Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

179th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

Zoom Video Conference

March 1, 2023

This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO.

Participants

Chair	Hana M. El Sahly, M.D.	Professor, Baylor College of Medicine	Houston, TX
Voting Members	Adam C. Berger, Ph.D.	Director, Clinical and Healthcare Research Policy, NIH	Bethesda, MD
	Henry (Hank) Bernstein, D.O., MHCM, FAAP	Professor, Zucker School of Medicine	New Hyde Park, NY
	Amanda Cohn, M.D.	Chief Medical Officer, National Center for Immunizations and Respiratory Diseases, CDC	Atlanta, GA
	Holly Janes, Ph.D.	Professor, Fred Hutch Cancer Center	Seattle, WA
	David Kim, M.D., M.S., M.H.A.	Director, Division of Vaccines, HHS	Washington , DC
	Steven Pergam, M.D.	Professor, Fred Hutchinson Cancer Center	Seattle, WA
	Stanley Perlman, M.D., Ph.D.	Professor, University of Iowa	Iowa City, IA
Consumer Representative	Jay Portnoy, M.D.	Professor, University of Missouri Kansas City School of Medicine	Kansas City, MO
Alternate Industry Representative	Gregg Sylvester, M.D., M.PH.	Vice President of Medical Affairs, Seqirus Inc.	Summit, NJ
Temporary Voting Members	Daniel Feikin, M.D., M.S.P.H.	Respiratory Diseases Consultant	Coppet, Switzerland
	Marie Griffin, M.D., M.P.H	Professor, Vanderbilt University School of Medicine	Nashville, TN
	James Hildreth, Sr., Ph.D., M.D.	President, CEO, Meharry Medical College	Nashville, TN
Guest Speaker	Ann R. Falsey, M.D.	Professor of Medicine, University of Rochester	New York, NY
FDA Participants/Staff	Peter Marks M.D., PhD.	Director, CBER, FDA	Silver Spring, MD
	David C. Kaslow, M.D.	Director, Office of Vaccines Research and Review (OVRR), CBER, FDA	Silver Spring, MD
	Goutam Sen, Ph.D. (Speaker)	Microbiologist, Division of Vaccines and Related Products Applications (DVRPA), OVRR, CBER, FDA	Silver Spring, MD
	Joseph Toerner, M.D., M.P.H.	Acting Deputy Director, OVRR, CBER, FDA	Silver Spring, MD
	Lucia Lee, M.D.	Lead Medical Officer, Clinical Review Branch I, DVRPA, OVRR, CBER, FDA	Silver Spring, MD
	Nadine Peart Akindele, M.D. (Speaker)	Medical Officer, DVRPA, OVRR, CBER, FDA	Silver Spring, MD
	Nicholas Geagan, D.O., STN (Speaker)	Staff Fellow, DVRPA, OVRR, CBER, FDA	Silver Spring, MD
	Santosh Nanda, DVM, Ph.D. (Speaker)	Microbiologist, DVRPA, OVRR, CBER, FDA	Silver Spring, MD

	Sudhakar Agnihothram, B.Pharm., Ph.D.	Biologist, OVRR, CBER, FDA	Silver Spring, MD
Designated Federal Officer (DFO)	Sussan Paydar, Ph.D.	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
Alternate DFO	Valerie Vashio, B. Pharm, RPh, RAC	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
Director	Prabhakara Atreya, Ph.D.	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
Committee Management Specialist	Lisa Johnson	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
Committee Management Officers	Karen Thomas	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
	Joanne Lipkind, M.S.	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD

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Call to Order and Welcome

Dr. El Sahly: Good morning, everyone. Welcome to the 179th VRBPAC committee meeting. This is day two of our meeting. During today's meeting, we will be discussing, in open session, the safety and effectiveness of RSV Vaccine Recombinant, Adjuvanted, manufactured by GSK, with a requested indication in BLA application, BLA125775 for active immunization, for the prevention of Lower Respiratory Tract Disease caused by RSV-A and RSV-B subtypes in adults 60 years of age and older.

I'd like to remind the committee members that we encourage questions, and please use the reaction button at the bottom of your screen to raise the hand so I can call upon you to ask your questions or your comments and turn on your camera and microphone for that.

We begin with Dr. Sussan Paydar, who is the Designated Federal Officer for the meeting today, and she will be now walking us through some housekeeping items and the COI statements.

Dr. Paydar: Thank you, Dr. El Sahly. Good morning, everyone. This is Dr. Sussan Paydar, and it is my great honor to serve as the Designated Federal Officer for today's 179th Vaccines and Related Biological Products Advisory Committee Meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, CBER, and the Committee, I'm happy to welcome everyone for today's virtual meeting.

Today, the committee will meet in open session to discuss and make recommendations on the safety and effectiveness of RSV, Respiratory Syncytial Virus Vaccine, Recombinant, Adjuvanted, manufactured by GSK, with a requested indication in Biologics License Application number 125775, SDN 125775/0, for active immunization for the prevention of Lower

Respiratory Tract Disease, LRTD, caused by Respiratory Syncytial Virus RSV-A and RSV-B subtypes in adults 60 years of age and older.

Today's meeting and topic were announced in the Federal Register Notice that was published on February 1st, 2023.

At this time, I would like to introduce and acknowledge outstanding leadership of my division director, Dr. Prabhakara Atreya, and the excellent work of my team whose contributions have been critical for preparing today's meeting, Ms. Valerie Vashio, Ms. Karen Thomas, Ms. Joanne Lipkind, and Ms. Lisa Johnson. I also would like to express our sincere appreciation to Mr. Derek Bonner in facilitating the meeting today. Also, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes, trying to ensure that today's virtual meeting will also be a successful one, like all the previous VRBPAC meetings.

Please direct any press media questions for today's meeting to FDA's office of the Media Affairs at fdaoma@fda.hhs.gov. We'll begin today's meeting by taking a formal roll call for the committee members and temporary voting members. When it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name, institution and areas of expertise, and when finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slides in which we will begin with the chair, Dr. Hana M. El Sahly. Dr. El Sahly, can we start please?

Committee Introductions

Dr. El Sahly: Thank you. Good morning, everyone. Hana El Sahly, Baylor College of Medicine, adult infectious diseases with interest and focus on clinical vaccine development.

Dr. Paydar: Thank you, Dr. El Sahly. Next is Dr. Adam Berger.

Dr. Berger: Hi, Adam Berger. I'm the Director of the Vision of Clinical and Healthcare Research Policy here at the National Institutes of Health. I'm a geneticist by training. Thanks.

Dr. Paydar: Thank you, Dr. Berger. Next is Dr. Hank Bernstein.

Dr. Bernstein: Good morning. My name's Hank Bernstein. I'm a professor of pediatrics at the Zucker School of Medicine at Hofstra Northwell. I am a general pediatrician with expertise in pediatrics and vaccines. Thank you.

Dr. Paydar: Thank you, Dr. Bernstein. Next is Captain Amanda Cohn.

Dr. Cohn: Good morning. I'm Dr. Amanda Cohn. I'm a pediatrician and medical epidemiologist of the Centers of Disease Control and Prevention with expertise in vaccine epidemiology.

Dr. Paydar: Thank you, Dr. Cohn. Next is Dr. Holly Janes.

Dr. Janes: I'm here. Thank you. Good morning. I'm Holly Janes. My training is in biostatistics. I'm a professor at the Fred Hutch Cancer Center, and my expertise is in vaccine trial design and analysis. Thank you.

Dr. Paydar: Thank you, Dr. Janes. Next is Captain David Kim.

Dr. Kim: Good morning. This is David Kim with the National Vaccine Program and the Office of Infectious Disease and HIV aids policy. That's in the office of the Assistant Secretary for Health, and I'm here on behalf of the Assistant Secretary for Health. And my office is particular interested in vaccine policy. Thank you.

Dr. Paydar: Thank you. Next is Dr. Steven Pergam.

Dr. Pergam: Thanks, Dr. Paydar. I'm Steve Pergam. I'm a professor at Fred Hutch Cancer Center with training in adult infectious diseases, and my main focus is on infections in immunocompromised hosts.

Dr. Paydar: Thank you so much. Next is Dr. Stanley Perlman.

Dr. Perlman: Good morning. I am a professor of microbiology and immunology at the University of Iowa, and my expertise is in pediatric infectious diseases and in coronaviruses.

Dr. Paydar: Thank you, Dr. Perlman. Next is Dr. Jay Portnoy, our consumer representative.

Dr. Portnoy: Good morning. I'm Dr. Jay Portnoy. I'm a professor of pediatrics at the University of Missouri, Kansas City School of Medicine. I'm an allergist immunologist in the section of allergy immunology at Children's Mercy Hospital in Kansas City.

Dr. Paydar: Thank you, Dr. Portnoy. Next is Dr. Gregg Sylvester, our alternate industry representative.

Dr. Sylvester: Good morning. My name is Gregg Sylvester. I'm the Chief Health Officer for CSL Seqirus, a vaccine manufacturer. My background, I'm a physician, pediatrician, and preventive medicine specialist.

Dr. Paydar: Thank you, Dr. Sylvester. Next, we'll do a roll call of our temporary voting members. We begin with Dr. Marie Griffin.

Dr. Griffin: Good morning. My name is Marie Griffin. I'm professor emerita of Health Policy at Vanderbilt University. I'm a general internist and pharmaco-epidemiologist.

Dr. Paydar: Thank you, Dr. Griffin. Next is Dr. Daniel Feikin.

Dr. Feikin: Hello. My name is Daniel Feikin. I trained in internal medicine and spent my career working as a medical epidemiologist at CDC. I'm currently a consultant, living in Geneva, Switzerland, specializing in respiratory diseases and vaccines. Thank you.

Dr. Paydar: Thank you, Dr. Feikin. And last but not least, Dr. James Hildreth.

Dr. Hildreth: Thank you, Sussan. I'm James Hildreth. I'm the president and CEO of Meharry Medical College. I'm also professor of internal medicine. I'm an immunologist and my research focuses on the immune response to viruses. Thank you.

