sero-conversion show a similar pattern.

Now moving to the secondary objective of persistence, the results at days 181 and 366 were consistent across all three strains with the non-inferiority results at day 22. In addition, at 6 and 12 months, the lower bound of the H3N2 strain exceeded 1.

In addition to our pivotal study, we have data from an additional 15 randomized controlled trials and seven revaccination trials which support our application. These support findings in our pivotal trial and a consistent response after repeated yearly vaccinations.

We took a look at trends across randomized controlled trials involving older adults by performing a meta-analysis including 15 RCTs and the pivotal trial. All RCTs included in the meta-analysis tested aTIV against a non-adjuvanted comparator. They were observer-blinded and included measurements of pre and post-vaccination HI antibody responses. In four of these trials, HI antibody responses to heterologous influenza strains were also evaluated.

To observe the immunogenicity of aTIV with repeat dosing in consecutive seasons we evaluated the immune response of participants in seven revaccination studies.

The results from the meta-analysis of the 16 RCTs are supportive of the observations from pivotal study V70_27. The meta-analysis showed higher seroconversion rates and higher GMT ratios for aTIV versus TIV for all three strains tested.

Three trials, in addition to the pivotal study, evaluated antibody responses to influenza antigens not

included in the vaccine composition. The results of the three trials shown here below the pivotal trial are supportive of the pivotal study. GMT ratios for heterologous strains of the aTIV are in general higher compared to TIV.

Results from a retrospective analysis of revaccination studies suggested that the increased response of aTIV versus TIV was consistent with repeated annual vaccinations. Five extension studies evaluated the annual administration of two consecutive vaccinations, and in two studies we also followed subjects for a third dose. Again, for simplicity, this slide shows the results for the H3N2 strain.

In all of these studies, the point estimates suggested high GMT ratios in aTIV compared to TIV for repeat doses. Although not shown here, the sero-conversion rates also showed a similar profile with repeat dosing. Additionally, when we looked at the H1N1 and B strains we saw consistent results.

In conclusion, the immunogenicity data support accelerated approval of aTIV for the older population as aTIV was non-inferior against a U.S.-licensed comparator. Immediately after vaccination, aTIV generated higher antibody titers against homologous and heterologous

influenza A and B strains. In addition, we showed that aTIV versus TIV generates higher antibody titers for H3N2 up to 12 months post-vaccination. The higher antibody titers for aTIV versus TIV were also consistent after annual revaccination.

Now I would like to introduce Dr. Lindert to present aTIV safety profile.

Agenda Item: Safety, Kelly Lindert, MD, Novartis

DR. LINDERT: Thank you. I'm Kelly Lindert, Head of Development, and in my presentation today I will describe the safety data collected based on aTIV administration to older adults in different clinical settings. These data include 15 randomized controlled trials inclusive of our pivotal trial, seven revaccination studies, and 17 years of post-marketing experience based on more than 76 million doses of aTIV distributed outside of the United States.

The pivotal trial was a large randomized controlled study that compared the safety experience of aTIV with non-adjuvanted TIV. Safety data collection included solicited and unsolicited adverse events that were monitored within the period immediately after vaccination. A subset of the unsolicited adverse events were monitored for the full year.

The safety assessments demonstrated no differences in unsolicited adverse events -- 1.5 percent and 1.3 percent of individuals within the aTIV and TIV groups died within the year follow-up. Seven percent of participants experienced serious adverse events within the same interval. Fewer than 1 percent of subjects in each vaccine group withdrew from the study due to adverse event. Within the first three weeks after vaccination, 16 percent of individuals in both vaccine groups experienced unsolicited adverse events.

The sole noteworthy difference between vaccine groups was an increase in solicited adverse events within the week following vaccination. Let’s look more closely at the solicited adverse events.

There were two types of solicited adverse events collected in this study, local and systemic. This slide shows overall solicited local adverse event reporting. Overall, solicited local adverse event reporting was low. The more prevalent events were pain and tenderness at the injection site. While reporting rates were higher in the aTIV group, the majority of these events were mild to moderate in severity, and similar to other influenza vaccines.

The next slide examines the percentages of study

participants who reported severe solicited local adverse events. For solicited local adverse events, the number of study participants experiencing severe solicited local adverse events was low for each event, and the percentages were similar across the two vaccine groups. Additionally, no one reported a solicited local adverse event that was regarded as potentially life-threatening, or PLT.

Let’s now turn to the solicited systemic adverse events. Overall reporting of solicited systemic adverse events was low. Fewer than 20 percent of study participants reported any systemic adverse event even when solicited. Most of the events were mild to moderate in severity, and the most commonly reported events included myalgia, headache and fatigue. Among the solicited systemic adverse events, the greatest difference in reporting between vaccine groups was 6 percentage points for myalgia. As was observed for solicited local adverse events, few individuals experienced severe or potentially life-threatening events, and reporting of these events was balanced across both vaccine groups.

One important measure of solicited adverse events is how well they were tolerated by participants. In the pivotal study, the data reflect that the majority of participants did not require additional intervention due to

the solicited adverse events. Specifically, study participants were asked to report if they used analgesics or antipyretics specifically to mitigate the solicited adverse event. They were also requested to indicate if they stayed at home due to a solicited adverse event. In the study, 4.6 percent of those in the aTIV group reported use of analgesic or antipyretics to manage these events compared to 3.5 percent in the TIV group. And those individuals who stayed at home due to a solicited adverse event represented 3.0 and 2.4 percent of the study population, respectively.

Now I will review the unsolicited adverse events. This table shows the most common types of unsolicited adverse events observed in the three weeks following vaccination. As you can see, these are common symptoms that occur in an older population with and without vaccination, and the incidence of these events is similar between aTIV and TIV.

This next table summarizes the most common serious adverse events. These events were collected over a full year after vaccination. The percentages of individuals reporting serious adverse events were similar between vaccine groups, and the most commonly reported serious adverse events included types of infections,

cardiovascular events and exacerbations of other chronic diseases often experienced in an older population.

Here you see the percentages of individuals who died during the study. Importantly, the percentage of individuals who died were similar between the two vaccine groups, and most deaths occurred late in the observation period. The most common causes of death were cardiac disease, respiratory infections, cerebrovascular accidents and neoplasia.

Let’s discuss another type of safety category -- new onset of chronic diseases, or NOCDs. In this pivotal study we prospectively collected events referred to as NOCDs through the full year of safety follow-up. This is a relatively new safety endpoint that was added to influenza vaccine trial safety data collection. For this event, investigators were instructed to collect new reports of chronic diseases that were not otherwise experienced by people prior to vaccination.

As shown in this table, the reports of NOCDs in the aTIV and TIV groups were similar with approximately 6 percent of individuals in each group, and reporting across the system organ classes was comparable

We also have an additional source of clinical trial safety experience -- the randomized controlled trial

safety database. This safety database was selected for targeted analyses of less commonly-occurring events after vaccination. As this pooling of trials includes only observer-blinded, randomized controlled studies, it provides the most robust dataset to assess similarities and differences between aTIV and TIV in this older population.

The first type of events evaluated in this data pooling are referred to as adverse events following immunization, or AEFIs. The percentages of individuals reporting these events are similar between the two vaccine groups. These events are generally regarded as those that may represent an allergic, anaphylactic or pathophysiological response to vaccination. For this evaluation, the database was searched retrospectively for those terms listed here. We analyzed the individual case studies further and no safety concerns were identified.

This next slide shows the commonly detected adverse events of special interest. The most frequently reported AESIs in the aTIV group were arthritis, rheumatoid arthritis and hyperthyroidism. No safety concerns were identified, and the percentages of individuals experiencing these events fall well within the expected incidence of these types of conditions in an older population.

I would like to turn our discussion to the safety

experience following revaccination with aTIV and TIV vaccines. As mentioned earlier, there are seven clinical trials that included revaccination with aTIV and TIV. For these seven trials study participants received the same vaccination in years two and three, as was assigned in the original randomized controlled trial. I'd like to show you two different analytical approaches used in the evaluation of these revaccination studies.

In both analyses we saw similar trends in adverse event reporting. In the first analysis we focused only on individuals who were evaluated in both the parent as well as in at least one of the extension studies. Subjects who did not continue in the extension studies were not included in this analysis.

We saw that reporting of both solicited and unsolicited adverse events was decreased in year three relative to the parent vaccination study. However, in both vaccine groups there was an apparent rise in reporting of solicited and unsolicited adverse events in year two.

In the second analysis we included all subjects participating at any point in the parent and revaccination studies. This was to understand the more serious events such as AEs leading to hospitalization and death. As in the first analysis, overall safety reporting declined by

year three, but there was a rise in adverse event reporting in year two in both vaccine groups. Closer review of the clinical data did not suggest a pattern in the events, and the clinical significance of the year two trend is unclear.

Overall, the safety data in the revaccination studies reflected similar patterns to the safety data from the primary vaccination studies. There was no difference in unsolicited adverse event reporting including more serious adverse events, and somewhat higher reporting of mild and moderate solicited local adverse events in recipients of the aTIV vaccine.

Let me know move to our post-marketing experience. As we have over 17 years of experience in the collection of spontaneous safety data reporting following the distribution of over 76 million doses, for this filing, this safety database was also analyzed for reporting of potential AEFIs and AESIs. In addition, ongoing routine surveillance of all spontaneously reported cases has demonstrated a safety profile consistent with other licensed influenza vaccines and without detection of any novel safety signals.

Before we discuss the post-marketing data it may be helpful to review the approaches for the data analysis. Because post-marketing is not a direct head-to-head

comparison, as is performed in clinical trials, we use other methods to compare data. Every case that is reported in post-marketing is evaluated qualitatively to determine if there is a plausible association between the event and vaccination. In addition, several of these events are already expected to occur following vaccination, and the cases are examined for any signs of increased frequency or severity. As such, we focused on the next approach to determine possible signal detection.

Quantitative analyses are performed across all cases to understand if there is an imbalance for the event. The questions asked of the data are: is the event more common this year than in previous years for this vaccine, and, if one looks at the incidence of reporting of this event across all cases reported for aTIV, is it similar to relative reporting of this event for another vaccine? With the quantitative approach, statistically significant differences are referred to as disproportionality.

In order to demonstrative quantitative disproportionality, three criteria must be met: the number of cases in a time interval must be greater than two; the proportionate reporting ratio, or PRR, must be greater than or equal to two; and the Chi Square test for difference is greater than or equal to four, which corresponds to a P

value of less than 0.05. If all three criteria are met, a quantitative signal is identified. With this in mind, let's review the data.

This slide shows the events evaluated as potential AEFIs or adverse events following immunization, in the aTIV post-marketing database as well as in the safety database of a licensed non-adjuvanted influenza vaccine. The search terms by standardized medical query, or preferred term, mirror the same search parameters used to query the clinical database. The PRR is less than two in all cases, and the Chi Square is less than four. Note there were no AEFI categories that demonstrated disproportionality for aTIV as compared to the non-adjuvanted influenza vaccine.

The post-marketing database was then evaluated for the same terms used to search the clinical database for adverse events of special interest. Across categories ranging from arthritis to muscular autoimmune disorders to Guillain-Barre Syndrome none of the AESI categories demonstrated disproportionality in reporting for aTIV as compared to non-adjuvanted TIV in this older population.

I would like to spend a moment on the topic of narcolepsy. We have closely examined our data for any signs of narcolepsy following aTIV vaccination. It's

important to note that no cases suggestive of narcolepsy have been observed in any of our clinical studies, nor have cases been reported in 17 years of post-marketing. To examine for this issue we looked into both databases for cases resembling narcolepsy via a broad customized search for sleep disorders.

We found six sleep disorder-related cases in the first-dose randomized controlled trials and 13 sleep disorder cases in the post-marketing database. With the sole exception of one case of hypersomnia occurring two days after vaccination, none of the other 15 cases met Brighton collaboration case definitions for narcolepsy. Furthermore, no disproportionality for these sleep disorders was observed when compared against cases reported for a non-adjuvanted influenza vaccine.

In summary, aTIV has a well-characterized and acceptable safety profile. Data from several thousands of subjects exposed in the pivotal trial and a pooling of trials from the randomized controlled studies demonstrates that, overall, unsolicited adverse event reporting is similar between vaccine groups, including reporting of unsolicited adverse events evaluated by specific categories of events. The only noteworthy difference in safety reporting was an increase in mild reactogenicity following

vaccination with aTIV. In the revaccination studies, safety patterns were similar between aTIV and TIV.

Finally, analysis of 17 years of post-marketing safety data supports that the safety of aTIV is consistent with the favorable safety profile of other licensed influenza vaccines. This is supported by its continued acceptance and use in older populations outside of the United States.

Thank you. I will now turn the presentation over to Professor Van Buynder.

DR. MOORE: Can we ask questions?

DR. DAUM: What I wanted to do is to do it their way. At Novartis' request (and I conceded), we are going to wait until all their presentations are done and then I really want to encourage you to save it. So if committee members would write their clarifying questions so that we can ask them all at the end. That would be better. Thanks.

Agenda Item: Benefit-Risk, Paul Van Buynder, MD, MPH, Simon Fraser University

DR. VAN BUYNDER: Thank you and good morning. I am very pleased to be here today to talk about a topic that I consider to be of great importance. Currently, I'm a practicing public health physician in Queensland in Australia and I chair the Australia Influenza National

Guidance Committees. For 20 years I have studied the impact of influenza, and in my practice I have come to see the positive effect of adjuvanted influenza vaccines on both individuals and on public health.

Importantly, I was the principal investigator on the Canadian comparative effectiveness study which looked at the effectiveness of aTIV versus TIV in a real world setting. This study provided additional insights beyond the trials that Dr. Heijnen spoke about as to how aTIV may prevent the morbidity and mortality associated with influenza in older adults.

The H3N2 strain typically causes the greatest mortality and morbidity in the older population, and it also has the greatest likelihood of drift. I'm sure everybody in the room remembers how severe influenza was last year with the highest elderly hospitalization rate for 10 years. And two years before that, in 2012-2013, H3N2 was again the main circulating strain and we saw high hospitalization rates and high mortality in the elderly.

Even with high coverage levels, current vaccines did not prevent the extensive impact. In 2012-2013 when drift was minimal, TIV was still poorly effective against H3N2, so any incremental enhancement to current vaccines against H3N2 will benefit people 65 and older who have few

other effective options.

Why was I interested in the use of adjuvant vaccine in the elderly? At the time, I was a member of the Canadian National Advisory Committee on Immunization, or NACI, and I was also a member of the NACI Influenza Subgroup, so I had access to data from aTIV studies submitted by Novartis to support the Canadian licensure. These studies demonstrated increased antibody response and looked promising for enhancing protection for the elderly. I also at that time had access to the early results from the Lombardie Influenza Vaccine Effectiveness Study, or LIVE, which again suggested potential enhanced effectiveness when aTIV was used in the elderly.

This LIVE study was a very large multi-season community-based observational study. In this study, physicians preferentially gave high-risk patients aTIV, so the patients vaccinated with aTIV had more comorbidities and showed higher functional impairment. In the period prior to the commencement of the study, the aTIV patients were 17 percent more likely to be hospitalized. During the study period, after adjusting for confounders, this risk of hospitalization for influenza and pneumonia in those receiving aTIV was reduced by 25 percent.

In Canada, after looking at these datasets, we

were excited about the potential for enhanced responses with aTIV. We applied for and were given permission to use the adjuvanted vaccine for elderly patients in two health authorities in British Colombia, but this approval was contingent on my unit evaluating and reporting the findings of the use of the aTIV.

We applied for an investigator-initiated grant to study the clinical effects, and Novartis agreed to contribute to the cost of the study with most of the study provided by the Fraser Health Authority. Importantly, this was an independent study conducted by my research unit.

So what did we find in Canada? In the program's first year I formally investigated the impact of the vaccine via a case-controlled test-negative community-based observational study. This observational study design is widely used to assess vaccine effectiveness. My unit was in the perfect position to conduct the study. In British Columbia, all influenza tests are done at a central reference laboratory, and all positive test results, by law, are referred to public health. So we had information on everyone tested in the study zone, around 500,000 people 65 years of age and older.

However, there were challenges that season. It was a very quiet season. At one stage, CDC described it as

the quietest influenza season in 30 years. This led to reduced testing in the community so that in our study population half of the patients were 85 years of age and older, and half lived in long-term care facilities. These older patients had high levels of comorbidities and are traditionally poor responders to influenza vaccine.

When we looked at the amount of our recruitment, our power calculation suggested we would not have sufficient patients to show a difference in clinical effectiveness, but we were surprised by the results. Firstly, the general community data were very similar to the LIVE study. In community dwelling residents, aTIV was 73 percent effective versus 42 percent for TIV, a 31 percent absolute difference. When we included the older patients with more comorbidities in long-term care, aTIV effectiveness dropped to 60 percent, but TIV became ineffective, so the comparative attributable benefit of aTIV over TIV was 63 percent.

Although this was a very quiet year, the predominance of H3N2 was associated with poor TIV effectiveness and this pattern we have seen a poor TIV effectiveness against H3N2 repeated again in subsequent years since then. In our study, it served to magnify the benefit of aTIV. So our clinical benefit findings were

consistent with the pivotal trial data that Dr. Heijnen presented and the randomized controlled trials available before our study that were the basis of our decision.

In the pivotal trial study, aTIV met non-inferiority for all three strains, met superiority for H3N2, and generated higher antibody titers compared to TIV for all vaccine strains. The titers were higher for up to 12 months post-vaccination. This persistence was especially seen for the H3N2 strain which causes the most morbidity and mortality amongst the elderly. Also, in the supportive revaccination studies, titers for aTIV were consistently higher compared to TIV, so we see a clear pattern of benefit from both the RCTs and the observational studies.

I want to briefly recap the safety data. The safety of aTIV is well recognized with robust clinical trial data and years of post-marketing experience. Pivotal trial safety data showed similar findings between vaccine groups with the exception of solicited adverse events. Importantly, aTIV has almost two decades of post-marketing safety experience with tens of millions of doses distributed and no novel safety signals have been observed.

Our Canadian experience is not as long but Canada has a robust adverse events monitoring system. Adverse

events are reported both locally to public health and centrally to Health Canada. We saw no new signal in our three years of use with over one million doses, and of those, around 100,000 of those doses were administered in long-term care facilities and directly observed by public health staff.

In summary, despite our current vaccines, influenza in the elderly causes substantial morbidity and mortality and is a major cause of residual disability -- in the United States, 150,000 hospitalizations in this age group on average. Those of us who treat the elderly know that reducing hospitalizations is critical because many of these patients never make it back to baseline. They start at home; they go to hospital with influenza, and they are often too frail afterwards to go back home, and this is magnified in those years when H3N2 circulates.

The limitations of conventional influenza vaccines leave us with the need for vaccines that can provide us more consistent protection against influenza.

aTIV demonstrates a positive benefit-risk ratio based on its ability to elicit strong and persistent immune responses and its demonstrated effectiveness in observational studies. These results suggest that the enhanced immune responses with aTIV can translate to a

clinical benefit. Importantly, aTIV has a well-tolerated acceptable safety profile which is similar to other licensed vaccines.

We all know that observational studies have methodological challenges, but I'm excited about the consistency of the enhanced effectiveness across these studies. The extent of benefit from using adjuvanted vaccines will vary from year to year with both the circulating strain and the extent of the drift from the vaccine strain. That number may not be 25 percent or 31 percent in any given year, but with an average of 150,000 hospitalizations, any incremental benefit that can prevent an elderly person from getting the flu or keep one who does get influenza out of hospital is an important step.

Thank you for your attention. Dr. Lindert will now return to take your questions.

DR. DAUM: We have a few moments for clarifying questions from the committee. We will have a more general discussion later. Dr. Levy, I know you have been eager to ask a question. Why don't you go first.

DR. LEVY: In looking at the data presented by the Novartis team, one element that seems to come out is perhaps an increased frequency of some solicited adverse events, perhaps pain or tenderness at the injection site if

I understood correctly, in the MF59 adjuvanted formulation. My question is a lot of the data is presented as frequencies, and it appeared that the frequency of those SAEs was higher in the adjuvanted group. My question is what about the magnitude of that symptom. There are scales, as you know, for reactogenicity. NIH has put them out. Does Novartis have any analysis that looks at not just the frequency but also the severity or magnitude of the pain/tenderness at the injection site? That's question number one.

Question number two, there was some numeric difference in the frequency of analgesic use in elderly individuals receiving the adjuvanted vaccine. That appeared to be a slightly higher number, and my question was whether that was a statistically significant difference between the group receiving the adjuvanted vaccine and the non-adjuvanted vaccine. Thanks.

DR. LINDERT: We did not use the NIH reactogenicity scales. What we had were the measurements of severity as mild, moderate or severe as assessed by the subjects in the diary cards. If you like, I can review those data again, but we did not use the other scales.

We do have additional data, though, that might be illustrative at least in terms of the pattern of duration

of the adverse events. This is all severities reported. What these curves reflect is that in both the aTIV and TIV groups, the timing of onset was similar between aTIV and TIV; however, as noted in the original presentation, the frequencies are higher in the aTIV group.

In addition, you asked whether or not there was a statistical comparison for analgesic use. We did not evaluate the safety data for statistical significance.

DR. DAUM: Other clarifying questions from the committee? Dr. Tsai and Dr. Sawyer.

DR. TSAI: Just a follow-up to that question. I was wondering if you had compared rates of what you called severe solicited adverse events, local adverse events, with the Fluad versus the high-dose Fluzone vaccine, which is also indicated for adults over 65 years of age, because your vaccine and the high-dose Fluzone vaccine would be used in the same age group.

DR. LINDERT: We have not performed a head-to-head comparison between Fluad and high-dose Fluzone, and I don’t think it’s appropriate for us to comment on the relative reactogenicity, but the data are in the high-dose label.

DR. DAUM: Dr. Sawyer?

DR. SAWYER: My first question is about the

revaccination experience which was shared in Slides 75 and 76. Relatively small numbers. I'm wondering, again, about statistical comparisons between those different year experiences, and if you have additional data that would be reassuring with regard to what could be interpreted as rising adverse events with repeat doses.

DR. LINDERT: With respect to statistical comparisons, for all of our safety comparisons we did not perform statistical evaluations. I would say that our clinical experience above and beyond these revaccination studies that offer some additional perspective on revaccination would include, for example, safety data collected in the LIVE study. The LIVE study had 170,000 patient years of exposure in both vaccine groups, and as part of that, for example, we looked at adverse events of special interest and saw no difference in trends.

As part of that, I should mention, subjects participating in that study were vaccinated up to three times. However, we did not specifically analyze by vaccination.

In terms of more perspective on the safety data from revaccination, I can provide a more detailed summary if that helps to illustrate this. This is a rather busy slide, but I would like to point out that by the third year

of revaccination the overall trend was downward in terms of unsolicited and solicited adverse event reporting. Again, apologies for the rather busy slide, but in each column it is reflecting Fluad as compared to a non-adjuvanted comparator vaccine, and across the solicited and unsolicited adverse events you, in general, see a decline by year three.

We discussed the year two rise. We don't have a clinical explanation for why that occurred. However, I should have noted in the backdrop here that in years 1 and 2 there were five studies, and in year 3 there were two studies participating, so it may be that some of the shifts in terms of the study composition may have contributed to this. But again, we don't have a clear explanation.

DR. SAWYER: I had a second question. This is related to the narcolepsy data shown in Slide 82. I just was confused because this appears to show an increased relative risk, but I thought, in the follow-up slide, you said there were no cases of narcolepsy in any of your trial experiences. Could you just clarify that?

DR. LINDERT: This is the data from the post-marketing experience, and with this -- I should be very clear -- There are no cases of narcolepsy present behind that. What's referred to there is a custom term, a

different constellation of sleep disorders, and I can show you the individual events in a second.

Nevertheless, when compared against a non-adjuvanted influenza vaccine, the PRR is greater than 2, which is true, but the corrected Chi Square is less than 4. So this, in addition to number of cases, informed the disproportionality, and there was no disproportionality observed.

It may also be helpful to take a look at what these cases were to illustrate what was behind this. As shown in this slide, there were 13 cases in the post-marketing database. Again, we were searching across broad sleep disorder-related terms. The majority of these were somnolence or sedation, and there was one case of hypersomnia that occurred the day after vaccination.

When we looked across all of these cases, none of the cases in the post-marketing database, except for the onset of hypersomnia in the day after vaccination, was thought to be suggestive of narcolepsy.

DR. DAUM: Dr. Englund?

DR. ENGLUND: I have several clarifying questions but they’re not all for you. Slide 52, which is your persistence, I want to know the duration of time between those vaccines. Were they all approximately one year?

When you say they got two or three doses, they were approximately one year apart; is that correct?

DR. LINDERT: Actually, this slide here is reflecting the antibody titers after a single vaccination at day 1.

DR. ENGLUND: But the slide that you showed --

DR. LINDERT: The repeat vaccinations were up to three annual vaccinations.

DR. ENGLUND: Separated in time by --

DR. LINDERT: By one year.

DR. DAUM: You can ask your other questions and we'll get the appropriate Novartis person to respond.

DR. ENGLUND: This first appears in Slide 43. You have a persistence subset, which is perhaps the reactions as well as the immunogenicity. I want to know how that subset was determined, because it was a smaller amount. How was that subset chosen?

DR. LINDERT: I'll let Dr. Heijnen describe that.

DR. HEIJNEN: The persistence subset was taken from sites in the U.S., and the first 50 subjects were from eight sites in the U.S. were selected to provide persistence blood sample for analysis.

DR. ENGLUND: Thank you; that is helpful. I have a virology question which I believe is on Slide 56, which

is the question where they show reactions to the heterologous strains. You have the cross-reactivity to the Malaysian and the Panama B strains, and I am not familiar. I would like to know how differently or distinctly those were related to the vaccine.

DR. LINDERT: I'll ask Dr. Otten from immunology if he can speak on the strain characterization.

DR. OTTEN: I am Gib Otten from Novartis Vaccines. What we will have to do is try to find that information for you. I do not have off the top of my head the antigenicities of those strains.

DR. LINDERT: I can comment a little further on the data. We did at least look for whether or not these strains were consistent with or antigenically similar to or dissimilar to the strains. With the strains that we referred to for heterologous testing in the pivotal trial we looked at ferret antisera to look at the antibody responses, again, trying to understand if these were related to the vaccine strains. In short, they did show that these were antigenically distinct from the parent strains included in the vaccine.

DR. DAUM: Dr. Pebsworth, could you introduce yourself and also ask your question.

DR. PEBSWORTH: Yes. I'm Vicky Pebsworth and I

am here on behalf of the National Vaccine Information Center. My question is sort of a general one and it has to do with the pivotal sample study.

Approximately 30 percent of the study subjects were from the U.S., and what we see here is racial and ethnic distribution that's quite different from what we have here in the U.S., with 53 percent of subjects comprising the sample when here in the U.S. I believe that Caucasians are 80 percent or greater.

We also note that there are diseases and conditions that vary by ethnicity and rate and I'm interested in finding out whether you conducted sub-analyses of the adverse events and other kinds of conditions that parse out the U.S. portion of your sample so that we can more easily interpret the extent to which these findings could or should be generalized to Americans. Thank you.