Conflict of Interest Statement

Dr. Paydar: Thank you, Dr. Hildreth. Thanks everyone. We have a total of 13 participants, 12 voting and one non-voting member. Now I'll proceed with reading the FDA conflict of interest disclosure statement for the public record. The Food and Drug Administration, FDA, is convening virtually today, March 1st, 2023, the 179th meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972.

Dr. Hana El Sahly is serving as the chair for today's meeting. Today on March 1st, 2023, the committee will meet in open session to discuss and make recommendations on the safety and effectiveness of RSV, Respiratory Syncytial Virus Vaccine Recombinant, Adjuvanted, manufactured by GSK with a requested indication in biologics license application number 125775, SDN 125775/0 for active immunization for the prevention of lower respiratory tract disease, LRTD, caused by Respiratory Syncytial Virus RSV-A and RSV-B subtypes in adults 60 years of age and older.

This topic is determined to be a particular matter involving a specific party, PMISP. With the exception of industry representative member, all standing and temporary voting members of the VRBPAC are appointed special government employees, SGEs, or regular government employees, RGEs, from other agencies, and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, including but not limited to 18-USC Section 208, is being provided to participants in today's meeting and to the public. Related to the discussions at this meeting, all members, RGEs, and SGE consultants of this committee have been screened for potential financial conflict 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 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are current or under negotiation. FDA has determined that all members of this advisory committee, both regular and temporary members, are in compliance with federal ethics and conflict of interest laws.

Under 18-USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts of interest, when it is determined that the agencies' need for special government employee services outweighs the potential for a conflict of interest created by the financial interest involved, or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Based on today's agenda and all financial interests reported by committee members and consultants, there has been one conflict of interest waiver issued under 18 US Code 208 in connection with this meeting. We have the following consultants serving as temporary voting members, Dr. Marie Griffin, Dr. Daniel Feikin, and Dr. James Hildreth. Dr. Gregg Sylvester of

Seqirus Incorporated will serve as the alternate industry representative for today's meeting. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the committee.

Dr. Jay Portnoy is serving as the consumer representative for this committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee. FDA encourages all meeting participants, including open public hearing speakers, to advise the committee of any conflict relationships that they may have with any affected firms, its products and, if known, its direct competitors.

We would like to remind standing and temporary members that if the 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 inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record.

This concludes my reading of the Conflicts of Interest statement for the public record. At this time, I would like to hand over the meeting to our chair, Dr. El Sahly.

FDA Introductions

Dr. El Sahly: Thank you, Dr. Paydar. The FDA introductions are next on our agenda. And first off, I'd like to welcome Dr. David Kaslow, who will provide the welcome to the meeting.

Welcome — Dr. Kaslow

Dr. Kaslow: Thank you, Dr. El Sahly. And welcome back to the 179th convening of VRBPAC for day two. Today the committee meets an open session to discuss and make recommendations on the safety and effectiveness of a second RSV vaccine candidate, as was presented in the first session yesterday morning, this convening of VRBPAC focuses on Respiratory Syncytial Virus disease in older adults.

Yesterday, the committee considered a bivalent candidate without adjuvant, and today the committee considers a monovalent prefusion F protein with an adjuvant. The particular product and the available data for consideration today is by the sponsor, GSK, submitted in BLA125775. As with yesterday's discussion, data being reviewed today come from ongoing studies, and FDA is prepared to discuss only data submitted to the BLA. While the presentations yesterday morning by doctors Thornburg, Havers, and Talbot on the virology epidemiology and the clinical considerations of RSV-And older adults will not be repeated today, they remain relevant for today's discussion, as do the presentations in yesterday's open public hearing.

The FDA asked the committee to consider the same two voting questions today as yesterday, but now for the safety and effectiveness of RSV, manufactured by GSK. So let me conclude this brief welcome by again thanking committee members for their time yesterday and today, thanking those from the FDA who reviewed these submissions and helped organize this meeting, thanking our presenters and thanking those who have joined this public open meeting virtually. We look forward to another productive meeting today. Back to you, Dr. El Sahly.

BLA for AREXVY in Adults 60 Years of Age and Older — Dr. Nanda

Dr. El Sahly: Thank you, Dr. Kaslow. Now Dr. Santosh Nanda, a review committee chair at the Division of Vaccines and Related Products Applications, office of Vaccine Research and Review at CBER, will go over the BLA for AREXVY, Respiratory Syncytial Virus Vaccine, Recombinant, Adjuvanted, in adult 60 years of age and older. Dr. Nanda.

Dr. Nanda: Good morning, everyone. This is Santosh Nanda from Office of Vaccine Research and Review. I'm going to introduce the BLA for RSV-Adjuvanted with the proprietary name AREXVY submitted by GSK. Here onwards, I'm going to refer to the product as AREXVY. Next slide please.

Here is the outline of my talk. I'm going to talk about the RSV disease. Then I'll provide description for the product RSV. I'm also going to provide an overview of clinical trials in support of licensor of RSV. After that, I'll talk about today's agenda. I'll conclude with the voting questions. Next slide, please.

RSV is a leading cause of Lower Respiratory Tract Disease in older adults. Older adults, particularly with underlying medical conditions, are at risk for the RSV disease. RSV causes a significant number of hospitalizations and death in the United States, particularly in individuals 65 years of age and older. And RSV disease represents a serious condition with an unmet medical need. There are no specific treatment options for RSV disease among adults. Next slide, please.

The vaccine is a lyophilized recombinant RSVPreF3 glycoprotein antigen derived from an RSV-A strain stabilized in the pre-fusion trimeric confirmation, reconstituted at the time of use with $ASO1_E$ adjuvant suspension. After reconstitution, each 0.5-mL dose of AREXVY contains 120 micrograms of recombinant RSVPreF3 antigen, 25 micrograms of MPL, and 25

micrograms of QS-21. $ASO1_E$ contains half the amount of MPL and QS-21 contained in the $ASO1_E$ adjuvant used in SHINGRIX.

AREXVY is administered intramuscularly as a single dose, single 0.5-mL dose. Applicants proposed indication is active immunization for the prevention of Lower Respiratory Tract Disease caused by Respiratory Syncytial Virus RSV-A and RSV-B subtypes in adults 60 years of age and older. Next slide please.

FDA received a BLA for AREXVY on September 2, 2022. The clinical package included data from five clinical studies to support the safety and effectiveness of AREXVY. Efficacy of AREXVY to prevent RSV-associated LRTD (that which is the primary endpoint) in adults greater than 60 years of age is evaluated in an ongoing, pivotal phase 3, randomized, placebo-controlled, observer-blind, international Study 006. A total of 24,966 participants were enrolled in the study. Next slide, please.

Our VRBPAC chair, Dr. Hana El Sahly, has already provided opening remarks, and Dr. Sussan Paydar has made her administrative announcements. Our office director, Dr. David Kaslow, welcomed you all after my introduction. Next slide, please.

GSK and team will talk about their product. My next slide, please.

My colleague, Dr. Nicholas Geagan, will present the Agency analysis and safety and efficacy data submitted by GSK. There will be a lunch break followed by open public hearing. There will be additional question and answer with FDA and sponsor presenters. Finally, the committee will discuss and vote on GSK RSV vaccine. The DFO will adjourn the meeting.

Now let me introduce our voting question. Number one, are the available data adequate to support the safety of AREXVY (RSVPreF3+$ASO1_E$) when administered to individuals 60 years

of age and older for the prevention of Lower Respiratory Tract Disease caused by RSV, please vote yes or no. Next slide please.

Here is our voting question number two. Are the available data adequate to support the effectiveness of AREXVY (RSVPreF3+AS01$_E$) for the prevention of Lower Respiratory Tract Disease caused by RSV in individual 60 years of age and older? Please vote yes or no. Next slide, please.

Now I'll be happy to answer if there are questions. Thank you.

Q & A

Dr. El Sahly: Thank you, Dr. Nanda. Committee members, please raise your hand function to ask questions to Dr. Nanda. I do not see hands yet. I have a brief question and it was in my notes yesterday, but I failed to ask it because it pertains to both days. For voting on question two, is the intention that we see if the data are adequate for efficacy or effectiveness? Did we use the word effectiveness just as a convention? Because what we are seeing is efficacy data.

Dr. Nanda: It's actually we are asking for effectiveness of the vaccine in the target population greater than 60 years of age and older with the available data that has been presented to the committee.

Dr. El Sahly: Got it. Thank you. So now hands are raised, Dr. Portnoy.

Dr. Portnoy: Okay, thank you. I guess my question occurs because there are two days' worth of meetings and we're having two separate presentations. When we consider today's vaccine, are we permitted to consider information we gleaned from the presentations yesterday in deciding about today? Or should we restrict our deliberations to only the data that's presented today?

Dr. Nanda: I would say that you would consider the VRBPAC committee members should consider the data that is presented today for the AREXVY product, and I would like if Dr. Kaslow would add something to it.

Dr. Kaslow: So David Kaslow. We would like you to consider the voting questions in the context of the data that were submitted to the BLA for this product.

Dr. El Sahly: Thank you. Dr. Cohn.

Dr. Cohn: Thank you. This is also a question I think that I meant to have for both days, but can you clarify if the BLA for today's vaccine, I'll just ask about today's, if there's a request to license this product to protect through one season or two seasons, and if that's clarified in the BLA submission?

Dr. Nanda: The sponsor has submitted data to this BLA for one season right now, so we should consider that as our option.

Sponsor GSK Presentation RSVPreF3 Vaccine for RSV in Older Adults

Dr. El Sahly: Thank you, Dr. Nanda and Dr. Portnoy and Dr. Cohn. I see no hands for additional questions, so we move to the next item on our agenda.

I'd like to welcome the GSK team, beginning with Dr. Bishoy Rizkalla, Vice President and Global Medical Affairs Lead. Dr. Rizkalla will go over the RSVPreF3 vaccine for RSV in older adults. Dr. Rizkalla.

Introduction — Dr. Rizkalla

Dr. Rizkalla: Thank you so much. Good morning. And firstly, thank you to the FDA and to the committee for available time today and for the opportunity to present an overview of the GSK candidate RSV vaccine. I'm Bishoy Rizkalla, GSK Global Medical Affairs Lead for RSV vaccine. Here is our presentation and our agenda for our presentation today.

But before we get started, I'd like to take a brief moment to thank all of the study participants, all of the site staff, the study investigators, the GSK R and D organization, and our scientists who would not be possible to present to the committee today without the contribution of so many. Thank you to all involved with that. We'll get started.

Complications associated with RSV infection represent a significant health threat for older adults. There is currently no vaccine available, and the clinical standard currently remains as supportive care. GSK developed this RSVPreF3 older adult vaccine, which we will refer to as our RSV vaccine throughout the presentation today to address this high unmet medical need. Today, we'll present data supporting that a single dose of our vaccine offers high and consistent protection for adults 60 years of age and older against the broad spectrum of RSV-A and RSV-B associated diseases. The vaccine is well tolerated within acceptable safety profile.

The proposed indication for our RSV vaccine candidate is for the active immunization for the prevention of Lower Respiratory Tract Disease or LRTD caused by RSV-A and RSV-B subtypes in adults 60 years of age and older. The proposed administration and dosage is a single intramuscular administration of 120 micrograms of the RSVPreF3 antigen adjuvanted with $ASO1_E$, which is based on the ability to induce both the humeral and cellular immune responses in the target population. As a reminder, $ASO1_E$ contains the same components as $ASO1_B$, which is the adjuvant used in our shingles vaccine. However, $ASO1_E$ used in our RSV vaccine contains half of each of the immune-stimulants contained in the $ASO1_B$ adjuvant system.

To summarize the key regulatory milestones for the program, the IND for our RSV vaccine candidate in older adults were submitted in October, 2018. Fast track designation was granted in December, 2018. We've had multiple meetings and communications with the agency to align on clinical development and CMC plans.

The phase three studies were initiated in 2021, and we have data from these phase 3 studies with a median follow up of six to seven months. Our BLA was submitted in the third quarter of 2022 based on conclusive results from a pre-specified interim analysis of the efficacy study after one RSV season. The application was later granted priority review designation.

The clinical data supporting efficacy and safety comes from five clinical studies including four phase 3 studies. The clinical program began with a phase 1/2 study, Study 002, which supported the dose and formulation selection to be used in our phase 3 program.

The phase 3 program was initiated with Study 004 to characterize the humeral and cellular immune responses as well as the safety reactive genicity and immune persistence. Study 006 is our large ongoing efficacy study in the target population of older adults 60 and above. Study 006 was designed to establish confirmatory evidence of the efficacy of a single dose of the RSV vaccine.

We have two additional studies that have been completed, Study 007, a co-administration study with a quadrivalent influenza vaccine and study 009, the lot-to-lot consistency study. Almost 32,000 adults were evaluated in the clinical program with more than 15,000 exposed to the vaccine. Our vaccine demonstrated an efficacy of 82.6% in the prevention of RSV-associated Lower Respiratory Tract Disease in adults 60 years and older.

A high level of protection was observed consistently over an entire season, regardless of RSV disease severity, advancing age, presence of comorbidities, and RSV-A and RSV-B

subtypes. The RSV vaccine was well-tolerated with an acceptable safety profile. Now with that brief introduction, I'll now turn the floor over to Professor Ann Falsey.

Burden of Respiratory Diseases in the Older Adult Population — Dr. Falsey

Dr. Falsey: Thank you. Hello, and good morning. I'm Ann Falsey, a professor of medicine at the University of Rochester, and I'm pleased to be here to provide some background on the burden of RSV, and to share my perspective on the need for a vaccine in adult populations. I've spent my career focused on defining the epidemiology and impact of Respiratory Syncytial Virus in adult populations, and I've been involved in numerous adult surveillance and vaccine studies.

I've been compensated for my travel today, but I am not being compensated for my time.

RSV is a highly contagious human pathogen that causes yearly epidemics during the winter seasons in temperate climates. There are two major subtypes of RSV-A and B, and these may co-circulate with predominance of one type, varying by year and by geographic location. RSV does not infer long-term immunity as we heard, and thus reinfection with RSV occurs throughout life and is common in all ages.

Adult symptoms may range from mild colds to pneumonia and respiratory failure. The major groups at risk for severe RSV disease are young children, older adults, and adults with comorbid conditions.

So one way to look at the burden of disease is simply by infection rates. For this, serology is really needed to understand the true burden of infection. These two studies were done 15 years apart of first in the US by our group and the other in Europe by Corstin and colleagues more recently, and importantly, both used nasal PCR and acute convalescent serology. Notably,

both studies yielded nearly identical results with RSV infections being 5.5 to 5.7 per 100 persons per season, compared to influenza A and influenza B at 1 to 3%.

Now, it's very important to note that many of the patients or subjects were vaccinated for influenza, but it's also important to note that only 10% of the serological conversions in our studies were asymptomatic for natural infection. So being conservative, one could estimate the 3 to 4% of older adults experience a symptomatic RSV infection each year.

Now, one of the most significant measures of the burden of disease is hospitalization rates. And in a recent three-year population-based study, adults with ARI or decompensated cardiopulmonary disease were tested by PCR, and rates were adjusted by the market share of the hospitals upstate New York and Rochester and downstate in New York City. Upstate is shown as the solid line and downstate as the dotted line.

So as you can see, there was a very clear, effective age with the incidence rates increasing with each decade of life for older adults. The rates were lowest in the 18-to-49-year-old group at 8 to 12 per hundred thousand, and highest in people over 85 with rates of 207 to 666 per hundred thousand in those over age 80.

Another recent study looked at potential predictors of RSV hospitalization using the national Medicare database from 2011 to 2015. Using multivariate logistic regression, hospitalized patients were compared with those who were never hospitalized. Significant predictors of hospitalization after adjusting for other co-variants are highlighted in the light blue color.

Again, we see the effect of age, but in addition, we see COPD, congestive heart failure, hematologic malignancies, stroke, and chronic kidney disease, were also significant independent risk factors.

There are less data on the outpatient burden of RSV disease and medically attended illness, but this is a good study from the Marshfield Clinic. Although it was an add-on to an influenza vaccine efficacy study, a broad ARI definition was used and PCR testing was done, and thus it provides an accurate assessment. Overall, the rate of medically attended illness was 15.4 per thousand, which did vary a bit, as you can see over the four years, but was relatively constant, and importantly, about 6% progressed to hospitalization. Similar to hospitalization, we see an age effect with the highest rates of about 20 per thousand in those people over age 70.

Finally, I think it's important to consider some of the non-respiratory impacts that RSV infection can have in this population. Functional independence is one of the most important goals for older adults.

This graph is data from a three-year perspective study that assess function in older adults after hospitalization with RSV infection. The patients were assessed pre-hospitalization, at discharge, and six months post-hospitalization. Importantly, of those living completely independently prior to the admission, 14% had lost independence at discharge, and 8% had persistent functional loss at six months.

Lastly, there are data accumulating that RSP infection may in fact lead to decompensation of heart failure, but also arrhythmias and thromboembolic events similar to what has been observed for influenza infection. So trying to put it all together using the best estimates from a variety of studies, it is likely that each year in the US among adults 60 years and older, RSV causes up to 3.4 million respiratory illnesses leading to 1.7 million outpatient visits, 108 to 177,000 hospitalizations, and finally, eight to 14,000 deaths.

In summary, RSV is a frequent cause of respiratory tract disease in adults. Older age and underlying medical conditions are risk factors for severe disease. RSV ARI in older adults is

associated with a significant long-term lower quality of life. And RSV in adults results in a high burden on the healthcare system. In addition to respiratory illnesses, we are just beginning to understand the substantial impact of non-respiratory complications due to RSV, such as loss of function and cardiovascular complications. Importantly, no effective treatment for RSV infection is available, and therefore an effective vaccine would be highly impactful. Thank you, and I will now turn the presentation back to Dr. Rizkalla.

Efficacy & Immunogenicity — Dr. Rizkalla

Dr. Rizkalla: Thank you so much, Professor Falsey. We will now transition to the efficacy and the immunogenicity of our RSV vaccine, starting with an overview of how we designed our vaccine in order to induce or boost a protective immune response to RSV in older adults.

As we've just heard from Professor Falsey, older age is a substantial contributor to the risk of severe complications associated with RSV infection. This is, in part, due to age-related decline in immunity where we see a diminishing quantity and quality of immune cells with advancing age. We see this with other respiratory diseases such as flu and non-respiratory diseases such as shingles, where tailored approaches using adjuvant-containing vaccines have been used to help overcome this age-related decline in immunity.

This is also evident with RSV where on the right of the slide you can see pre-existing RSVPreF3 specific T-cell levels in older adults, 60 to 80 years of age, being well below those of young adults 18 to 40 years of age. Although a correlative disease remains to be established, age-related decline in RSV specific T-cell and functional antibody responses are considered to be associated with a higher risk of RSV disease severity.

On this basis, we have designed our vaccine for RSV and older adults with the aim to potently boost both the functional RSV neutralizing antibody responses and the RSVPreF3 specific T-cell responses. To achieve this, our vaccine candidate is a combination of a recombinant purified antigen with an adjuvant system.

Detailed overview of our phase 1/2 dose selection and formulation selection study has been provided in the briefing book. However, to summarize here, the formulation selected for phase 3 contains 120 micrograms of the RSVPreF3 antigen, which is highly conserved across RSV-A and RSV-B subtypes adjuvanted with $ASO1_{E,}$ as together, this formulation demonstrated high neutralizing antibody responses against both RSV-A and B, high polyfunctional RSVPreF3 specific T-cell responses compared to the unadjuvanted formulation. These TH1 dominant T-cell responses in older adults approach the level seen in young adults who can also be infected with RSV, but generally do not develop severe RSV disease.