DR. LINDERT: I would like to ask Dr. Heijnen to describe our position on the demographic data and I will comment further on the safety data in subgroups.

DR. HEIJNEN: In the pivotal trial, about 30 percent of the subjects were enrolled from the U.S. and this reflected about 2,000 subjects enrolled in the trial from the U.S. If we compare the demographics from those

subjects in the U.S. with the general population in the U.S. 65 years and older, you can see in this slide that, in general, it's more or less generalizable with the exception of the ethnic origin because we had a lower percentage of black people in our trial.

However, if you then look to the impact this might have had on our analysis, and we take a look to the analysis per country and compare the U.S. with the other two countries who enrolled subjects in the trial, you see that immunogenicity response from the U.S. and the three other countries is comparable for all three strains.

In addition, when we go back to the analysis per race, we also will show that if you look at the different races we didn't find a difference for the different races included in the trial with regards to immunogenicity response, as also shown on this slide.

DR. LINDERT: You also asked about the safety analyses. We did conduct similar analyses by subgroup, analysis by race. Overall, the reporting of solicited and unsolicited adverse events was similar, albeit, again, with the fluctuating sample sizes some of these percentages did vary from group to group. Nevertheless, overall trend was that, for example, looking at aTIV unsolicited adverse events, in the racial groups where there was moderate

representation overall unsolicited adverse event reporting for aTIV was similar to TIV.

So, if you compare vaccine to vaccine for each racial group, the safety profile was roughly similar with the same pattern that we observed in the overall population -- that within each racial group, for example, there will be increased local and systemic reactogenicity that is mild in nature within those subgroups.

DR. PEBSWORTH: May I just follow up here? On this chart, it shows that for Caucasians in the aTIV group, the percent -- I'm assuming this is percent -- of subjects reporting serious adverse events is twice as high, being 10 percent, as Asians, being 5 percent, and then also down below, solicited adverse events local being, again, almost twice as high.

Again, this is interesting and it's helpful but it's not exactly providing us with the data by country of origin. Is that available, by any chance?

DR. LINDERT: By country of origin, I believe we only have a slide for U.S. versus non-U.S. for the safety profile. For the non-U.S. countries in the pivotal trial, the countries included Philippines, Colombia and Panama and maybe one more country. Within this, what we observe here is that for unsolicited adverse events the reporting was

similar between the U.S. versus non-U.S. population. However, we did see higher percentages of death and SAE in both vaccine groups in the non-U.S. population as compared to the U.S. population.

Also, there were differences in terms of reporting of local solicited adverse events, whereas systemic solicited adverse events appeared roughly similar. But the patterns comparing aTIV versus TIV remained consistent with the overall pivotal trial.

DR. DAUM: Dr. Piedro?

DR. PIEDRO: In Slide 57 you demonstrate the geometric mean titer ratios, but you never commented on the geometric mean titer itself. What was happening between first to second and to third vaccination? Was there a decrease? Did it remain the same? Was there a boost?

DR. LINDERT: We have data relative to that. I'll have Dr. Heijnen describe it. Please note, too, that the evaluation across all strains was not always feasible due to strain changes, but we do have data on one of the strains where the strain remained the same across the revaccination.

DR. HEIJNEN: As Dr. Lindert mentioned, the titers changed from season to season which makes a direct comparison difficult. We have a few trials in which the

same strain was used in the vaccine over repeated years, and this slide shows an example of a trial in which the H1N1 strain did not change over three seasons. They were vaccinated three times with the same H1N1 strain, and as you can see, we saw a consistently higher response for aTIV versus TIV, so the blue dots are aTIV and the yellow are TIV. Also, there was no decrease after repeated vaccinations with the adjuvanted vaccine.

DR. DAUM: Dr. Levandowski?

DR. LEVANDOWSKI: I would like to switch gears a little bit and ask probably Dr. Singh about some of the physical properties of the vaccine.

He mentioned that MF59 does not act as an antigen depot, and on Slide 23 there's a cartoon of I guess what one of the micelles look like. I'd like to ask where in that micelle does the influenza antigen fit in?

DR. SINGH: One of the key attributes that MF59 as an adjuvant provides is the lack of association of the antigen to the oil droplets or the surfactants coating the oil droplets. So, as I mentioned, alum, which is one of the most commonly used adjuvants, works by the process of adsorption of those antigens. But in the MF59 formulation, the flu antigen actually floats around in the aqueous space, which is a water phase which is greater than 95

percent of the composition, and does not actually associate itself to the micelles or to the squalene droplets.

DR. LEVANDOWSKI: How is potency measured for this vaccine?

DR. SINGH: The underlying mechanism by which MF59 works is by increasing the influx of immune cells at the site of injection. One of the properties that the oil droplets, by their physical nature, do is to call in more immune cells that, by definition, pick up a greater amount of antigen, leading to a high transport into the lymph node, and that is the underlying property of how the enhanced immune response is observed.

DR. LEVANDOWSKI: That's not really the question. How is the potency -- how do you measure the amount of antigen that's in the final formulated vaccine?

DR. SINGH: Okay, I can go back to the computation of the flu dose. The final composition of the Fluad is a one-to-one mixture of MF59 adjuvant blended with a known amount, 15 micrograms, of each of the three antigens, which together than make up the 0.5 ml total volume. That is the composition and that is how the computation is done.

DR. LINDERT: I can comment further. The HA is released by SRID assay -- if that was the question, for

the potency.

DR. LEVANDOWSKI: Yes. That was my question. So it's SRID. Okay. Is that modified in some way for this vaccine product?

DR. LINDERT: Are you referring to whether or not we tested in combination with the adjuvant? I would like to come back after the break just to confirm the answer before I provide it. I think I know, but I'd rather check.

DR. DAUM: Okay. Dr. Tsai and then Dr. McInnes, then Dr. Levy and then Dr. Long.

DR. TSAI: I have a follow-up to Dr. Piedra's question on revaccination, whether in the pivotal study you did a subgroup analysis on subjects who had been vaccinated in the previous season.

DR. LINDERT: Yes. We did look at individuals who had been previously vaccinated within the six months prior to the study. Dr. Heijnen, would you like to review the data?

DR. HEIJNEN: In the pivotal trial we looked into previous H1N1 vaccination, so the pandemic vaccine, if they received that vaccine in the season before. The other thing we did is we looked into was whether sero-positivity at baseline -- so having a titer greater or equal than 10 at baseline -- did have an impact on the immune response

for any of the three strains, and the subgroup four-days' analysis was similar.

DR. TSAI: Just to further clarify, it sounds like you did not collect this but I just want to confirm. My question is whether you had asked the subjects whether they had received a seasonal vaccine in the previous year or frequently or infrequently in the previous five years, because there are data that show that frequent seasonal immunization can actually reduce efficacy of the vaccine in the current season.

DR. LINDERT: Just to confirm, we did not collect the data that went back five years in terms of the number of previous influenza vaccine doses, but again, the year prior to the conduct was the pandemic so we did collect the H1N1 vaccine.

DR. DAUM: Dr. McInnes?

DR. MC INNES: Thank you. I have two questions. Both in the written material and in the presentation the statement was made that the pivotal study was observer-blinded. Did that mean that the subjects or participants were not blinded? Did they know which vaccine they got?

DR. LINDERT: The only person who knew which vaccine was to be administered was an unblinded person who performed the vaccination. It's both the subject as well

as the persons collecting subsequent data who were unaware of the treatment assignment.

DR. MC INNES: Thank you. Going back to Slide 75, I would like to understand this *n* equals 492 -- this is from your pooled studies of repeat vaccination. Could you please tell me, of those 49, which you then show again year 2 which is exact numbers, and then you go down to year 3. Could you just go through these numbers, please?

DR. LINDERT: Just to confirm, this was one of two analysis approaches that we did for the safety data, so what this reflected was that the individuals reflected in 492, for example, in year 1 and year 2, reflect only those individuals who continued into that subsequent revaccination study.

As I mentioned, there were five studies in the backdrop of year 1 and year 2 and it went down to two studies in year 3, so this is why there is also a drop-off, is because there wasn't a third revaccination, if you will, for three out of five studies. That's why the numbers are dropping.

Again, to better understand, those individuals who continued, we wanted to understand for that individual what did their solicited and unsolicited adverse events do as opposed to being, if you will, potentially influenced by

the data of those who did not drop out.

DR. MC INNES: The second part to this is if you go to Slide 76, the next one, the size of your group in year 1 -- where do these folks come from?

DR. LINDERT: These now include those individuals who were in the parent study and who did not continue into the subsequent studies. We put these data back in to provide more perspective here, because the five studies running in the background between years 1 and 2 included individuals who were institutionalized. Many of the adverse events that we observed, particularly for AEs leading to hospitalization and death, were coming from those populations, and we felt for that it would be appropriate to understand the broader safety experience across all of those.

DR. DAUM: Dr. Levy?

DR. LEVY: Earlier in the presentation the statement was made that one of the potential advantages of this adjuvant is its filterability, sterility and stability. I was wondering regarding stability, does Novartis have data about the size of the micelles, for example, dynamic light-scattering? Does that vary with storage? And does any variation with storage in any way impact frequency of reactogenicity?

DR. LINDERT: Dr. Singh, I'll have you comment on the first part and I'll follow.

DR. SINGH: The MF59 antigen, the nanoemulsion is a very stable emulsion, and the mean particle size stays around 155 nanometers plus/minus 25. And it's a stable size distribution which, even for the course of several years, does not change its mean size or the distribution. Even by the addition of the antigen, the properties don't change.

DR. LINDERT: Also to your question about the safety experience, for example, relating to micelle size, we do have one trial -- we don't have a slide prepared, but we did look at, for example, Fluad administration a year after it had been sitting on the shelf. We also, in many of our pandemic studies, sometimes have more perspective of shelf life and its clinical use but we did not organize an analysis for this presentation.

DR. DAUM: Dr. Long and then Dr. Piedra.

DR. LONG: In relation to Slide 52, it was said in multiple presentations that the durability of the antibody response was spatial. I can't see that here. Can you explain this a little bit better?

DR. HEIJNEN: This slide shows the non-inferiority bound which is 0.67 and 1, which is the GMT

ratio, and if the GMT ratio is 1 that means that both vaccines have like a similar response. However, as we see in this slide for H3N2, the lower bound of the 95 confidence interval level is above 1, and for that reason we say that the antibody response for H3N2 at 6 months and 12 months is higher if you compare aTIV to TIV. So the slide shows aTIV versus TIV, the relative difference between those two vaccines.

DR. LONG: So you're using this to infer superiority, but in fact your superiority definition isn't upheld here. Am I confused on that?

DR. HEIJNEN: Indeed, the superiority for this trial was defined as 1.5, so that is correct.

DR. LINDERT: But we are not inferring superiority from these data. The data only show a trend towards higher titers.

DR. LONG: One more question, a similar question. People have mentioned that higher antibody titers are known to correlate with better protection. That may be generally true depending on what those antibody titers and the differences are. Are there any data that you have that the differences in antibody titers between the adjuvanted and not play out into any increased protection?

DR. LINDERT: I'll ask Dr. Talbot to comment on

this topic.

DR. TALBOT: The high dose vaccine was actually licensed because of its higher antibody response, and then went on for a Phase 3b, Phase 4 study. What they found with the higher antibody responses was a very marked improvement in clinical response with decreased pneumonia and decreased influenza.

DR. LONG: In a trial and in data that you haven't shown us. Or maybe it's the same trial but --

DR. LINDERT: These are not our data. Dr. Talbot, I believe you were referring to other data?

DR. TALBOT: The higher antibodies were the ones seen in the high-dose vaccine, and that was a study published in the New England Journal.

DR. LINDERT: It is not Novartis data.

DR. LONG: I see. Not these antibodies.

DR. DAUM: Dr. Piedra, and then we will take a break.

DR. PIEDRA: I have one immunogenicity question and two safety questions, if I may.

DR. DAUM: You may.

DR. PIEDRA: With regard to immunogenicity, a lot has been stated about the H3N2 and its tie with greater disease severity in older adults, and thereby I think it

also would be important to understand what is the immune response to the H3N2 with consecutive vaccination. Did the H3N2 component change each time you looked at the revaccination years?

DR. LINDERT: The H3N2 component was changing in the backdrop of those revaccination studies.

DR. PIEDRA: Okay. I have a couple safety questions. One is with the revaccination second dose or third dose, was there a higher dropout rate than expected with the revaccination?

DR. LINDERT: I'd like to show this slide perhaps to illustrate, just to look at this quantitatively. What we aren't showing here is year 3. I'm sorry, we don't have those data. If you'd like to see it we can bring that back after the break. However, this is just comparing those individuals who were in the parent study versus those who did not enroll in the revaccination study. What this is reflecting -- you have to actually subtract this mentally. I'll show a different slide perhaps to better illustrate this.

This is enrollees versus non-enrollees. In other words, if you look from left to right, the 492 versus 221, there was almost a 50 percent dropout rate in the aTIV group versus 331 and 171 in the TIV group, so again, a

little more than 50 percent there. Again, there were similar dropout rates between these.

We did not have a preconceived dropout rate in mind when these studies were enrolled. We just asked subjects to participate in revaccination studies on a voluntary basis.

DR. PIEDRA: Okay, if I may.

DR. DAUM: One more, then Dr. Gellin and then the break.

DR. PIEDRA: You did not mention, in the issue of the revaccination, the issue of severity. So, in the most severe manifestation, was there an increase there?

DR. LINDERT: We have more detailed data I can show you. There were, of course, three different years so we had a display issue, if you will. We picked the most commonly reported adverse events, solicited adverse events, so this includes pain and headache, and I have another slide to look at two other events.

With this we broke this out by severity where mild is in the dark green and the striped green is moderate and the red shading reflects severe. Overall, there was no increase in severe reporting across all of the solicited adverse events including those we did not display. However, there was in general for pain a modest rise

overall in terms of reporting for aTIV, and I would say an unclear pattern in the TIV within that year.

Let's look at the other events as well. For headache, again, there were no noteworthy trends there in terms of increasing severity. The next slide is myalgia and fever -- and you can understand why we didn't put more slides here because you can hardly see the bars at this point. Overall, there wasn't a noteworthy trend in terms of percentages of severe reactions across the revaccination studies.

DR. DAUM: Just before the break, Dr. Gellin.

DR. GELLIN: I want to pick up on Dr. Long's question and comment about the persistence. Your slide talks about ratios. I wonder if the data or some of you have some insights into persistence over time and how that might advise the right to be vaccinated, for either of these vaccines.

DR. LINDERT: I'll ask Dr. Heijnen if she can comment on the question.

DR. HEIJNEN: I can show you the absolute GMTs over the period. What you see is that the antibody, the absolute titer, has declined during the period of time. You can also see, if you look to the GMTs on the left side of the slide, you have aTIV versus TIV, and you see the

absolute titers after 6 months and after 12 months. If we look at H3N2, it's 62 for aTIV and 46 for TIV, and after 1 year of time it's 35 versus 27.

DR. DAUM: Among the reasons for a vaccine like this are, we heard, immunosenescence and maybe people with immuno-compromised functions, but they are excluded from these trials. I wonder if you have any experience from Europe or elsewhere about how these perform in people who weren't in your formal studies.

DR. LINDERT: We do have several smaller trials that were conducted in targeted populations -- for example, HIV. The subjects in these trials were largely non-elderly. Within each of these four trials we had individuals where in some cases there was an HIV-negative control, and in all of these we were comparing aTIV versus TIV. In general, what was observed was that the vaccine was immunogenic; it was also well tolerated. In two of the studies, the titers were higher with the aTIV vaccine compared to the TIV and without any other concerning changes in terms of clinical perspectives, such as impact on CD4 count or HIV viral load that one might be concerned about in an HIV population.

We also have other smaller studies looking across a variety of other targeted diseases such as renal

transplant. Overall, what we have seen across these studies is that aTIV continues to have higher antibody titers with a robust safety profile in those populations.

Dr. Von Buynder has a comment that he might add.

DR. VON BUYNDER: Thank you. Because of the design of the study and what happened in Canada, in fact, half of the population that was vaccinated in the Canadian studies were people who were in long-term care and who had decreased immune capacity and had significant comorbidities.

I think one of the exciting aspects of it was that, even when the study became more difficult because the other health authorities decided after the first-use results to start vaccinating the elderly in those health authorities, and we lost, to a large extent, our control group, we had relatively consistent protection against hospitalization that continued in those particular groups. So there was maintained an effectiveness that was clear and, in fact, probably more clear in the groups that don't respond to TIV than there was in the groups that were immune-competent.

DR. GELLIN: And my last question -- This group assembles annually to try to figure out what the right strain is, and when we miss, we hope that adjuvants might

help to make up some of that difference.

Do you have any experience from this past year about how it did?

DR. LINDERT: Yes, we do. We did look at some antibody responses, and I should say these data are very new. They were not included in the filing.

With that, I'd like to ask Dr. Otten if he could describe the results of what we are about to see. This was exploratory testing because we were interested ourselves to understand response to the vaccine.

DR. DAUM: Before you do, these data have not been reviewed by FDA or anybody?

DR. LINDERT: These data have not been reviewed by FDA.

DR. OTTEN: We have very recent data comparing aTIV to TIV showing that, compared to TIV, aTIV increased titers against an antigenically drifted H3N2 strain. In this study, individuals 65 and older were vaccinated in the 2013 season with a trivalent vaccine containing A/Texas. Serum antibodies were tested by micro neutralization at 22 days.

Approximately 32 percent of the subjects vaccinated with aTIV showed seroconversion as measured by a fourfold or greater increase in antibody titers over pre-

vaccination titers against a cell version of the A/Texas, which would have represented the strain circulating at that time. Only 13 percent of those vaccinated with TIV showed seroconversion.

The A/Hong Kong strain represents an antigenically drifted H3N2 strain that predominated in the 2014-2015 season and is significantly antigenically different from A/Texas. Here, 40 percent of those vaccinated with aTIV seroconverted against the A/Hong Kong strain, whereas only 15 percent of those given TIV seroconverted.

DR. DAUM: And efficacy?

DR. LINDERT: These are antibody responses only. We have an ongoing efficacy trial in children. The data are not yet available, but we're looking forward to understanding those answers as well.

DR. DAUM: Okay, thank you. On that note, I think we'll take a break --Dr. Moore, is that you?

DR. MOORE: Sorry, yes it is. I'm having audio problems here. Can I ask a quick question before the break, and that is -- (off-mic). Are there any post-market studies or at least indications that there is an effect of the adjuvant on influenza and pneumonia mortality? Also, is there any effect on vaccine coverage in that if persons

who are being revaccinated do develop adverse effects they may not get vaccinated a second time. So is there any change in coverage in any of these studies that you're aware of in influenza and pneumonia mortality rates?

DR. LUNDERT: I'm sorry. Could you repeat the question? There was a little bit of interference.

DR. DAUM: The questions concern coverage and mortality with the adjuvanted vaccines presumably in those countries where it's licensed.

DR. LINDERT: In other words, have we collected mortality rates in those countries? No. We haven't with aTIV. However, if Dr. Talbot wants to comment on overall influenza vaccines and mortality rates and coverage in the U.S.-based population -- I may not have understood the question.

DR. DAUM: It is not licensed here. I'm trying to speak up for Dr. Moore. It is not licensed here so the coverage question would not apply here.

DR. VON BUYNDER: We don't have data specifically from Canada on the mortality associated with the change in using aTIV. Most of the mortality data associated with flu is data that comes out of predictions and data that comes out of calculations. It's very difficult, particularly in the very elderly, to attribute all-cause mortality and

what's associated with vaccine or otherwise.

What I can talk about is the revaccination in regard to the side effects. In the first year of the study there was a head-to-head comparison of the three available vaccines in Canada at that time, the intradermal, the TIV and the aTIV. There was a difference as seen in the pivotal study that they were more likely to have localized temporary pain with aTIV than with TIV, and the intradermal was closer to the aTIV than the TIV.

The acceptability of the vaccine was over 95 percent with all three of the vaccines, and while there were more localized reaction it had no impact on coverage rates at all. So the elderly were very accepting of something that gave them a short-term sore arm or an increased fever for a short period of time, and it had no effect on coverage whatsoever.

DR. DAUM: Thank you very much. We are now going to take a break. We will reassemble at 5 minutes to 11:00 promptly with Dr. Browne.

(Brief recess)

DR. DAUM: We had a question left hanging at the break and we'll call on Novartis to answer it.

DR. LINDERT: Thank you. We had a question about the SRID assay and how this is evaluated. It's evaluated

in both the drug substance as part of the release in the monovalent, and it's also tested in the drug product as well.

DR. DAUM: Now I'd like to call on Dr. Browne of the FDA to make the FDA presentation on the data that we heard this morning.

Agenda Item: FDA Presentation, Sara Browne, MD

OVRR, DVRPA

DR. BROWNE: My name is Sara Browne and I am going to speak about the clinical data submitted to the Fluad BLA. The goals of my presentation will be to briefly describe the background, the investigational vaccine Fluad and its proposed indication; to review the accelerated approval licensure pathway; to present the materials submitted to support the licensure of Fluad including the pivotal Phase 3 study, its design and results, the 49 supportive safety studies that were submitted, as well as the post-marketing pharmacovigilance plan; and then to briefly summarize.

Very brief background. Influenza illness, as we all know, is the result of infection with influenza virus. Hemagglutinin and inhibition antibodies result from either vaccination or natural infection, and a specific HAI titer has not been absolutely correlated with protection,

although a titer of greater than 1:40 has been associated with protection from influenza in up to 50 percent of subjects.

Currently, there are nine seasonal trivalent influenza vaccines that are available to persons greater than or equal to 65 years of age. There are three seasonal quadrivalent influenza vaccines; none of these are formulated with adjuvant.

The proposed indication for Fluad is for active immunization of adults 65 years of age and older against influenza disease caused by influenza subtypes A and Type B contained in the vaccine. In terms of the vaccine products used in the Phase 3 trial, V70_27, we have Fluad, the influenza vaccine adjuvanted, which is a trivalent subunit influenza vaccine containing 15 mcg each of hemagglutinin in A/H1N1, A/H3N2 and B. It's produced using the same manufacturing process as Agriflu and it contains a squalene-based adjuvant MF59C.

It was first registered in Italy in 1997. It is currently authorized in 38 countries which include Canada as well as 15 European countries, and these are all through individualized regulatory authorities. It is generally indicated in those greater than or equal to 65 years of age with the exception of the Philippines, South Africa and

Canada where the indication is for a broader age group. Over 85 million doses have been estimated to have been given through April 30, 2015.

Agriflu, the comparator vaccine in the Phase 3 trial V70_27, is also a trivalent seasonal vaccine. It's formulated without adjuvant and is approved for use in the United States in persons 18 years of age and older.

The MF59 adjuvant is an oil-in-water emulsion manufactured to generate uniformly sized squalene oil droplets. It is included with the intent of enhancing the immune response to vaccine antigens.

To review the accelerated approval pathway, per 21 CFR 601.41, licensure is based on a surrogate marker that is reasonably likely to predict clinical benefit -- in this case, the day 22 post-vaccination response as measured by HAI titers. A confirmatory efficacy trial in this case is required to verify clinical benefit of the product, and this efficacy trial is planned. As for any vaccine, it must be demonstrated as both safe and effective.

Now to present the material submitted to the Fluad BLA, this was a Phase 3 clinical immunogenicity and safety trial, V70_27, and additionally 49 supportive studies that were submitted to provide safety data.

Trial V70_27 was randomized, multi-center and

observer-blind. It had an active control of Agriflu in its comparator arm. Healthy or medically stable adults who were greater than or equal to 65 years of age were enrolled, and the randomization was stratified by age into two groups, 65 to 75 years of age and those greater than 75 years of age. 7,104 subjects were enrolled, evenly divided between the two arms, and this was at 38 sites across four countries.

The primary immunogenicity objectives were to demonstrate, first, immunologic equivalence of three consecutive production lots of Fluad at day 22; then to demonstrate immunologic non-inferiority of Fluad compared to Agriflu for all three vaccine strains as measured by both GMT ratios and seroconversion rate differences at day 22; and, finally, to look at immunologic superiority of Fluad compared to Agriflu for at least two of three homologous strains, again measured by GMT ratios and seroconversion rate differences at day 22.

There were also a number of secondary immunogenicity objectives. Some of the selected ones included here were to demonstrate non-inferiority of Fluad compared to Agriflu with regards to all homologous strains in high-risk subjects as measured by GMT ratios and seroconversion rate differences at day 22, and high-risk

was defined as subjects with chronic medical conditions; then, to demonstrate superiority of Fluad compared to Agriflu for at least two of three homologous strains, again in high-risk subjects by day 22 GMT ratios and seroconversion rate differences.

Further selected secondary immunogenicity objectives included to demonstrate non-inferiority of Fluad compared to Agriflu with regards to three heterologous strains that were selected by the applicant, again, by day 22 GMT ratios and seroconversion rate differences; and to demonstrate superiority of Fluad compared to Agriflu with regards to two of the three heterologous strains selected by the applicant by the same GMT ratios and seroconversion rate differences.

The final selected secondary immunogenicity objective I'll mention was the durability of immune response between Fluad and Agriflu recipients. This was GMT ratios for homologous strains at 6 months and 1 year post-vaccination. Due to small sample size this was not powered to demonstrate significance for difference in persistence.

Reviewing the results we will first look at subject disposition. I will go on later to define the per protocol set and the full analysis set, but the study

anticipated a 10 percent attrition rate and you can see in the per protocol set that was achieved with 92 percent completion rate. The full analysis set was larger at 98 percent, and the safety set was nearly 100 percent completion.

If we look at subject demographics you see that there were more females than males but this was evenly balanced between both treatment arms. You can see that more subjects were enrolled in the 65 to 75 age cohort stratification group than the greater than 75 stratification group, but again, this was evenly balanced between treatment arms. Finally, most subjects came from the Philippines with 30 percent from the United States -- again, evenly balanced between treatment arms.

Looking at the primary immunogenicity analyses -- this was immunogenicity to homologous vaccine strains -- the first primary objective of lot equivalency was met, and so the three lots of Fluad were pooled for the non-inferiority and then superiority analyses.

This is the non-inferiority analysis in the per protocol set. The per protocol set was defined as all randomized subjects who received correct vaccine and were stratified to the appropriate age group and had no other major protocol deviations that might impact immunogenicity

results. The most common of those was having a day 22 blood draw outside the pre-specified window, which was day 22 plus 3. There were three subjects who didn't have a blood draw at day 22. Other things were not meeting the inclusion and exclusion criteria.

Success criteria were met if the lower limit of the 95 percent confidence interval was greater than .67, and what you can see outlined in red is that for all three vaccine strains, looking at both the point estimates and in parentheses is the 95 percent confidence interval showing that for the GMT ratios of Fluad to Agriflu, the 95 percent confidence interval was greater than .67.