The RSVPreF3 $ASO1_E$ adjuvanted vaccine was well tolerated with an acceptable safety profile, which builds on the extensive experience we've accumulated with more than 80 million doses of $ASO1_E$-containing vaccines distributed.

Transitioning now to our phase 3 clinical program. The clinical development program for the RSV vaccine included four phase 3 studies. Overall, this program enrolled close to 30,000 participants and approximately half of them received at least one dose of the RSV vaccine. I will focus most of my presentation on the pivotal efficacy study, Study 006, but will also present supportive data from Studies 004 and 007. Study 009 demonstrated the consistency of the manufacturing process and is included in the briefing document.

Now turning to the large-scale efficacy, immunogenicity and safety study, Study 006. This study randomized approximately 25,000 participants across 17 countries and 266 sites

around the world. The majority of participants were recruited from the Northern Hemisphere countries, including approximately 9,000 participants enrolled from North America. Study 006 is a randomized, observer-blind placebo-controlled study. A total of 24,966 participants received either the one dose of the RSV vaccine or one dose of placebo. Today, we'll present data from the first RSV season denoted by the dash line. It is important to highlight that this study is ongoing and will cover three RSV seasons.

Through the subsequent two seasons of the study, we'll be able to demonstrate the efficacy of a single dose of our vaccine over three RSV seasons, and also the consistency of our vaccine administered annually.

All participants had a blood sample taken prior to and one month after vaccination. A subset of participants had their samples tested by neutralization assay to determine functional antibody responses against RSV-A and B. All participants were followed for efficacy and safety evaluations. The primary objective of the study was to demonstrate the efficacy of the RSV vaccine in the prevention of LRTD, confirmed by RT-PCR as associated with RSV-A and/or RSV-B in adults 60 years of age and older. A pre-specified interim analysis of efficacy was triggered when a minimum of 35 RSV-confirmed LRTD cases had been accrued and adjudicated in the primary cohort of efficacy by the end of the first season in the northern hemisphere.

Other objectives included the evaluation of vaccine efficacy against RT-PCR-confirmed LRTD by individual RSV subtype, by age categories, by baseline co-morbidities, and by frailty status. Vaccine efficacy against RT-PCR-confirmed severe LRTD and vaccine efficacy against RT-PCR-confirmed acute respiratory illness, or ARI, were also evaluated. All RSV LRTD cases and severity of LRTD were adjudicated by an independent external committee.

In addition, the impact of the RSV vaccine against patient-reported outcomes was evaluated using the PRO health questionnaires, in addition to the immunogenicity and safety. The following case definitions were used to assess RSV disease progression from ARI to LRTD and severe LRTD.

These case definitions were discussed and agreed with the regulatory agencies. Acute respiratory illness was defined as a study participant experiencing at least two respiratory symptoms or signs, or a participant experiencing at least one respiratory symptom or sign and one systemic sign, for a minimum of 24 hours.

This definition really casts a wide net to capture a broad symptomatic spectrum of disease, including upper, lower, and systemic signs and symptoms. LRTD was a subset of ARI and was defined as an ARI with lower respiratory tract symptoms or signs. It was defined as a participant in experiencing either two lower respiratory signs or symptoms of which one must include a lower respiratory sign, or a participant that experiences at least three lower respiratory symptoms from a minimum of 24 hours.

Severe LRTD was defined as a participant experiencing an LRTD with at least two lower respiratory signs were assessed as severe by the investigator. A second definition for severe LRTD also captured participants experiencing an LRTD that had a requirement for additional supportive therapy such as oxygen supplementation or CPAP.

Three analysis sets were used in study 006. The exposed set includes 24,966 participants representing those who received at least one dose of the study vaccine or the placebo. This is the primary cohort for the analysis of safety. The modified exposed set includes all participants from the exposed set who did not report an RSV-confirmed ARI before day 15 post-vaccination. This is the primary population for the efficacy analysis. The per protocol set for immunogenicity

includes all participants with post-vaccination immunogenicity data and without any protocol deviations leading to elimination.

I will now shift focus to the demographics. Overall, the demographic characteristics were well balanced between groups. The demographics for the study in the overall exposed set is shown on the left, and the US specific demographics on the right. More than half the study participants were between 60 and 69 years of age, 36% were between 70 and 79, and 8% were 80 years of age and older. Approximately half of the participants were female. In terms of racial distribution, about 80% were White or Caucasian. Approximately 8% identified as Asian, and 9% were Black or African-American in the exposed set and approximately 15% in the US cohort specifically, not shown on this slide, but I'll mention it here, 9.2% of the US population were Hispanic or Latino.

About 40% of the study participants were considered as frail or pre-frail. In the study, frailty was determined on the basis of a gate speed test that was administered to study participants at the first visit. Around 95% of study participants had at least one pre-existing co-morbidity at baseline, 39% had at least one co-morbidity of interest, which is defined as co-morbidities associated with an increased risk of severe RSV-associated disease.

These include chronic cardiopulmonary diseases such as COPD, asthma, coronary artery disease, and congestive heart failure, which represented 20% of participants at baseline. Approximately 26% of participants at baseline had endocrine metabolic conditions such as diabetes.

Now shifting focus to efficacy. The primary objective of Study 006 was met with a vaccine efficacy of 82.6% in the prevention of RSV confirmed LRTD during the first RSV season. 47 cases of RSV-confirmed LRTD were adjudicated by an external independent

committee. Of those, seven occurred in the RSV vaccine group and 40 in the placebo group. The lower limit of the 96.95 confidence interval was 58%, well above the predefined threshold for licensure of at least 20%, which was agreed upon with the FDA.

The efficacy of the vaccine over the follow up period of the first season is illustrated by these cumulative incidence curves, which show a clear separation between the RSV vaccine group and the placebo group in terms of the accrual of cases over a median for life period of 6.7 months. This supports the efficacy of the vaccine over the course of an entire RSV season.

The RSV vaccine not only showed more than 82% vaccine efficacy against RSV-confirmed LRTD, but also provided protection against the spectrum of RSV-associated symptomatic disease. The vaccine efficacy against RSV-confirmed ARI was 71.7%, which is important considering the broad capture of this definition, which includes upper, lower respiratory tract infection. Considering the large burden of symptomatic RSV each year, this is an important benefit. Importantly, the vaccine efficacy against RSV-confirmed severe LRTD was 94.1%. These are important results in the context of the substantial burden of disease and high unmet medical need associated with RSV infection.

Vaccine efficacy was also consistent across the different age categories in both the 60 to 69 and the 70 to 79 pre-specified age strata. Vaccine efficacy against RSV-confirmed LRTD was 81% and 93.8% respectively. In the subgroup above 80 years of age, there were too few cases reported to be able to conclude vaccine efficacy.

As stated earlier, the RSV F protein is highly conserved across RSV subtypes, and consistent efficacy was demonstrated for each individual RSV subtype. This was in the context of a season, which was predominantly RSV-B, with two-thirds of LRTD cases associated with

RSV-B infection. The vaccine efficacy against RSV confirmed all LRTD was 84.6% for RSV-A and 80.9% for RSV-B.

Looking now at efficacy in the vulnerable subgroups. We observed high inconsistent efficacy in these at-risk populations with an observed efficacy of 94.6% in the prevention of RSV LRTD in those with pre-existing co-morbidities of interest that are known to increase the risk of severe RSV-associated disease, specifically an efficacy of 92.1% in those with at least one cardiopulmonary condition and an efficacy of 100% in those with at least one endocrine metabolic condition.

We also observed an efficacy of 92.9% in the prevention of RSV LRTD in the pre-frail population. Due to too few cases observed, we unable to conclude a vaccine efficacy in the frail population. The flu patient-reported outcome, or flu PRO, was developed to quantify symptom severity influenza-like illness and has been validated for use in RSV for older adults. On a scale of zero to four, the median maximum flu PRO chest cold was 1.86 in the placebo group and 1.07 in the RSV vaccine group.

The difference of 0.79 between the arms is considered both statistically and clinically meaningful. The difference of 0.79 is more than three times higher than the minimal clinically significant change and represents a 42% reduction in the severity of chest symptoms. Based on the results, the conclusion is that participants with breakthrough cases of RSV in the vaccine group experienced less severe symptoms, including trouble breathing, cough, and chest tightness, compared to the cases in the participants of the placebo group.

Turning now to immunogenicity of the RSV vaccine. The immune response to the RSV vaccine was evaluated in a subset of participants in Study 006, as well as in Study 004, starting with the immunogenicity from Study 006. This graph shows the neutralization response for

RSV-A on the top and for RSV-B on the bottom. For both subtypes, the vaccine induced a large increase in neutralizing antibodies, not only in the overall study population, but also consistently across the different age categories evaluated. Overall, the vaccine increased neutralization titers by approximately ten times baseline levels, 30 days following vaccination. Study 004 was an open label study specifically designed to characterize the immune response to the RSV vaccine in terms of humoral and cell-mediated immune response.

1,653 participants were involved for more than 40 sites, including the US. In the first year, all participants have received one dose of the RSV vaccine. Data from this study show a similar pattern; as we saw in Study 006, a large increase of RSV-A and RSV-B neutralization titers observed one month post vaccination.

This is true both for the overall population and per each age strata, including those 80 years of age and older. Neutralization titers remain at least three times baseline levels through the 12 months post vaccination with kinetic subneutralization titers, similar across the age strata. The cell-mediated immune response in Study 004 also shows a similar pattern.

Polyfunctional CD four T-cell response induced by the vaccine was shown to peak one month post vaccination and persist for at least 12 months at levels well above baseline. Again, the kinetics of T-cell response was similar across all age groups. Transitioning now to Study 007, which was conducted to evaluate the co-administration of the RSV vaccine with a licensed influenza vaccine.

This was an open label randomized controlled multi-country study that enrolled 880 adults 60 years of age and older. Study participants were randomized to receive either the RSV vaccine co-administered with a licensed influenza vaccine or to receive both of these vaccines administered sequentially.