This is the non-inferiority analysis in the per protocol set for seroconversion rate differences, again, for homologous strains. Seroconversion was defined as a pre-vaccination titer of greater than 10 with a post-vaccination titer of greater than or equal to 40, or at least a fourfold rise in HAI titer for those whose pre-vaccination titer was greater than or equal to 10. Success criteria were met if the lower limit of the 95 percent confidence interval of Fluad minus Agriflu was greater than -10 percent, and what you can see is that non-inferiority was met for all three vaccine strains by the lower bound of the 95 percent CI.

Because non-inferiority was met, superiority was evaluated. This used the full analysis set which was pre-specified in the statistical analysis plan as agreed between the applicant and CEBR statisticians. The FAS included all randomized subjects who were vaccinated. Unlike the PPS, it included subjects with major protocol deviations including those who received the wrong vaccine or were stratified to the wrong age group.

Here is the superiority analysis in the full analysis set for GMT ratios against homologous strains. When you look at the lower bound of the 95 percent confidence interval it meets criteria for superiority, which is the ratio greater than 1.5, for H3N2 but not for H1N1 or influenza B.

Similarly, when we look at the superiority analysis for seroconversion rate differences for homologous strains, you see that the success criteria were met if the lower limit of the 95 percent confidence interval was greater than 10 percent for at least two of the three strains, and what you can see here is that for H3N2, the lower bound of the 95 percent confidence interval is greater than 10 percent but not for H1N1 or influenza B.

Going on to look at the selected secondary analyses, the methodology was similar to that of the

primary immunogenicity analyses. If non-inferiority criteria were met, then superiority analyses were performed. The same success criteria for both GMT ratios and seroconversion rate differences applied.

Looking at the superiority analysis in the full analysis set, these are homologous strains in high-risk subjects. What we can see is within the full analysis set 36 percent of subjects met criteria for high risk, and the disorders were equally balanced between groups including, in order of descending frequency, neuromuscular and metabolic disorders including diabetes, COPD, asthma, CHF, renal insufficiency and liver disease.

These are GMT ratios as well as seroconversion rate differences, so for GMT ratios, again, the lower bound of the 95 percent confidence interval needed to be greater than 1.5, and you can see that superiority was not met here. For seroconversion rate differences, the lower limit of the 95 percent confidence interval was greater than 10 percent as success criteria, and you can see it is less than that.

This is another superiority analysis in the full analysis set for selected heterologous strains. These were strains selected by the applicant to include two H3N2 strains and one influenza B strain. Heterologous strains

were defined as generally regarded as antigenically distinct from those included in the vaccines. The same criteria applied for GMT ratios as well as seroconversion rate differences, and you can see the point estimates with the lower bound of the 95 percent confidence interval for both GMT ratios and seroconversion rate differences.

The final selected secondary immunogenicity endpoint was antibody persistence of homologous strains, and this again was a descriptive evaluation of durability of immune response. Here we're looking at the GMT ratio of Fluad to Agriflu at 6 months and 1 year post-vaccination -- 189 subjects were enrolled into the Fluad group and 191 subjects were enrolled in the Agriflu group. What you can see here is that the point estimates are around 1 for influenza H1N1 and influenza B with the confidence intervals crossing 1 for each of those. For H3N2 at both 6 months and 1 year, the point estimate is around 1.3 and the lower limit of the 95 percent confidence interval does not cross 1.

In terms of safety, there were a number of selected safety analyses that we'll discuss. Local and systemic reactions occurring within 1 week of vaccine administration were assessed. This was in clinic at 30 minutes post-vaccination as well as via diary card and via

a phone call made at day 8. Unsolicited reactions were monitored through day 22 captured via diary card as well as a day 22 clinic visit, and all SAEs including death, new onset of chronic disease and AEs of significance were collected through day 366.

In terms of adverse events within 30 minutes of vaccination, there were no anaphylactic events reported. You can see that the events were equally balanced between each arm and that moderate and severe events were both rare and balanced between arms.

This is a slide showing reactogenicity within 7 days of vaccination. What you can see is that, overall, Fluad had higher rates of local reactogenicity compared with Agriflu, and these were mostly limited to mild, although there was some increase in moderate reactogenicity as well, but severe reactogenicity was evenly balanced between groups.

Looking at systemic reactogenicity within 7 days of vaccination you can see that systemic reactogenicity again was increased for Fluad compared with Agriflu overall, but most of it was, again, mild, and moderate and severe reactogenicity was evenly balanced between groups.

This is more systemic reactogenicity within 7 days of vaccination, again underscoring that most of the

reactogenicity we see, although slightly larger in the Fluad group, was distributed with slight increases for mild reactogenicity across groups.

I don't have a table for unsolicited AEs within 22 days of vaccination essentially because they were balanced between groups, 16 percent each. Possibly or probably related AEs were also balanced between groups with 4 percent for Fluad versus 5 percent for Agriflu. The most common of these were nasopharyngitis, headache and cough, and they were distributed evenly across system organ class. You can see it's less than 1 percent per group.

In terms of SAEs, deaths, AEs leading to study withdrawal or new onset chronic disease, again, you can see that these are balanced evenly between Fluad and Agriflu groups. Importantly, there were no deaths noted within 22 days of vaccination. There was no evidence of relatedness or imbalances by system organ class.

Moving on to the next slide, I just want to point out that there were no imbalances in rates of cardiovascular-associated deaths.

Moving on to the supportive safety studies, there were 49 clinical studies which were conducted over 16 years. These were mostly in elderly; that is, adults greater than or equal to 65 years of age, although there

were five studies submitted that were in young adults, and that was about 1,000 subjects. The total *n* of subjects receiving either MF59 or an unadjuvanted trivalent influenza vaccine was approaching 28,000 subjects.

These studies were small and of varied design. There were four different formulations of Fluad used. Not all of the comparators were licensed in the United States. It included open label, uncontrolled and/or non-randomized studies, and the validation status of the immunogenicity assays was unknown. Therefore, CBER agreed to review studies for safety only.

This is a schematic of these safety studies which were submitted. You can see the 49 safety studies -- the five studies in young adults, one Phase 4 study, and there were seven repeat dose studies which left us with 36 first-dose studies in the elderly, 21 of which were uncontrolled studies, which left 15 randomized first-dose controlled studies in the elderly, 10 of which had greater than or equal to 6 months follow-up.

The safety data were pooled to conduct multiple analyses from these 49 safety studies. Specifically, unsolicited AEs were looked at within 30 days of vaccination, and this was found to be balanced. You can see 25 percent in the Fluad group versus 27 in the

unadjuvanted TIV groups, and there were less than 2 percent of unsolicited AEs for any given system organ class. Similarly, SAEs, deaths, AEs leading to study withdrawal and adverse events of special interest were balanced overall.

There was a safety evaluation we looked at of pooled revaccination studies. There were five studies which included at least one revaccination. In my previous diagram I said there were seven studies, and that's because all five studies were included with an administration of a second annual dose, plus two additional studies that went on for one-third of a year. What we found was that in year 2 there was an imbalance of deaths noted, but it's important to recognize that there were no imbalances noted in year 1, and there were no deaths noted in year 3.

These are the data from the deaths across pooled revaccination studies. You see here in the Fluad group, out of 492 subjects that received a second dose of Fluad there were 17 deaths, at 3.5 percent. Here, there were six deaths at 1.8 percent. Dose 3, there were no deaths for either.

Most of this imbalance came from one study, Study V7_25X1, in which there were 8 deaths in the Fluad group versus none in the control group. This was a randomized

controlled trial of Fluad versus an unadjuvanted influenza vaccine. The vaccine was Vaxigrip which is not licensed in the United States. There were 89 subjects in the Fluad group and 91 subjects in the unadjuvanted group so the study was small. These were nursing home residents with a median age in both groups of 85, and the age range was similar for both groups as well. The causes of death were extremely varied, and there was a highly varied temporal association to vaccine administration. There was one death within 30 days of vaccine administration, but the range was 11 to 151 days post the second dose.

If we look at the causes of these deaths across these pooled vaccination studies, you see that congestive heart failure was the most common for both groups with a similar percentage, and there was an extremely varied cause of death including trauma, malignancy, GI bleed and other cardiovascular problems. There was only one case in the Fluad group as well as one case in the unadjuvanted group that occurred within 30 days of vaccination.

Just some considerations about these revaccination studies. They were small-numbered pooled studies in an aging population. Cardiovascular events occurred in subjects with both underlying cardiovascular disease as well as other comorbidities. There were no

imbalances in deaths in year 1 and year 3, and there were no imbalances in non-fatal cardiovascular events in the Phase 3 study, V70_27. The manner of death was varied and removed temporally from vaccination, and there have been no safety signals in 16 years of post-marketing surveillance including over 81 million estimated doses administered.

To review the post-marketing pharmacovigilance plan, it was based on the assessment which included review of the pre-licensure clinical safety data, review of adverse event summaries including the 81 million doses sold outside the U.S., and no safety signals were identified. There was also review of an investigation of reports related to the temporary suspension of Fluad in Italy in 2014. There were four death reports in elderly people post-vaccination. The investigation found no causal link between Fluad and the deaths, and the suspension was lifted with no regulatory action.

We also reviewed the safety information from two publications that were submitted which described the post-marketing observational studies comparing adjuvanted to non-adjuvanted seasonal trivalent influenza vaccine. No safety concerns were identified in these papers.

The pharmacovigilance plan includes routine pharmacovigilance. This is post-marketing reporting of

adverse experiences in accordance with 21 CFR 600.80. It also includes enhanced 15-day expedited reporting to VAERS, which includes all serious and non-serious cases of specified potential immune-mediated conditions.

There will also be enhanced passive surveillance. This aims to improve the capabilities to rapidly detect, evaluate and act on unexpected changes in reactogenicity or other adverse immune responses from one season to another.

For the enhanced passive surveillance, the first 1,000 recorded vaccinations at participating sites in Italy or all vaccines administered by November 24th of the same season will be evaluated, whichever comes first. In this case, vaccine recipients will be instructed to report adverse events occurring within 1 week of vaccination. They will be provided a call center number and a vaccination card with information on brand, batch number and date of vaccine administration.

The analysis will include reporting rates for adverse events based on the number of spontaneously reported adverse events per dose administered. Observed rates will also be compared to expected rates, which will be defined prior to the start of surveillance, and a final report will be made available to the agency.

To summarize the Phase 3 trial supporting

licensure, V70_27, we looked at the primary immunogenicity analyses which included homologous strains in the per protocol set, and this was evaluation of GMT ratios and seroconversion rate differences comparing Fluad to Agriflu at day 22. This study met criteria for both lot equivalency and non-inferiority but not for superiority.

The secondary immunogenicity analyses included statistical analyses of day 22 GMT ratios and seroconversion rate differences for Fluad versus Agriflu for homologous strains in high-risk subjects. Non-inferiority again was met, but superiority criteria were not met. Heterologous strains for three strains selected by the applicant -- non-inferiority criteria were met; superiority criteria were not met, as well as immunologic durability. No important differences were noted at days 181 and 366, although for AH3N2 the lower bound of the 95 percent confidence interval did not cross 1 for GMT ratios and did not cross 0 for seroconversion rate differences.

In terms of safety, there was increased mild and moderate local reactogenicity seen after Fluad administration. Fluad demonstrated increased systemic reactogenicity overall, but only slight differences for any given parameter. There were no imbalances in severe, local or systemic reactogenicity. There were no imbalances in

unsolicited AEs, and there were no imbalances in deaths, SAEs, withdrawals due to AEs or new onset chronic disease.

In the pooled safety analyses there were 49 studies conducted over 16 years, small and highly varied and conducted outside the United States. There were no imbalances in unsolicited AEs, deaths, SAEs, AEs leading to study withdrawal or AEs of special interest. Observed imbalance in deaths was noted at year 2 upon the analysis of five revaccination studies, but this was in a small number of subjects with a lack of similar trends in first-vaccination studies, and with lack of observed deaths in year 3 revaccination studies in subjects with chronic comorbidities including cardiovascular disease.

Thank you for your time.

DR. DAUM: Thank you, Dr. Browne, for your presentation. We have a few moments for committee-initiated clarifying questions of Dr. Brown, and I'll begin with Dr. Hudgens.

DR. HUDGENS: Slide 13 mentions an efficacy trial being planned in the event that the accelerated approval is granted. Can you describe a little bit the details of that planned efficacy trial?

DR. BROWNE: I'd like to defer to Novartis.

DR. DAUM: That is not a clarifying question but

it is one that we need to hear, so I would like you to repose that question during the committee discussion this afternoon.

DR. PIEDRA: Is there any data on reactogenicity or immunogenicity with co-administration of pneumococcal vaccine in this age group?

DR. BROWNE: We didn't review that data for this file.

DR. DAUM: Any other committee-initiated clarifying questions? Dr. Gellin.

DR. GELLIN: Could you tell us a little bit about the philosophy behind superiority criteria of 2 or more and greater than 1.5? How does that play out as vaccines have more than three strains?

DR. BROWNE: I think we looked at superiority criteria for each of the strains. In the quadrivalent the criteria would be the same, and this is based on a 2007 guidance from the FDA which defines these criteria.

DR. GELLIN: Other than citing guidance about the philosophy of why that's the right number?

DR. DAUM: Do you want to clarify this point?

DR. KRAUSE: Maybe I can. Obviously, we have non-inferiority criteria which a vaccine needs to meet in order to be shown to be non-inferior to the comparator.

What we do not want is a situation where one vaccine is superior to the other one but the other one is still considered non-inferior to the one that's superior to it. So these criteria need to be non-overlapping.

If the non-inferiority bound is .67, or two-thirds, then in order to show superiority you need to, in essence, have one over .67, which is 1.5. Otherwise, you would have a situation of an asymmetry where one vaccine is superior and the other is non-inferior, and that would make no sense. In fact, if you look at it mathematically, it really is a continuum with that cutoff.