The primary objective of the study was to demonstrate non-inferiority of co-administration compared to each vaccine being administered alone with respect to the influenza hemagglutinin response and RSV neutralizing titers. Non-inferiority of the co-administration of RSV-And influenza vaccine was demonstrated, for influenza and RSV responses, the upper limit of the two-sided 95% confidence interval on the GMT ratio, that is sequential administration versus co-administration group was below 1.5.

As illustrated on the graph, these criteria were met and show that the RSV vaccine can be co-administered with a licensed quadrivalent influenza vaccine. It is important to note there are the, there are two additional studies ongoing to demonstrate the co-administration of the RSV vaccine with high dose flu vaccine and with the adjuvanted fluid vaccine. We anticipate results in the coming months from these studies. So, to bring this all together, data from our clinical development program demonstrate that our RSV vaccine offers a high level of protection against RSV confirmed LRTD with an efficacy of 82.6%.

The vaccine showed consistent protection against the spectrum of symptomatic RSV disease, including acute respiratory illness and severe low respiratory tract disease protection was sustained against RSV-A and RSV-B subtypes. And across age groups, we observed very high efficacy in individuals at particular risk of developing severe RSV disease because of pre-existing comorbidities within efficacy of 94.6% and 92.9% in those with pre-frail status.

The vaccine induced robust humeral RSV-A and RSV-B neutralizing antibody and T-cell responses. These responses were comparable across age groups and persisted for at least 12 months after vaccination. In addition, our RSV vaccine can be co-administered with seasonal influenza vaccine.

I would like to thank you once again for your attention. Now, I'd like to invite Dr. Peggy Webster to the lecture.

Safety / Benefit Risk — Dr. Webster

Dr. Webster: Hello, I'm Peggy Webster, head of Vaccine Safety at GSK. Today I'll review the safety data from the RSV Vaccine Development Program where a single dose of our RSV vaccine was shown to have an acceptable safety profile. The total safety database includes more than 15,800 RSV vaccine recipients from five studies.

The largest data set comes from Study 006 with more than 12,000 participants vaccinated with the RSV vaccine. The remainder of my presentation will focus primarily on this study, which provides a well-characterized and robust safety profile. Let me briefly review how safety follow-up was conducted.

As a reminder, participants were randomized one-to-one to receive the vaccine or placebo from the day of vaccination. A subset of participants recorded solicited administration site and systemic adverse events using paper diary cards for four days. Unsolicited events were collected for all participants for 30 days post vaccination.

Serious adverse events and potential immune mediated diseases were collected through six months. Additionally, SAEs and potential immune mediated diseases that might have a causal relationship to vaccination as well as fatal SAEs are collected for the entire study in Studies 002 and 006 An independent data monitoring committee or IDMC periodically reviewed and evaluated the accumulated unblinded data and made recommendations to GSK regarding the study conduct.

My presentation will include safety data up to the safety data lock point with a median follow up of nearly 12 months. In Study 006, safety was evaluated in two groups. The exposed set includes more than 12,000 participants who received one dose of RSV vaccine adverse events reflecting vaccine reactogenic were obtained from the solicited set.

I'll begin with data from the solicited set. A subgroup containing 879 RSV vaccine recipients from which our reactogenic profile is primarily derived. Overall in this set, solicited adverse events were more common in the vaccine group compared to placebo. 72% of RSV vaccine recipients reported a solicited adverse event administration site.

Events were reported in more than half of the vaccine recipients and systemic events were reported in roughly half. It's important to note that there were few grade three events in either group. Next, I'll review the solicited events in more detail. Shown here are the administration site events within four days after vaccination. Pain was the most commonly reported event followed by erythema and swelling.

Most were mild and severity and transient with a median duration of two days. Here we see the systemic adverse events within four days after vaccination. Fatigue, myalgia and headache were the most frequently reported. Similar to the administration site events, most of the systemic events were mild in severity and resolved quickly. Importantly, few participants in either group reported a fever.

Next, I'll review the unsolicited adverse events which were collected from the whole exposed set for 30 days post vaccination. Overall, the frequency of unsolicited adverse events was higher in the RSV vaccine group compared to placebo, which I'll address on the next slide.

Potential immune mediated diseases and SAEs, which were collected up to six months post vaccination were both balanced across groups. Deaths also occurred at similar rates. The

difference in unsolicited adverse events is primarily due to more events in the general disorders and administration site conditions category for the RSV vaccine group with more injection site events such as pain.

Serious adverse events within six months following vaccination were balanced between groups. The most frequently reported events were infections and infestations, mainly due to COVID-19 infections and pneumonia, followed by cardiac disorders. These data are representative of conditions found in the target population.

Importantly, the incidence of SAEs at the preferred term level was similar in both the RSV and placebo groups, and there was no apparent clustering of events. The incidence of fatal SAEs up to the datalock point was balanced between groups. 0.7% of deaths were reported in the RSV vaccine group and 0.8% in placebo.

The most frequently reported events in both groups were cardiac disorders. There were no safety concerns from the IDMC after monthly unblinded data review. This slide summarizes the solicited and unsolicited events observed in Study 007, where participants received either RSV vaccine co-administered with seasonal influenza vaccine, or control the influenza vaccine followed by RSV vaccine one month later.

For the control arm ,solicited adverse events are shown for the RSV component. Unsolicited events are shown for the aggregated influenza and RSV vaccinations. We see a greater reporting of solicited adverse administration site in systemic events like the 006 Study, pain, fatigue, myalgia, and headache we're the most commonly reported solicited events in the co-administration group and grade three events were infrequent.

The percentage of participants reporting any unsolicited event, medically attended event, or SAE, including deaths, was balanced between groups.

Two events of acute disseminated encephalomyelitis considered related to vaccination by the investigator occurred in the co-administration group, and I'll share more information about these two events in a few minutes.

Next, I'll review safety events of special interest. Anaphylaxis following immunization is a serious but rare occurrence, so to identify any potential cases featuring hypersensitivity reactions, including anaphylaxis searches were conducted using the standardized MedDRA queries for hypersensitivity and anaphylactic reaction.

Most events identified by the searches were those of rashes at the injection site, and there was no case of anaphylaxis related to the vaccine. We will closely monitor for hypersensitivity reactions reported during the ongoing clinical development program and in the post-marketing setting.

Atrial fibrillation was reported in 14 participants within 30 days following vaccination, ten in the RSV vaccine group and four in placebo. Six events were of new onset atrial fibrillation occurring in participants who all had risk factors in predisposing or concurrent medical conditions, placing them at high risk of developing the condition. And eight events occurred in participants with an established history of atrial fibrillation reflecting the expected course of this condition, which is characterized by recurrent episodes of symptomatic events.

The median time to onset of the atrial fibrillation event, regardless of whether new onset or recurrence, was approximately 18 days in the RSV vaccine group and 10 days in the placebo group. The IDMC performed a focused review of all events of atrial fibrillation and has not recommended any changes to the study.

At six months post vaccination, there was a similar incidence in both groups. We will actively monitor all events of atrial fibrillation as this study continues. Potential immune

mediated diseases are hypothesized as potential risks for any vaccine. Our available data shows that PIMDs are equally distributed between groups and were reported at a frequency of less than 0.5% in both RSV vaccine and placebo groups.

Across the full safety database with data from the entire development program, three PIMDs of medical interest occurred in open-label studies. A single case of Guillain-Barre Syndrome was reported in Study 004. The participant's muscle weakness started nine days after vaccination, and she recovered with treatment. Two cases of acute disseminated encephalomyelitis or ADEM were reported two weeks apart from a single investigator in the 007 co-administration study, the first participant's symptoms began seven days after the RSV and flu vaccinations. He was hospitalized and unfortunately died.

For the second ADEM case, the diagnosis was based only on clinical symptoms, which started 22 days after vaccination. This participant recovered comparing case details against the Brighton Collaboration diagnostic certainty criteria, all were classified at the lowest level.

We will continue to diligently monitor all PIMDs, including cases of GBS and ADEM. During the course of the ongoing studies and as part of post-marketing surveillance. I'll now provide additional details on our proposed enhanced post-marketing pharmacovigilance plan.

GSK will use our established pharmacovigilance system to monitor the emerging post-marketing safety profile diligently with collection and frequent analysis of spontaneous adverse event reports. We will regularly conduct reviews of published literature and signal detection. Evidence from all sources, including the ongoing clinical studies will be assessed in aggregate, and we will conduct enhanced surveillance, which I will describe next, for events of interest.

For atrial fibrillation, we will implement active surveillance in our ongoing and planned clinical studies including 006, which will remain ongoing following two RSV seasons.

We will also closely monitor and follow up pIMDs, including GBS and ADEM in all ongoing studies. For predefined pIMDs, including GBS and ADEM we will use follow up questionnaires to collect structured data in the post licensure setting, and we will leverage GSK's custom MedDRA query for pIMDs for signal detection.

These measures will allow a proactive approach to detect and respond to emerging safety concerns swiftly with flexibility to include new adverse events of interest based on the combined clinical study and post-marketing evidence.

In summary, the available safety data in more than 15,000 vaccine recipients show that a single dose of the RSV vaccine is well tolerated with a clinically acceptable safety profile in adults 60 years and older.

The reactogenicity profile is well-characterized with administration site and systemic adverse events reported at a higher rate in the RSV vaccine group. The majority of these events were mild to moderate in severity and of short duration.

Overall, medically attended adverse events, SAEs, pIMDs, and deaths were balanced between groups with no clustering of events. An enhanced pharmacovigilance activities are in place to further characterize reported events of atrial fibrillation and pIMDs.

Let me now close with a benefit risk assessment. Overall, our RSV candidate vaccine for older adults has a positive benefit risk profile. As a reminder, we currently have an unmet need without any tools to treat or prevent RSV in older adults who have an increased risk of morbidity and mortality from RSV infection. Our vaccine provides high and consistent protection across the spectrum of RSV symptomatic disease with an efficacy of 82.6% for LRTD, 71.7% for acute respiratory illness, and 94.1% for severe lower respiratory tract disease.