DR. DAUM: Thank you very much. Dr. Hudgens, did you have one more clarifying question?

DR. HUDGENS: I was just wondering about any regulations that say to what extent the safety and immunogenicity data have to come from U.S. populations in these sorts of considerations.

DR. BROWNE: I may need to defer to some of my supervisors for that, but what I will say is that we did pre-specify that at least 30 percent of the subjects in the study come from the United States, and they met those goals.

DR. DAUM: Does anyone at FDA want to comment?

DR. GRUBER: This is Marion Gruber speaking. Dr.

Browne is correct. We actually want representative percentage of U.S. populations in these safety studies, but we also look at the feasibility sometimes of how these trials can be conducted where they are conducted. For influenza vaccines, for immunogenicity and safety, we really have taken the position that the data from other populations, by and large, can be extrapolated.

Of course, there is always the question -- and we would look at this -- of what do the populations look like, are there underlying conditions that are different, how different are they in terms of ethnicity and other factors, so all of this has been taken into consideration.

But, as Dr. Browne stated, we have about one-third U.S. population and that would satisfy the regulatory considerations.

DR. DAUM: I would like to remind the committee that we're taking clarifying questions only; that is to say, what Dr. Brown presented, what didn't you understand or would like to hear spoken more clearly. Dr. Tsai, Dr. Levy, and then we'll try to break for lunch.

DR. TSAI: I hope it meets your criteria of clarifying. I was just wondering whether the experience with the MF59 adjuvanted pandemic vaccine bears upon the safety database that you considered, because although it

was a monovalent vaccine it did include an antigen that's still contained in the seasonal vaccine.

DR. DAUM: That is not a clarifying question, but we would like to have that question asked and we must have it asked, but can you hold it until this afternoon? Dr. Levy.

DR. LEVY: Regarding the presentation we just heard on Slides 39 and 40, we were hearing about local and systemic adverse events within 7 days of vaccination. I guess I have a similar question to the presenter that I had to some of the Novartis presenters. There are columns here for the adjuvanted versus the non-adjuvanted formulas with numbers and percent incidence of pain, tenderness, et cetera. Have you looked to see which of these differences are statistically significant?

DR. BROWNE: No. This is descriptive only. We did not apply statistics to it.

DR. LEVY: Is that not a standard thing to do? I am just wondering.

The other question I have is have any of the data been looked at for male versus female study participants?

DR. BROWNE: They were divided by gender, and I don't recall there being any appreciable differences based on gender or ethnicity, but I don't have those data

specifically available for this presentation.

DR. DAUM: Dr. Pebsworth.

DR. PEBSWORTH: This is quite a complicated presentation and dataset. From the perspective of the consumers, could you summarize the FDA's findings as Fluad was found to be not superior to Agriflu and was also found to be more reactive? Is that a fair summary?

DR. BROWNE: I think the way we would phrase it would be that it was found to be non-inferior, and for a product to be licensed we have to demonstrate that it's both safe and effective. To demonstrate effectiveness we look, in this case, for non-inferiority against the comparator, which was Agriflu.

DR. DAUM: Thank you very much. We are going to break for lunch now. We're five minutes behind schedule and we will reassemble at 12:15 in the Eastern time zone for the open public hearing.

We have eight speakers who have asked to speak in the open public hearing. I would like to arm each of these eight people with the following information.

You will be limited to five minutes each, and it is not a question and answer session for the committee. Please feel free to make your statement and then we will move on.

Thank you very much.

(Recess for lunch.)

AFTERNOON SESSION

Agenda Item: Open Public Hearing

DR. DAUM: We are going to begin the afternoon session with the open public hearing. There are now seven individuals signed up to speak. I would like to first read the statement.

Welcome to the open public hearing. Please state your name and affiliation if relevant to this meeting. The Food and Drug Administration believes that the agency and public benefit from a transparent process. It helps ensure that FDA decisions are well informed by the advice and information FDA receives from its advisory committees. I hope they feel that way after today.

If you have any financial interests relevant to this meeting, FDA encourages you to state this interest as you begin. Such interest may include a company's or group's payment of your travel or other expenses, or grant money that your organization receives from the sponsor or a competitor. If you do not have any such interest you may wish to state that for the record. If you prefer not to address financial interest you can still give comments.

With that, there are seven people signed up, as I

mentioned. I would like to point out that this is not a committee question and answer session, so we will listen to your comments and probably move on. Each person who speaks at the open public hearing has five minutes, and Dr. Vijh will help me monitor the five minute upper limit for each person.

We will begin with a man who I don't know how he would wish to be called, but it's John Joseph Monroe, Jr. Is he in the room and would he come to the microphone if he is and share with us any affiliations he cares to mention and also his open public comment.

DR. MOORE: Thank you, Dr. Daum. I work for Walter Reed National Military Medical Center. I have been working there for the last 10 or 11 years. I'm a retired medical Army medical officer. I spent 25 years on active duty. I have no financial interests and I'm here not to speak for the Department of Defense or the government but just for myself.

Just very quickly, I had the experience of dealing with many reactions to anthrax vaccine, and some of those vaccines had squalene in them. I noticed that the studies that were cited -- we had, if we're lucky, 3 years out for long-term data, but I still think we're collecting data on the Gulf War Syndrome. The Gulf War Syndrome had

no identifiable consistent series of symptoms.

Anyway, I'm just mentioning that.

DR. DAUM: Thank you very much, Dr. Moore. The next speaker is Sumiya Nakagura. I apologize if I'm mispronouncing your name but I can't read the writing very well. Is Sumiya Nakagura in the room? Then we will pass over and go to the next speaker who is Takashi Waki. Is Takashi Waki in this room? We will pass over that as well and go to Toku Onishi. Is Toku Onishi here?

This may be a short open public hearing. Steve Tian Orth from Vaxinnia? Is Sybil Tasker in the room? Barbara Low Fischer? Hello, Ms. Fischer.

MS. FISCHER: My name is Barbara Low Fischer. I'm with the National Vaccine Information Center, and I have no conflicts of interest.

Squalene adjuvants hyper-stimulate the immune system and have been linked with development of autoimmunity, narcolepsy and other chronic disease. Based on the very limited safety and immunogenicity evidence submitted by Novartis, MF59 adjuvanted Fluad vaccine should not be fast-tracked to licensure for use by seniors over age 65 in the U.S. for the following reasons.

One, FDA states there is uncertainty about how MF59 affects immune function, but it is thought to activate

local cells and has been shown to directly increase phagocytosis in human immune cells and to induce cytokines. If MF59 does that, it is an active ingredient and should be proven safe in a placebo-controlled trial.

Two, influenza vaccines induced immune-mediated responses whether adjuvanted or unadjuvanted. Comparing average responses following receipt of one adjuvanted bioactive product to those of an unadjuvanted bioactive product does not prove safety unless both are compared to an inactive placebo. Novartis did not compare Fluad to an inactive placebo.

Three, it is well known that responses to vaccination are affected by genetic factors. The pivotal study population clearly was not genetically representative of U.S. seniors over age 65, a population that’s over 80 percent Caucasian, 9 percent black, 7 percent Hispanic and 4 percent Asian. Fluad was only given to about 1,000 U.S. seniors, while more than 2,400 Fluad recipients were from countries with high majority Asian or Hispanic populations.

Four, the trial exclusion criteria is so broad that the health of most of the study participants does not match that of the majority of U.S. seniors over age 65, of whom two-thirds have two or more chronic conditions such as heart, lung and kidney disease and will be candidates for

Fluad post-licensure.

Five, compared to Agriflu, Fluad produced a much higher number of pain, tenderness, redness and swelling reports, a higher number of systemic adverse events, and more deaths and cases of new onset chronic disease.

Six, the pivotal study provides no information about the safety of giving seniors with multiple chronic conditions repeated doses of squalene adjuvant in Fluad every year, and no information about how Fluad performs when given simultaneously with other vaccines.

Seven, using surrogate markers in the pivotal study, Novartis was not able to demonstrate that Fluad was superior to Agriflu with regard to immunogenicity, while Novartis was able to demonstrate that squalene adjuvant in Fluad is more reactive.

Why does Fluad need to be fast-tracked to licensure for seniors without additional evidence? There is public concern that fast tracking Fluad is really about fast tracking MF59 to licensure so it can be added to lots of new vaccines targeting infants, pregnant women and every American without adequate evidence for safety or effectiveness. Thank you.

DR. DAUM: Thank you, Ms. Fischer.

Agenda Item: Committee Discussion and Vote

DR. DAUM: We will now turn to open committee discussion in preparation for voting on the questions that FDA has asked us to consider. I have four people already lined up to speak who are committee members. They are Ofer Levy, Ted Tsai, Patrick Moore and Melinda Wharton. We're going to start with them and then we'll continue.

The way I like to do it is to have the committee sort of free associate and say whatever is on their mind, and then once I start to hear things more than once I'll realize that it's time to vote. It's an airplane day, and the meeting is scheduled to end at 2:30.

With that, I'll call on Dr. Levy first.

DR. LEVY: If I might, I just wanted to briefly review how we started this meeting, and the first speaker I think represented FDA. I don't have the line-up in front of me now so forgive me, I lost track of her name. That was Brenda Baldwin. I believe one of the slides she showed gave some FDA test guidance in terms of what is required when an adjuvant is considered in terms of approval. I'm wondering if it's possible to briefly pull up that text and take a quick look at it again.

DR. DAUM: Dr. Baldwin do you mind if we look at your slide again?

DR. LEVY: Slide 8.

This is from Code of Federal Regulations. As I read it, an adjuvant shall not be introduced into a product unless there is satisfactory evidence it does not adversely affect the safety or potency of the product.

From this -- this is just a general discussion point for the committee. One is the topic of safety. To my understanding, that also subsumes reactogenicity, although one notes in certain academic literature that sometimes people try to distinguish acute reactogenicity from longer-term safety considerations.

But my first question to FDA would be, in this text, does reactogenicity fall under the safety category here?

DR. GRUBER: Reactogenicity would fall under safety consideration, that is right.

DR. LEVY: It would. Now I have a much more general question. Setting aside this particular example of MF59, in general, one can imagine a scenario where adding an adjuvant would make sense. You only add it if you need it, but you can imagine a scenario where it makes sense if you have a population that is not responding well and you're getting a benefit. Then it's really a risk-benefit decision, and that's alluded to in the bullet point below. On the same slide it says benefit-risk profile.

So you can imagine a situation generically where the decision is made by the government to approve something or move it forward even recognizing that you might have more of a reactogenicity signal because there are many other benefits in terms of immunogenicity and public health.

So I'm having a little trouble reconciling the different elements in this slide because, read very narrowly, that quoted sentence suggests that if the addition of the adjuvant leads to any additional reactogenicity it cannot be introduced, strictly interpreting that sentence. But that doesn't seem to be a logical conclusion. Am I misreading that?

DR. GRUBER: We do not interpret the regs in that way. What's really important here -- and this is why we added the benefit-risk profile bullet there -- is that looking at all data, the immunogenicity data in this case, the safety information including local reactions, systemic reactions, everything, that is how we make a decision that the benefits of giving this adjuvant to the targeted population that it is proposed for outweigh the potential risks.

That's the decision that we're making, so we don't really -- It's really looking at the whole dataset

and not just zeroing in on local reactogenicity that may be somewhat higher.

DR. LEVY: Acute reactogenicity or whatever. That makes sense to me. I just wanted to hear it from FDA.

The other discussion that's very pertinent here, as I understood it, the data presented today supported that the adjuvanted product is non-inferior, but with respect to the predetermined definition of superiority it fell short. That said, there seemed to be trends, or maybe there were even significant improvement, in immunogenicity. It was described to us very logically why the superiority definition needs to be the way it is to have clean categories, and I understood and accepted that explanation.

Does FDA have any further analysis for this particular adjuvanted flu vaccine given the type of data that was shown today from Novartis that the inclusion of the MF59 adjuvant seems to allow higher titers -- for example, antigen-specific titers -- that may fall short of the predetermined superiority definition but still may represent a real advantage of the formulation? Does FDA have any analysis projecting what the clinical impact would be on flu infection and morbidity and mortality?

DR. GRUBER: We don't have that additional analysis and we don't have any additional clinical data.

That being said, this vaccine if approved will be approved under the accelerated approval regulations, and we would base licensure on the immunogenicity data as a marker reasonably likely to predict the clinical benefit.

The company would then have to confirm the benefit, verify the clinical benefit by conducting a clinical endpoint efficacy study where the endpoint then is protection against influenza. That is in the regulations. That's a required step that the company will have to take.

It was asked this morning would efficacy have to be demonstrated, and the answer is yes, of course. Per our regulations, we could withdraw the approval or the license if it is shown that this vaccine does not have clinical benefit in terms of protecting against influenza disease.

I just wanted to make another point. These regulations pertain to constituent materials, and adjuvants per our law, per the regs, are folded in under the constituent materials and fall under this Reg, 610.15. That means that from a regulatory point of view, the agency, because of this law, does not consider adjuvants active ingredients. Therefore, we don't license adjuvants separately.

We have formulated policy by which we say -- and it's also in our guidance document -- that the added

benefit should be demonstrated. It can be done in early clinical trials showing enhanced immune response, for instance, of the adjuvanted formulation over the unadjuvanted formulation. We also will accept data from animal studies. The FDA has reviewed the data submitted by the applicant and we felt that the added benefit of this adjuvant as part of this vaccine formulation has been demonstrated, and it is further supported by the data that you have seen from the pivotal study that has been conducted.

So, even though the pre-specified statistical criteria for superiority have not been met for two out of three homologous strains, you have seen that superiority was clearly demonstrated against the H3N2 strain. There also, in general, seemed to be a higher immune response when the adjuvanted formulation was given versus the unadjuvanted formulation, and that's something that we summarized in our clinical guidance.