The protection was sustained against A and B subtypes and across age groups. Importantly, we observed very high efficacy in older adults at particular risk of developing severe RSV disease because of pre-existing comorbidities The vaccine was well tolerated with a clinically acceptable safety profile.

Overall, our conclusion is that the benefits of our RSV vaccine outweigh the risks. Thank you for your attention. I will now turn it back to Dr. Rizkalla to address your questions.

Q & A

Dr. El Sahly: Thank you, Dr. Webster, Dr. Rizkalla, and Dr. Falsey. I would like to invite our committee members to raise their hand for questions, knowing that we will have also in a couple of hours, a longer interval to be able to ask questions beginning the first question with Dr. Pergam?

Dr. Pergam: Thank you to GSK for that clear presentation and for the briefing document that they provided to the committee. Dr. Rizkalla, I had a specific question that maybe you could clarify. The briefing document included patients that had comorbidities, either one or two, but there wasn't a table of the different comorbidities and the percentages of each within those, is that available for the committee to review?

Dr. Rizkalla: Yeah, we do have that. I'll bring that up for you in this in a moment. Just bear with me. I'll bring up a slide and I'll walk you through this. Apologies. I don't have a slide that I can show, but I can share the details. So regarding COPD we had 1,131 participants in the RSV group and 1,113 participants in the placebo group for asthma. 193 in the RSV group and 1,112 in the placebo group. For Diabetes Mellitus we had 2,829.

It would've been much easier if I could have shared this on a slide, but I have the data, so bear with me as I read it out. So for Diabetes Mellitus 2,829 in the RSV group and 2,875 in the placebo group with chronic heart failure representing 3.2% of the recruited population and liver disease, 0.9% of the enrolled population and advanced renal disease of 5% of the total population.

So just, I have exactly the slide to show you, Dr. Pergam, so I'll bring that up for you. So just to summarize my long-winded answer this gives you the percentages on the left showing the exposed set proportions and looking at the census data for the US on the right for relative representativeness of the population recruited. I hope that addresses your question.

Dr. Pergam: Yeah, thank you very much. That's very helpful.

Dr. El Sahly: Second question comes from Dr. Griffin.

Dr. Griffin: Hi. Marie Griffin. That was a really great presentation and I love the study design, so I'm just wondering if this vaccine were licensed and recommended, what would happen to that three-year study design, and would it be considered unethical to continue the placebo group?

Dr. Rizkalla: Enrollment for season two has taken place. Surveillance runs up to the end of April in the Northern Hemisphere, we anticipate results from season two in Q2 this year. If a vaccine should become available ahead of the third RSV season, we will communicate openly to all study participants and inform them and give them the option to seek an RSV vaccine or to continue participation in the study.

Now, one thing to note here, is that we've made provisions for dropouts in each subsequent RSV season. We've catered for 20% dropout rate in each of season two and season three. And so far in season two, we're well below this dropout rate that we had catered for. So it gives you a perspective we'll openly communicate to all study participants and give them that option.

Dr. Griffin: Okay. I just have one more question. You can present data on hospitalizations. Do you have those data?

Dr. Rizkalla: Yeah, we have two hospitalizations in vaccine efficacy analysis one, we have three in a subsequent analysis. All of these occurred in the placebo arm, but that is the information we have currently.

We can be really confident in the profile of the vaccine, in the prevention of severe RSV disease. Looking at severe LRTD, and in particular, as we heard yesterday from Dr. Havers from the CDC, there is a real correlation between comorbidity and hospitalization and having very high efficacy of 94.6% in the context of this tremendous burden in this group in particular, is really important data that we've been able to demonstrate from this first season.

Dr. El Sahly: Thank you, the third question comes from Dr. Bernstein.

Dr. Bernstein: Thank you that really was a very well organized and clear presentation by all the speakers, so thank you for that. I have one question for Dr. Rizkalla and one for Dr. Falsey. Dr. Rizkalla, I believe I understood you to say that the adjuvant that's being used in the vaccine is the same, that's in Shingrix, but half the amount.

Dr. Rizkalla: Exactly. Correct. Yes.

Dr. Bernstein: Can you summarize the experience of that adjuvant in Shingrix and what you're seeing in the studies using the AREXVY?

Dr. Rizkalla: So, experience with Shingles has been established with over 18 million doses distributed and used in this older adult population. It's first been made available in 2017, and with really compelling efficacy that has been demonstrated and has since been demonstrated to have 10 years of duration of protection with this adjuvanted vaccine for older adults to prevent shingles complications.

So very extensive experience and a well-established safety profile. Having had more than 80 million doses distributed, now we contain specifically 25 micrograms of each of the immunostimulants. The shingles ASO1 B vaccine has 50 of each of, so 25 NPL and 25 QS21. Hopefully that addresses your question, Dr. Bernstein.

Dr. Bernstein: Yeah. So, the side effects with administration, you'd expect to be less than what was sometimes seen with administration of Shingrix. I'll defer to my colleague Dr. Webster, our head of safety. And then we'll come to Professor Falsey.

Dr. Webster: Yes, I'm wondering if we could bring up slide SH-4, please. Very good, thank you. I just want to use this slide to demonstrate what we saw in the Shingrix clinical trials in terms of solicited local symptoms that were reported. There was a slight difference in the way that the data was collected here. These are reported within seven days, but as you can see the frequency of the reported solicited local symptoms is higher. There still are very few grade-three events that are reported.

Dr. Bernstein: Thank you. And Dr. Falsey, I was interested to hear a little bit more about how does the long-term impact on functional status and health after an RSV infection compare with that seen after flu or Covid or other respiratory pathogens?

Dr. Falsey: So when looking at functional loss after a hospitalization, it's sometimes quite difficult to ascribe it to a specific virus. It's probably the hospitalization that really leads to the disability. There have been comparisons of RSV hospitalizations and non-RSV illnesses. There is a recent publication where they looked at quality of life indices after that and that RSV was significantly, although modestly worse for all the domains social functioning, vitality, emotional problems.

If we can bring up slide B? So this was an SF 36, and this was not specifically in hospitalized individual, but they looked at short-term and then long-term scores on the SF 36. And the RSV illnesses seem to be worse than the non-RSV illnesses, which are – you can see short term six to seven months and 12 to 13 months. And the little star shows where it was significantly greater than a non-RSV illness. Not specifically flu, but non-RSV. So, the quality of life and the bothersome impact of some of these illnesses. It may not be hospitalization, but I thought it was important to note in this study that 15% of the cases were judged as severe. And so, they're not all just colds, they're medically significant illnesses.

Dr. Bernstein: And it may not be pathogen specific then?

Dr. Falsey: That's true. we don't have comparison with these different functional indices to show that it's pathogen specific. But there have been studies of hospitalized adults that actually show worse outcomes comparing specific pathogens with RSV, but notably, the RSV population is often slightly older, with slightly more comorbid conditions to begin with.

Dr. Bernstein: Thank you.

Dr. El Sahly: Next question is from me. And it's brief, and it's a corollary really to what Dr. Bernstein was asking. I've written it down. Do we have any head-to-head comparison in a study of the reactogenic of half dose of AS01, versus full dose of AS01 regardless of the antigen used?

Dr. Rizkalla: Sure. We have that information for you, Dr. El Sahly. I'll invite my colleague, Dr. Webster to address your question.

Dr. Webster: Yes. Let me put up a slide for you. So going back to our 002 Study, we looked at in this study, a combination of unadjuvanted vaccine adjuvanted with ASO1-E, and adjuvated with ASO1-B and as you can see here, we do get higher reactogenic in terms of frequency with the ASO1-B, which is again, twice the dose of the adjuvant that we see in ASO1-E.

Dr. El Sahly: Okay. Thank you. The two last questions are going to be asked shortly. And I'd like to remind everyone that we will have the opportunity to ask the sponsor many more questions in an hour or two. Dr. Berger.

Dr. Berger: Hi. Thanks, and much appreciate the really clear presentation from all of you. I just had a quick question about the assessment of persistence here in terms of how the protection might actually affect across seasons and whether GSK plans to evaluate this in the future. I thought, Dr. Rizkalla, you had mentioned this in your opening that you were initially going to be looking at this as a single season dose, but the persistence seems to last over a year, even though it does drop about – at least from what I can tell by the numbers, it looks like the neutralizing titers and the CD four T-cell responses dropped in about half.

So I'm just curious if you're going to be looking at a single dose over two seasons providing protection.

Dr. Rizkalla: That's an excellent question, Dr. Berger. So what we've been able to demonstrate through this final analysis of season one, which will support the licensures efficacy of the vaccine over one entire RSV season.

Now, important questions that will be answered from season two and season three of the study. I'll talk through on design of the of the study. So those that received the vaccine in the first season will be re randomized to either receive placebo or to receive the RSV vaccine each year. So in those participants that receive placebo in season two and season three, we're looking at the persistence of efficacy of that single dose over the three RSV seasons.

But we'll also be able to establish the efficacy of annual vaccination as well through this randomization in season two and season three. It's a very important element of the design of our study.

Dr. Berger: Thank you.

Dr. El Sahly: Dr. Kim.

Dr. Kim: Oh, thank you very much for that for that terrific presentation by all the speakers. Yesterday we talked a lot about co-administration of RSV vaccine with other age appropriate and indicated vaccines. And in your presentation, Dr. Rizkalla, you described to some detail about co administration with the Vale flu vaccine, and you had, and on top of that, you also mentioned the co-administration with high dose flu vaccine – the adjuvant flu vaccine, which was terrific. From GSK's perspective on whether it is systematic or anecdotal collection of data with Covid wasn't discussed.

And I wonder if you have any data, like I said, anecdotal or otherwise, on co administration of the of your RSV vaccine with the Covid vaccine.

Dr. Rizkalla: So that's definitely a priority for us supporting the programmatic implementation to really address the public health needs of the population absolute priority.

So this is a planned study for us, where in advanced stages of planning for that COVID and RSV co administration study. There is a study that has been done with an ASO 1 containing vaccine with an mRNA vaccine that has demonstrated non-inferiority in terms of the immune response and equivalent reactogenic.

So that was looking at shingles vaccine with a mRNA COVID vaccine. But this is a priority and definitely it will go beyond COVID. So all RSV vaccines for this age are being prioritized to support programmatic implementation of this vaccine.

Dr. Kim: Thank you.

FDA Review of Efficacy and Safety of AREXVY in Adults 60 Years of Age and Older — Dr. Geagan

Dr. El Sahly: Thank you all. Next on our agenda is the FDA's review of efficacy and safety of RSV, Respiratory Syncytial Virus Vaccine Recombinant, Adjuvanted, in adults 60 years of age and older. To go over the review, Dr. Nicholas Geagan is with us. He's a staff fellow at the Division of Vaccines and Related Products application at CBER, Dr. Geagan.

Dr. Geagan: Thank you and good morning. My name is Nicholas Geagan. I am a medical officer from the Office of Vaccines Research and Review in the division of Vaccines and Related Products applications. Today I will be presenting the FDA review of the safety and efficacy data submitted to support the biologics licensing application for RSV. Next slide. This is the outline for today's presentation. I will start by providing an introduction and then we'll discuss the clinical studies submitted to the biologics licensing application. Then I will discuss the efficacy data with subsequent presentation of the safety data. I will finish by summarizing the pharmacovigilance plan and finally the summary of the data and present the questions for the VRBPAC. Next slide.

Now we'll start with the introduction. Next slide. AREXVY, which I will be referring to as RSVPreF3 for the duration of this presentation is a candidate vaccine containing a recombinant RSVPreF3 antigen with ASO1-E adjuvant that is administered intramuscularly as a single 0.5 mL dose containing 120 micrograms of antigen. The RSV fusion protein was derived from the RSV fusion surface glycoprotein of an RSV-A strain and a stabilized in the prefusion trimeric confirmation of the naturally occurring F protein. The liposomal based adjuvant system, ASO1, contains 25 micrograms of QS21 and 25 micrograms of MPL. Of note, the licensed

Shingrix vaccine is also adjuvanted with ASO1 at twice the concentration with 50 micrograms of QS, 21 and 50 micrograms of MPL. The applications the applicant's proposed indication for RSVPreF3 is active immunization for the prevention of lower respiratory tract disease caused by respiratory syncytial virus, RSV-A and RSV-B subtypes in adults 60 years of age and older. Next slide.

Next, I will discuss the clinical studies submitted for FDA review. Next slide. Data from five clinical studies with RSVPreF3 were submitted to support the biologic licensing application. The primary data to support safety and advocacy of RSVPreF3 in individual 60 years of age and older is from RSV0A= ADJ06, which I would referring to as study 06.

Study 06 is an ongoing phase three randomized placebo-controlled observer blind multi-country study. In the study, 24,966 participants were randomized to receive a single dose of RSVPreF3 or placebo. This study is being conducted in 278 active centers in 17 countries. Study 07 is a phase three open label, randomized controlled, multi-country study to evaluate the safety and immune response of RSVPreF3 vaccine.

When concomitantly administered with quadrivalent influenza vaccine in adults sixty years age and above. A total of 885 participants were randomized to either receive RSVPreF3 and flu vaccination, concomitantly or flu vaccination, followed by RSVPreF3 30 days post-vaccination. Results from studies 006 and 007 will be discussed in detail in this presentation. Safety data from 004 and 009 will be described in the aggregated safety assessment, but I will briefly summarize these studies here. Study 009 is a phase three randomized double-blind multi-country study to evaluate consistency, safety, and react immunogenicity of three, lots of RSVPreF3 administered as a single dose in adults aged 60 years and above.

This study met the predefined success study success criteria for demonstration of similar immune response across three lots of RSVPreF3. Study 004 is an ongoing phase three randomized open-label multi-country study to evaluate the immunogenicity safety, reactogenicity, and persistence of a single dose of RSVPreF3 and different revaccinated schedules up to three years following a single dose. The groups included are annual flexible revaccination, in which participants receive two doses, and a single dose group. At the time of the BLI submission, each group has only received a single dose of the investigational vaccine. Finally, not included on the slide is study 002, which is a supportive phase 1/2 two dose and formulation study evaluating three dosages with or without an ASO1 adjuvant. The safety and immunogenicity data provided in this study supported the selection of 120 micrograms of RSVPreF3 adjuvanted with ASO1 E administered as a single dose for further evaluation in the phase three studies. The study will not be discussed further in this presentation. Next slide.

Here, I'm presenting the design of the pivotal study 006. As noted previously, study 006 was designed as a phase three efficacy and safety study. A total of 24,966 participants were randomized one to one to receive either RSVPreF3, or placebo consisting of normal saline. The study is planned to cover three consecutive RSV seasons in the northern hemisphere and at least two consecutive RSV seasons in the southern hemisphere with primary efficacy assessed during the first season. The study began in May of 2021 in the Northern Hemisphere and in June in 2021 in the Southern Hemisphere.

Participants enrolled included both healthy adults and those with stable chronic medical conditions, including COPD, asthma, any chronic respiratory or pulmonary disease, diabetes mellitus, chronic heart failure, advanced liver, or renal. Of note, there was a planned enrollment by age subgroup with 40% planned enrollment in the 60 to 69 year of age group, 30% in the 70

to 79 age group, and 10% in the 80 years of age and older subgroup with the remaining 20% of participants being distributed freely.

Starting 14 days post-vaccination, participants were actively monitored for onset of acute respiratory illness symptoms in participants with ARI symptoms. Self-collected nasal samples were collected, and RT-PCR was performed only as subject's first episode of RT-PCR confirmed. RSV LRTD was considered in the efficacy analysis.

In regards to safety monitoring, a subset of patients underwent monitoring of solicited local and systemic adverse reactions for four days. All participants underwent unsolicited adverse event monitoring for one month. Potential immune made diseases and serious adverse event monitoring was performed throughout the entire study.

Next slide. This slide demonstrates the plan to season one timeline of the study with highlights of key dates. The study design figure covers season one, but as stated previously, the study is planned to cover three consecutive RSV seasons. After informed consent, participants underwent a pre-vaccination blood draw, and all participants received the study intervention as randomized on study day one.

After vaccination study monitoring was initiated with monitoring of local and systemic solicited reactions for four days post vaccination and a solicited safety subset, and for elicited unsolicited AEs for one month in all participants. Serious adverse events and potentially immune media diseases will be monitored through safety to threat study and active surveillance of ARI symptoms was initiated in all participants on day 15, and additional blood sampling occurred at one month post vaccination.

The data cutoff for this study was April 11th, 2022, at which time participants had a median duration of follow up of efficacy of 6.7 months. Please note that an analysis of immunogenicity endpoints was submitted but have not been included in this presentation. Next slide. Now we'll discuss the efficacy data from study 006 with subsequent discussion of the concomitant administration data. As noted previously, starting 14 days after study vaccination, all participants were actively monitored for onset of ARI symptoms. Participants met the criteria for ARI if they experienced at least two respiratory symptoms or signs for at least 24 hours, which include nasal congestion/rhinorrhea, sore throat, new or increased sputum, or new or increased cough or at least one respiratory symptom plus one systemic symptom or sign for at least 24 hours, which include fever, fatigue, body aches, and headache.

If AR symptoms were experienced, self-collected nasal swabs were collected and sent to a central laboratory for RSV testing, and an illness visit was scheduled within seven days of symptom onset.

As a visit to onwards, the site staff will would contact the participants regarding regularly – during the study period to check if they experience any respiratory symptoms meeting the ARI case definition, these contacts were performed every two weeks during the RSV season and every month during the inter-season periods, participants met the criteria for lower respiratory tract disease or LRTD if they experienced at least two lower respiratory symptoms or signs for at least 24 hours. Including at least one respiratory sign or at least three lower respiratory symptoms for at least 24 hours. Lower respiratory symptoms include new or increased sputum cough or dyspnea, and lower respiratory signs include new or increased wheezing, crackles, or bronchi based on chest auscultation. Respiratory rate greater than or equal to 20 respirations per minute, lower decreased oxen saturation or need for ox oxygen supplementation. RT-PCR confirmed.

RSV-ARI, RSV LRTD and severe RSV LRTD met the conditions of the respective case definitions with at least one RSV positive swab detected by RT-PCR.

Next slide. Here's the primary objective being assessed for study 006. The primary efficacy objective assesses efficacy in the prevention of RSV confirmed LRTD in the first RSV season. The endpoint is the first occurrence of RT-PCR confirmed RSV-A and or B associated LRTD. Vaccine efficacy is defined as one minus the risk ratio. The study had a predefined success criterion of the lower limit of the two-sided confidence interval for vaccine efficacy being above 20%.

Next slide. The secondary descriptive objectives assessed vaccine efficacy by subgroup analysis including age category, baseline comorbidities, frailty, status, and subtype. Additional secondary objectives included vaccine efficacy against severe RSV confirmed LRTD and RSV-ARI. The immunogenicity objective was to assess the humoral immune response based on RSVPreF3, IGG specific antibody concentrations, and neutralizing antibody titers against RSV-A and or RSV-B and as stated previously, will not be presented in this presentation. Following discussion of the efficacy analysis one. I will discuss the safety data for study 006. Safety evaluations included monitoring for solicited local and systemic adverse events on days one through four unsolicited adverse events at 30 days. Serious adverse events up to the data lock point and potential immune made diseases up to the data lock point.

Next slide. The populations that were identified in the study included the exposed set, which included participants who received at least the first dose of study intervention, which there were 12,467 participants in the RSVPreF3 group and 12,499 participants in the placebo group. The modified exposed set, which included participants in the exposed set who did not report an

RSV confirmed ARI prior to day 15 after each vaccination, which there are 12,466 participants in the RSVPreF3 group and 12,494 participants in the placebo group.