So the agency feels that the applicant did satisfy the criteria for demonstrating added benefit of the adjuvant.

DR. LEVY: Let's say the committee decided to approve and move forward, with regard to the future study Novartis would have to undertake, it would be concurrent

with general use in the population, or it would first be contingent on that study being completed by Novartis?

DR. GRUBER: If we approve the vaccine based on the immunogenicity data under the accelerated approval regs, the vaccine could then be used concurrent with the applicant conducting the confirmatory study.

DR. DAUM: Thank you, Dr. Gruber. Thank you, Dr. Levy. Dr. Tsai, I think you're next.

DR. TSAI: I guess I would like to make an observation, number one. On Slide 16 of Dr. Talbot's presentation, the difference between responses of older adults and younger adults to TIV vaccination, the fold difference between the younger adult and older adult responses is somewhere between 1.2 and twofold higher in the younger adults. It just strikes me that that gap, if you will, is made up by the adjuvanted formulation where the GMT ratios of the adjuvanted versus the non-adjuvanted vaccine is around 1.5.

To the extent that one believes that the non-adjuvanted TIV in young adults has a reasonable efficacy let's say of 70 percent, and the extent to which HI titers correlate with protection, then one might extrapolate that that fold increase conferred by the adjuvanted vaccine might bring up the efficacy in older adults up to what you

see in younger adults.

DR. DAUM: Dr. Moore, are you available? You are next with your question of this morning.

DR. MOORE: I guess my only concern on this half of the conference is that it seems that there is some evidence for serious adverse effects and also deaths in the second dose and revaccination studies. I just want to throw out to the FDA the possibility that, in addition to having efficacy studies proven, also there be post-marketing surveillance that at least focuses on second-dosing adverse effects that may uncover something that otherwise we're not seeing in these smaller studies.

DR. DAUM: Thank you very much, Dr. Moore, I appreciate that. Dr. Wharton, I think you're next.

DR. WHARTON: I think this question is for Novartis. In the Novartis briefing document there is mention of a proposed confirmatory study scheduled to begin in October 2015, which I think is next month, and I was interested in hearing about that.

DR. DAUM: Does anyone with Novartis wish to comment? Please go ahead.

DR. HEIJNEN: I can show you the design of the confirmatory study in this slide set. It will be a randomized, observer-blinded, active controlled multi-

center study. The objective of the study will be to evaluate the clinical efficacy of aQIV to prevent influenza in subjects equal to or greater than 65 years. We plan to randomize approximately 10,000 subjects in this trial, so not 100,000 like it says on this slide, and the trial starts in October 2015.

Subjects will be randomized in a one-to-one ratio to aQIV, so to the quadrivalent vaccine, or to a licensed TDAP vaccine.

DR. WHARTON: And where will this be conducted?

DR. HEIJNEN: We plan to start the trial in October in Estonia and Poland, so that is the first season in which we enroll subjects. And depending on the outcome of the first season, we will continue in additional countries.

DR. DAUM: This will be with an adjuvanted quadrivalent vaccine?

DR. HEIJNEN: That is correct. Adjuvanted TIV and adjuvanted QIV are actually the same vaccine, produced the same rate. The only difference is an additional B strain which is added. We know they contain the same dose of MF59, and we also know from the literature and from our own research that addition of an additional B strain will not have an impact on the response for the other three

antigens or on the safety profile.

DR. DAUM: Thank you. Dr. Levandowski.

DR. LEVANDOWSKI: I've got a riff on what Dr. Levy was bringing up before, and I think probably Novartis will need an opportunity to respond to this if they wish to. This is coming back to the potency test.

This vaccine, as I understood it, is tested both at the monovalent concentrate stage, the drug substance, and then at the formulated trivalent stage with the adjuvant, the drug product. Testing the drug substance, the monovalent would be no big deal because that's the same as everybody else would be doing in the world. But testing the trivalent formulated vaccine, remember, dealing with 45 micrograms of hemagglutinin equivalent and 10,000 micrograms of another lipid type substance, the squalene that's added to it.

I bring this up because the SRID test is an immunologic test. It's based on reacting an antibody with the hemagglutinin antigen, and the way that's done is to embed the antibody in an agarose gel, punch holes in the gel, add the antigen into the wells and let the antigen diffuse out, and it's the interaction between the antigen and the antibody which can be stained and show the zone of how much antigen is present. The zone size is proportional

to how much antigen is present.

But this is dependent upon a detergent that's used to solubilize the hemagglutinin, and normally, the amount of detergent that's being used is enough to adequately solubilize the 45 micrograms of hemagglutinin, but I don't know how it reacts with the squalene and other things.

I bring all this up because if there's interference by squalene in the test -- and I don't know how they do it; we haven't heard that -- it would be on the side of under-estimating the amount of antigen that's present. If it's underestimated, it means that some of the results we're seeing in terms of immunogenicity may be explained just by additional antigen that's present. We haven't heard anything about studies that would be the equivalent of mixing the antigen and the adjuvant at the bedside, as compared to the pre-formulated material.

I just bring this up because if there is an under-estimation it's possible that the benefit of the vaccine results from just more antigen being added.

DR. DAUM: Thank you. Does Novartis care to respond?

DR. LINDERT: I'll start the response and I'll ask Dr. Singh also to comment. I should indicate we do

have early Phase 1 studies that were not reviewed extensively in the field that do refer to the bedside mixing, and the immunogenicity responses with MF59 given alone versus combined were comparable. So at least the human response was similar irrespective of the formulation used.

DR. SINGH: With regard to the estimation of the flu antigen in the presence of MF59, we use a unique feature of the MF59 adjuvant which is most of the antigen actually is not bound to the oil droplets; it's actually floating in the 95 percent aqueous base which the emulsion has. We spin up the emulsion so the oil phase actually spins to the top and you have a clear subnatant which contains all the antigen in it. That clear subnatant is then separated out and run on the SRID as you would run your monovalent antigen.

In our assessment, we did not find any interference of running the SRID assay in a monovalent form or trivalent form but also in combination with MF antigen.

DR. DAUM: Thank you very much. Dr. Sawyer.

DR. SAWYER: First a question for you. Are we going to address safety separately, because my question relates to safety. The question on the screen is efficacy.

DR. DAUM: Can we see question 2?

DR. SAWYER: My question relates to this. Do you want me to wait or ask it now?

DR. DAUM: I want you to ask it now.

DR. SAWYER: I share the concern that Dr. Moore started voicing about what we know about repeat doses, and I thought I heard him ask a question that FDA might respond to; that is, are the post-licensing studies that will be required for this accelerated approval, will they include safety data specifically with regard to re-vaccination, or not?

My second related question, and I'm not sure who could answer it, is I am somewhat reassured by the 83 million doses of this vaccine that have been used around the world. I'm wondering if the safety infrastructure in the countries in which it's used is good enough that we could assume we would have learned by now about problems with repeat doses.

DR. DAUM: I would ask the agency if they want to comment on either or both, and Novartis, also.

DR. BROWNE: Currently, the post-marketing pharmacovigilance plan does not intend to look at revaccination of elderly adults. There are some pediatric studies that are planned which do have extension phases, so we would have data in children, but so far, it would only

be voluntary reporting.

DR. DAUM: Does Novartis wish to respond to that?

DR. LINDERT: I think we should remind ourselves, though, that our post-marketing experience certainly has involved individuals who have received multiple vaccinations of Fluad in the 17 years that it has been available. With that, again, we have looked at disproportionality in terms of any safety signal as it relates to our other licensed non-adjuvanted influenza vaccines. While the trial was small numbers and did have some differences we couldn't explain, we have not seen this translate into a difference in continued use in the public.

And the second part of your question was --

DR. SAWYER: The safety infrastructure in the countries in which it is used routinely.

DR. LINDERT: The countries where aTIV is currently mostly used include Italy, Germany and Argentina. These are industrialized countries that have been reporting robust data, and roughly 50 percent of the doses that we have are sold in those markets.

DR. LEVY: I have two quick follow-up questions for FDA. One is to review just briefly the rationale for accelerated designation. Here I would imagine it's because flu vaccines still aren't as good as we hoped they would

be, particularly to a given target population like the elderly. But I just wanted to hear that briefly.

Secondly, regarding correlates of protection, obviously that's a huge issue, and obviously the HAI titers is what people are hanging their hats on right now although there is abundant scientific interest and literature that that may or may not be the be-all and end-all. We didn't hear as much about cellular correlates but I don't think there are any gold standard cellular correlates, but they might be important.

Has FDA concluded that the HAI is sufficient here to predict clinical efficacy in elderly individuals?

DR. DAUM: Does anyone at the agency want to take that question?

DR. GRUBER: I will at least take the first part of the question, and I would like to read from our guidance document, and that is why the accelerated approval regulations applied to Fluad or seasonal inactivated influenza vaccine, so here goes.

The option to pursue an accelerated approval pathway for seasonal inactivated flu vaccines is available to sponsors if a shortage of flu vaccine exists for the U.S. market at the time the new vaccine is approved. FDA interprets the accelerated approval regulations as allowing

accelerated approval of a flu vaccine during a shortage because influenza is a serious and sometimes life-threatening illness. Providing prophylaxis to those who would not otherwise be immunized during a shortage does certainly provide a meaningful benefit over then-existing treatments which are in short supply at the time. We understand a shortage to exist when the supply of flu vaccine is inadequate to immunize all persons for whom the CDC recommends annual vaccination.

That is the rationale for applying the accelerated approval regs to this product.

DR. DAUM: Are you saying that it would only be used during a shortage?

DR. GRUBER: No. If a shortage of flu vaccine exists at the time when approval of a new vaccine is considered, then the accelerated approval regulations will apply because if there is not enough flu vaccine available, then making this new vaccine available would be a benefit over existing treatments. Right now, the situation is that the doses of seasonal inactivated flu vaccine that are available year by year are short of what CDC recommends in terms of who is going to get the flu vaccines.

DR. LEVY: Thank you. With regard to the correlates of protection question, does anybody at FDA have

a position or opinion on HAI titers as a surrogate, particularly in the elderly?

DR. WEIR: I was prepared to answer it until you added that last part. Originally, I think your question was why HI may not be the be-all and end-all of assays. I think most folks in the field would agree that no assay is perfect, but HIs are still the ones that we have the most experience with, we've used for years, many manufacturers, many products. It's probably easier to standardize than any other assay, so I think there are more advantages to that assay than anything else, although for years we have encouraged sponsors to include other assays, serological assays or other types of assays, in their trials so that we can accumulate more data with other assays. So we're open to that. But HIs still have probably more history and we have more experience with them than anything else.

I can't answer the last question, how much reliance we would have on the HI predicting benefit in the elderly specifically. I don't know if we have that or not.

DR. GRUBER: We used the same criteria when we approved the high-dose inactivated flu vaccine Fluzone. It was also an accelerated approval, and the HI titer was used as a marker reasonably likely to predict clinical benefit, and that was subsequently verified in a clinical endpoint

efficacy study conducted with that high-dose vaccine.

DR. DAUM: Thank you, Dr. Gruber. Dr. Pebsworth.

DR. PEBWORTH: I think this is my eighth year or so on this committee; I keep being pulled back as the consumer rep. The very first meeting I was at I was asked whether I thought that MF59 in adjuvants should be separately licensed from vaccines, and I said, well, if they are bioactive and they cause the body to do something, then we should understand the effect of these adjuvants separate from the vaccines that they are included in. Otherwise, from a safety perspective you really don't know what is doing what. Well, that was years ago and here we are now, and the regulations are what they are.

It's very surprising to me that we find ourselves in the situation where we have nine flu vaccines that are available to seniors in the U.S. We have up for consideration a vaccine that has not been demonstrated to be more potent than a competitor vaccine, but is more reactive. The reactogenicity and the adverse events profile is extremely difficult to parse out from the data that we were provided.

I have tried very hard to go through this, and while everyone admits that there is local transient reactivity, there is a very consistent pattern across more

serious events where the adjuvanted vaccine has a higher number of reports of myalgia, arthralgia, fatigue, MIs, deaths, afib. There's a long list.

I can't help but wonder whether we are not getting a clear signal on some of these adverse events because of the size of the sample. The sample is small. I'm finding it extremely difficult to make sense of the pooled data we were provided. We're basically given apples, oranges and bananas to try to understand and sort out what the signal is in here.

At the same time, it's not hard to google MF59 and adverse events and find cases of autoimmune hemolytic anemia that hasn't been discussed in here, and I see bleeding disorders as a criterion for being excluded from the study. There are just a lot of unanswered questions, and I don't see the reason to rush at this point. Why do we have to rush to push through something that has the potential to cause harm in some people?

Additionally, lastly I will say -- this is sort of a question for the FDA on Slide 33 of the presentation. We were provided some data for high-risk subjects. As was stated earlier, 80 percent of the seniors in the U.S. have at least one comorbid condition; 68 percent have two or more. So we're provided on Slides 33 and 34 the

superiority analysis for both homologous and heterologous strains, and you see here in high-risk subjects that it's not necessarily not inferior.

I don't know what the profile is like for reactions in high-risk subjects, but I think that ought to be clearly understood since that is the population to whom this vaccine is going to be prescribed.

DR. DAUM: As we move forward towards voting on these questions, I would like to remind people seated at the table, committee members, that we want to hear from everybody. If you haven't spoken this afternoon, please consider that. As the discussion continues I would like to hear from everybody before we vote.

Who would like to speak? Dr. Piedra.

DR. PIEDRA: This is more of a commentary. I think the issue of risk versus benefit becomes very relevant. We know that for elderly adults, the standard influenza vaccine is not what we would like to have, so there is a real need to have a better vaccine and I think that's where the high-dose Fluzone came in, and in essence, that's what this one is trying to do.

There is clear evidence that for the H3N2 component, this vaccine is superior to their comparator vaccine. It's eliciting a higher geometric mean titer and

greater seroconversion, and that's the virus that causes the greatest mortality in older adults. It's unclear why it doesn't work as well for the influenza B and I wish they would comment on that, which has not been at least discussed.

Where I feel a little uncomfortable and I think you're hearing the same from other committee members is that we don't have good data in a controlled fashion on what happens with repeated immunizations. What is the safety in particular with repeated immunizations? There's a slight signal in year 2 that is confounded and we don't know what it means, and it disappears in year 3. It would appear to me that when one is considering efficacy, one also would think about safety not just in one year but think about what happens in safety in subsequent years. I hope that Novartis would consider that in their trial design.

DR. DAUM: Thank you very much, Dr. Piedra. Does anyone at Novartis wish to respond to Dr. Piedra's comment?

DR. LINDERT: We will take his comments under consideration with respect to the concerns. However, I would actually, if the opportunity allows, show the deaths that occurred in year 2, since this has come up in a few comments. I think that will help to illustrate what we're

looking at here.

As we described previously, there is a numerical imbalance -- 17 after aTIV vaccination versus 6. Within each group there is one death that occurs prior to 30 days following vaccination, and the rest were later in the follow-up studies.

The medical evaluations by the physicians overseeing the care of these individuals, who were largely those who were institutionalized, suggested no relationship to the study vaccine. When you look at the causes of death, these causes were consistent with their underlying medical conditions that put them in the institutionalized care to begin with.

DR. DAUM: Thank you for showing us those.

DR. ENGLUND: I just wanted to say, as a person who conducts clinical trials, I actually find this data quite reassuring. I think it needs to be really emphasized that doing clinical trials in this patient population is incredibly difficult. It takes time and effort, and this population is not easy.

DR. DAUM: You mean people over 65.

DR. ENGLUND: I mean people over 65, and particularly I mean the nursing home residents. I think it could have been a cleaner trial if they had left out those

nursing home residents, but in fact they included them, and I think that's important and I appreciate seeing the specific examples of the cause of death.

It has been commented even in the audience that there was no placebo group. It is totally unacceptable in this day and age to give placebo to this patient population, so I do not expect to see placebo. I think their comparator is a reasonable comparator. Follow-up is something that absolutely needs to be conducted, as Dr. Piedra said.

DR. DAUM: Dr. Long and Dr. Sawyer.

DR. LONG: I have questions related to what seems to be superiority of H3N2 in some population and the high sero-positivity rate in the individuals in the pivotal study. That was over 80 percent, and it was not different in the two groups, but it was quite high. I wonder how that compares with the U.S. population.

The second question would be it's possible, when you're not doing a study when you know those things about the patient, which I understand is what the Canadian effectiveness was about, that there could be differences in the groups you're looking at depending on who was sero-positive to begin with. That could potentially affect your outcome.

So the questions are do we know what the sero-positivity in the United States would be like. Would it be close to 80 percent in this group? Is there anyone who thinks that that has anything to do with the response to this vaccine and how it might have affected the effectiveness from Canada?

And the final thing which you may have mentioned but I didn't hear is who were these healthier patients. The ones in which there was the pretty dramatic difference in effectiveness in Canada was among healthier subjects or healthier people, and I didn't know what that meant.

DR. DAUM: You have asked two questions and I think both the agency and the company could comment on both or either.

DR. LINDERT: I'll ask Dr. Heijnen to discuss the sero-positive data, and then I'll ask Dr. Van Buynder to also comment on the Canadian experience with the healthy versus unhealthy subjects.

DR. HEIJNEN: With regards to the sero-positivity data, we looked into this for U.S. and for the other countries, what was the percentage of sero-positivity in those countries, and I can show you the slide.

For H3N2 it was more or less comparable. U.S., Philippines, Panama, Colombia, they all were about 80

percent sero-positive for H3N2. For H1N1 and for B, you see a difference between the U.S. and the other countries.

I think more importantly, if you look to the subgroup analysis comparing sero-positive patients and non-sero positive patients, we didn't see a difference in the response, any difference between aTIV and TIV.

DR. VAN BUYNDER: The Canadian population had obviously different arms because of the excess nursing home and very elderly that were in the aTIV group. What this would do, similar to what happened in the LIVE studies, is actually skew against benefit being seen with aTIV. In the same way Lombardie had a group of people who were 17 percent more likely before the study to be hospitalized because of their comorbidities, and then 25 percent less likely afterwards. The absolute benefit of 25 percent that was recognized in fact under-estimates the true benefit, which is more than that because of the group.

Perhaps it wasn't clear what I was saying about the relative benefit in the healthy compared to in the nursing homes in Canada. In the healthy population where we tried to actually standardize for less comorbidities and factor the confounders into the multivariate analysis, the absolute difference was 73 percent to 42 percent, and in that group it was very similar to the overall live data.

When we looked at the nursing homes, the difference was greater but the figures fell in both of them, so there was a lot of internal consistency in the data within Canada. The nursing home data suggested that aTIV was less effective in those with comorbid conditions who were very old, but TIV was actually ineffective that year in that group, as we've seen in America in 2012-2013 and 2014-2015.

Similarly, when we looked at all the other subgroup analyses, the older you were, as we moved to the 65+, 75+, 85+, the less likely it was that you had very high vaccine effectiveness data. So there was consistency in that while aTIV was better, and this was actually more marked in those with high comorbidities, the benefit of the vaccine decreased as you became less healthy yourself, and as you became older.

The only inconsistent data point that we saw was that the hospitalization benefit was excessive in the long-term care facilities compared to the non-long-term care facilities, which was unexpected but explicable on the basis that if you're 85 years of age and you have multiple comorbidities and you're living with dementia and you get influenza, there's a tendency for the physicians to not admit you to hospital anyhow, and that's why that wasn't

reported in the study data.

DR. LEVY: In the statements you just made to us, those were clinical efficacy data, is that right? Is that from microbiologically confirmed influenza infection? I know you showed those slides, but remind us of your definition of effectiveness.

DR. VAN BUYNDER: Correct. The difference between the three studies, the pivotal, the LIVE and the Canadian studies, was in their definitions of what was a case. In the Canadian study it was laboratory-confirmed influenza that was the definition.

DR. PEBSWORTH: Could we go back to a slide that was up there a few minutes ago? Is that saying that at baseline, when the study was started, about 70 percent of subjects had positive titers? Did I misunderstand?

DR. LINDERT: They were sero-positive, yes. They had an HI titer of 10 or greater, but not seroconverted at 40 or greater.

DR. PEBSWORTH: So help me understand. On the FDA's presentation on Slides 27 and 28, for example, influenza B for the homologous strains, the 28 there on the titers, what does that mean? Does that mean 28 subjects?

What does 28 mean on the row for influenza B? Is that 28 subjects had -- oh, that's the titer.

DR. BROWNE: Those are the absolute GMTs at day 22, and then for the ratio, which is where we look for non-inferiority, it's the ratio of that GMT to Agriflu. So it would be 28 over 24 which gives you a ratio of 1.15.

DR. PEBSWORTH: Okay. So what does this mean in terms of 70 percent of the study population already being positive at baseline?

DR. BROWNE: If you go to the next slide, that would really refer more to seroconversion rate difference. The way you define seroconversion is either a pre-vaccination titer of less than 10 and a post-vaccination of greater than or equal to 40. For those positive subjects, which you're talking about, it would be a fourfold rise in HAI titer if their pre-vaccination titer was greater than or equal to 10. So either one would be the definition of seroconversion.

DR. DAUM: Thank you, Dr. Browne. I have Dr. Sawyer next and then Dr. Hudgens.

DR. SAWYER: I just want to provide a last commentary on the safety question. Given the data we have already seen and the likelihood that additional clinical trials are going to further educate us about very rare side effects is low, and I think we are only going to learn in post-marketing studies about that. Having said that, I

would encourage FDA to consider asking the company to, in their post-marketing study, include a group with revaccination so we could at least start to address that question.

My next commentary is related to the use of the accelerated approval. I have a little trouble considering influenza vaccine in short supply since we end up throwing a lot away at the end of the year; however, we definitely, as Dr. Piedra mentioned, are in short supply of an adequate vaccine for seniors that works well. I don't think we're being asked whether it's appropriate to have this on the accelerated pathway, but using that logic I am comfortable with it.

DR. DAUM: Thank you, Dr. Sawyer. Dr. Hudgens.

DR. HUDGENS: I would just like to second Dr. Piedra's suggestion that the efficacy trial last 2 years instead of 1 year so we could look at revaccination.

I also have a question for the agency, whether or not it was acceptable to use the quadrivalent vaccine in the confirmatory efficacy trial, given that all the discussion here today is about the trivalent version of vaccine.

DR. DAUM: Does anyone at the agency wish to comment?

DR. GRUBER: The agency does consider it adequate to use the quadrivalent formulation in that efficacy study, and I think that has been done before. As was mentioned, there was the addition of the second B strain in there, and of course we'll have appropriate criteria and definitions around what a case is. I think that is considered adequate and we agreed to use the quadrivalent formulation.

DR. LEVY: I would also encourage FDA, if Novartis is asked to do another efficacy trial, to design and power it so that statements could also be made comparing male and female study participants based on a growing literature of sex effects on immunology and vaccine responses.

DR. DAUM: I'm starting to hear comments repeatedly and bringing things to a close is in the future. In the meantime, Dr. Long.

DR. LONG: I am wondering, if you're going to use the quadrivalent as the test vaccine, would you require non-inferiority for all four? Then what would superiority be, if this is an efficacy trial?

DR. GRUBER: The confirmatory study is not going to be an immunogenicity study. The endpoint is prevention of influenza disease, so that will be the endpoint.

DR. DAUM: Other comments from committee members?

DR. TSAI: It seems that many of the questions and comments have been directed at ascertaining whether the adjuvanted vaccine is superior or has increased benefit over the non-adjuvanted vaccine. But as I understand the question, it is not framed as a question around superiority. It's whether the vaccine works, so to speak, whether it's effective or efficacious, not whether it's better than the non-adjuvanted vaccine. Is that correct?

DR. DAUM: The question was on the screen. I don't think either of those is the question. What I mean by that is the question is are the immunogenicity data adequate to support the effectiveness of Fluad under the accelerated approval regulation for the prevention of influenza disease in adults 65 years of age and older. To me, the committee has to decide whether for this vaccine the immunogenicity data are adequate to support an accelerated approval in this age group. I don't think there's any other thing to read into it.

DR. LONG: But I don't think it's possible to dissociate the potential risk of what we don't know from our understanding of this vaccine as potentially being better than non-inferior, and for this age group who needs it most. I understand that the questions are separate and none of them have to do with superiority. Do you think

it’s possible for us to answer these two questions as if they are not connected in some way?

DR. DAUM: The second question being safety. Yes, I think it’s possible. Dr. Pebsworth.

DR. PEBSWORTH: Considering that we’re going to be asked to vote on effectiveness and the flu goes around every year, is there some reason that we can’t be or haven’t been provided with true effectiveness data? Does Fluad, and for that matter does Agriflu, prevent people from getting the flu?

DR. DAUM: I am not hearing anymore questions or comments from the committee. I think it’s time to vote. First, Dr. Vijh wants me to tell you this.

An electronic voting system in which the votes are cast simultaneously will be used. While you are in the process of voting, the buttons you have in front of you will keep flashing. Please press yes, no or abstain depending on your vote. While the vote is open, if you would like to change your vote simply press a different button. This will change your vote for the record.

The buttons will keep flashing until the voting is officially closed and your vote is locked in. The votes will be displayed on the TV screen. For the record, Dr. Vijh will read and tally the votes.

Any further discussion or any questions about the voting procedure? Okay. In that case we will consider question one, and I will read it.

Are the immunogenicity data adequate to support the effectiveness of Fluad under the accelerated approval regulation for the prevention of influenza disease in adults 65 years and older? That is question one, and the committee should now vote.

Dr. Moore has voted, and he has sent the votes to Dr. Vijh, and she will press the button for Dr. Moore.

(Pause)

DR. DAUM: My first time as Chairman of this committee we used to go around the table and ask each person to vote. I kind of liked it. We're waiting for the electronic version to come up.

DR. VIJH: I am going to read the individual votes and then present the tally. Dr. Long yes, Dr. Gellin yes, Dr. McInnes yes, Dr. Levy yes, Dr. Piedra yes, Dr. Levandowski yes, Dr. Sawyer yes, Dr. Moore yes, Dr. Daum abstained, Dr. Pebsworth no, Dr. Englund yes, Dr. Hudgens yes, and Dr. Wharton yes. If my math is correct, it's 11 yes, one abstain and one no.

DR. DAUM: Thank you, Dr. Vijh. We will now go to the second question. The second question is, are the

available data adequate to support the safety of Fluad when administered to adults 65 years of age and older?

(Pause)

DR. VIJH: Dr. Long yes, Dr. Gellin yes, Dr. McInnes Yes, Dr. Levy yes, Dr. Piedra no, Dr. Levandowski yes, Dr. Sawyer yes, Dr. Moore yes, Dr. Daum abstain, Dr. Pebsworth no, Dr. Englund yes, Dr. Hudgens yes and Dr. Wharton yes. That's a total of 10 yes, two no, and one abstain.

DR. DAUM: Thank you very much, Dr. Vijh, and thank you to the committee members for a wonderful airing of the issues related to this vaccine. I don't see any further reason to continue this meeting and, therefore, believe it should be adjourned, and thanks to the committee very much.

(Meeting adjourned at 1:25 p.m.)