The per protocol set included participants in the modified exposed set who have data available for efficacy endpoint measures and did not have any protocol deviations leading to exclusion, in which there were 12,142 participants in the RSVPreF3 group and 12,176 participants in the placebo group. The solicited safety set included participants in the exposed set who have solicited safety data, in which there were 879 participants in the RSVPreF3 group and 878 participants in the placebo book group. The primary and secondary vaccine efficacy analyses were based on the modified exposed set. The solicited safety population was used for the analysis of solicited safety.

Next slide. In the exposed set, the sex of the participants was equally distributed between male and female. The majority of participants were in the age range of 60 years of age through 69 years of age, with a median age at time of vaccination of 69 years for both study groups. Of note, although not a predefined age subgroup, the overall percentage of participants at least 75 years of age was 21.3%. Overall, the majority participants were located in the Northern Hemisphere at 92.2% for both groups with 27.8% of the participants being from the United States. With regards to frailty status, the majority participants were fit with 59.9% in the RSVPreF3 group and 62.2% in the placebo group. The majority of participants were reported to have at least one preexisting comorbidity of interest with 39.6% in the RSVPreF3 group, and 38.9% in the placebo group.

Next slide. With regards to race and ethnicity across both groups, the majority of participants were white at 79.4% and non-Hispanic or Latino at 94.5%. Next slide. As of the data lock point, there were 47 cases of first episode RSV LRTD occurring after day 15. The case split

was seven cases in the RSVPreF3 group compared to 40 cases in the placebo group with a vaccine efficacy of 82.6% and a lower limit of 57.9.

Next slide. The cumulative incidents curves present the cumulative of numbers of RT-PCR confirmed RSV LRTD reported from day 15 post vaccination up to vaccine analysis, one in both groups. Starting shortly after vaccination, the curves diverge with more cases accumulating in the placebo group than in the RSVPreF3 group. Cases continue to accrue at a faster rate in the placebo group compared to RSVPreF3 group through approximately seven months following vaccination, which was near the median duration of follow-up for participants in the study at the time of the data cutoff.

Next slide. Vaccine efficacy against RSV subgroups A and B were also individually calculated. Similar to the primary efficacy analysis, the observed vaccine efficacy against first occurrence of LRTD caused by RSV-A was 84.6%, and against RSDB was 80.9%.

Next slide. Vaccine efficacy was also assessed by age subgroup and was comparable to the overall efficacy results in the 60 to 69 year of age group subgroup, and 70 to 79 year of age subgroup with observed increasing vaccine efficacy. RSVPreF3. With age as seen by a vaccine efficacy of 93.8% in the 70 to 79 age subgroup compared to 81.0 in the 60 to 69 year of age subgroup. With the total of five cases between the two group the number of cases accrued of LRTD among participants, at least 80 years of age, was too small to make conclusions about vaccine efficacy in this age subgroup.

Next slide. Vaccine efficacy analysis was performed by baseline comorbidities. The vaccine efficacy was higher in participants with at least one preexisting comorbidity of interest compared to those with no preexisting comorbidities of interest at 94.6% and 72.5% respectively.

Next slide. The physical frailty status of all participants was assessed at baseline by gate speed test. Based on the time required to walk the selected length of walk, participants were categorized in a frail pre-fail or fit subgroups. The vaccine efficacy for RSV confirmed LRTD were 80% in fit and 92.9% in pre fail participants. A total of two RSV confirmed LRTD cases, one in each group occurred in 366 frail participants. The number of cases among frail participants was too small to make conclusions about vaccine efficacy and frail participants in this subgroup.

Next slide. Here I've included both definitions provided by the sponsor for severe RSV confirmed LRTD. The two definitions included definition one, which is based on clinical symptomatology and definition one includes presence of an LRTD with at least one of the following criteria, at least two respiratory signs and an LRTD episode assessed as severe by the investigator, which is defined an LRTD episode preventing normal everyday activities. Such an event would, for example, provide prevent attendance at work and would necessitate the administration of corrective therapies.

Definition two, which is based on the use of supportive therapy, included presence of an LRTD with at least one of the following criteria. Need for oxygen supplementation, need for positive airway pressure therapy, and need for other types of mechanical ventilation. Here we see the observed vaccine efficacy against RT-PCR, confirmed RSV, severe LRTD based on case definition one was 94.1%.

The number of RSV severe LRTD cases based on definition two, was too small with a total of two cases of severe LRTD in the placebo group to make conclusions about vaccine efficacy using this definition. Of note, the two cases of RSV severe LRTD that did meet definition two also met criteria for definition one.

Next slide. Here we see the efficacy data for RT-PCR, confirmed RSV-ARI. I've again included that case definition for ARI for your reference. Based on this definition, the observed vaccine efficacy of a single dose of the RSVPreF3 vaccine against first occurrence of RSV-ARI was 71.7%. No participants in either group reported more than one episode of RSV fi confirmed ARI. Next slide. Now we'll switch gears and discuss the study 007. The concomitant use with influenza vaccine study design. As discussed in the clinical overview study 007 is a phase three open label randomized controlled multi-country study to evaluate the safety and immune response of RSVPreF3 vaccine when concomitantly administered with quadrivalent influenza vaccine.

Specifically, Fluarix Quadrivalent in adults aged 60 years and above, both healthy and those with stable chronic medical conditions. The study occurred in 14 centers in three countries, New Zealand, Panama, and South Africa. A total of 885 participants were randomized to either receive RSVPreF3 and flu vaccination concomitantly or flu, followed by RSVPreF3 30 days post vaccination.

Participants in the co-administration group received a single dose of RSVPreF3 and a single dose of flu vaccine at day one. Whereas participants in the control group received a single dose of flu vaccine at day one, followed by a single dose of RSVPreF3 at day 31.

Next slide. The primary analysis of immunogenicity was performed to assess non-inferiority of immune responses to the vaccine antigens contained at each vaccine product. When administered concomitantly compared to when administered 30 days apart. The pre-defined success criteria were met at the upper limit of the two-sided 95% confidence interval on the group, geometric mean titers or GMT ratio, which is the control group divided by the COAG group, was less than or equal to 1.5.

The immune response to the RSVPreF3 antigen was assessed one month post vaccination by serum neutralizing assays to determine the titers of functional antibodies against RSV-A and RSV-B. Non-inferiority was met with an upper limit of the GMT ratio being 1.28.

The immune response to the flu virus strains flu A H3N1, flu A H1N1, flu B Yamagata, and flu B Victoria, were assessed one month post dose by the Hemagglutinin assay to determine the titers of functional hemagglutinin antibodies against each of the flu vaccine strains.

Non-inferiority of the COAG group compared to the control group was met with a range of the upper limit of the GMT ratios being 1.1 to 1.22 depending on the flu strain.

In regards to safety, the rates of solicited adverse reactions and unsolicited adverse events were comparable between the two groups. There was a numerically higher percentage of participants who reported solicited administrative site events in the COAG group compared to the control group, which was primarily driven by a injection site pain with 47.9 participants in the COAG group compared to 39.1% in the control group. No participants withdrew from the study due to an adverse event.

Two cases of acute disseminated encephalomyelitis were reported both in the COAG group, one of which was the reported cause of death of a participant. Further details regarding these cases will be provided in subsequent slides with the aggregated safety data. Additionally, SAEs, death, and pIMDs will also be further described in the aggregated safety data analysis.

Next slide. Here we'll be presenting the solicited unsolicited safety data for study 006 with discussion of SAEs pIMDs will be included in the aggregated safety analysis and subsequent slides.

Disposition of the 24,966 participants who contributed to the analysis of safety up to the data lock point for safety of April 30th, 2022, are presented here. Up to analysis one, a total of

764 participants, 372 in the RSVPreF3 group and 392 in the placebo group, were withdrawn from the study. The most common reasons for withdrawal were consent withdrawal, not due to an AE or an SAE with 335 participants overall. Loss to follow up with 208 participants overall and adverse events requiring expedited reporting 140 per participants overall.

Next slide. This is a safety overview for study 006. Safety evaluation include the following parameters, solicited and local and systemic AEs for four days post vaccination unsolicited non-serious local and systemic AEs through 30 days post vaccination. All serious adverse events and pIMDs up to six months following each dose, and all related SAEs, pIMDs and deaths from beginning until end of study.

The study used a data monitoring committee to review accumulative safety data throughout the study and interim analysis for efficacy. The DMC was independent of the study team and included only external members. The rates of immediate unsolicited AEs within 30 minutes following vaccination were higher in the RSVPreF3 group compared to the placebo group with 0.8% of participants in the RSVPreF3 group compared to 0.1 per percent of part participants in the placebo group.

This imbalance is primarily driven by general disorders and administrative site conditions with the most commonly reported event being injection site pain for both groups. 68 in the RSVPreF3 group compared to nine in the placebo group.

The second highest proportion of events was related to nervous system disorders, primarily being driven by headache, and no episodes of anaphylaxis occurred within 30 minutes after vaccination. The rates of unsolicited events within 30 days of vaccination was also higher among the RSVPreF3 group compared to the placebo group, which I'll be discussing in much more detail in subsequent slides.

SAEs were reported by 4.2% and 4.0%, in of participants in the RSVPreF3 group and placebo group respectively, with none of the SAEs being considered related to study intervention. At the time of the data cutoff deaths occurred in 0.4% of RSVPreF3 recipients and 0.5% of placebo recipients. In general, the causes of death among study participants were representative of the most common causes of death among the elderly adult population. None of these deaths were considered related to study intervention. AEs leading to withdrawal from the study occurred in 0.2 participants in each group and pIMDs occurred in 0.3 percent of participants in each group.

Next slide. Data unsolicited, local and systemic adverse reactions within four days following vaccination were collected from a subset of 1,753 participants within four days post vaccination the proportion of participants reporting grade one or higher local reaction were higher in the RSVPreF3 group compared to placebo group at 62, 2 0.2%, and 10% respectively. The most frequently reported local reaction in both groups was pain at the injection site reported by 60.9% of participants in the RSVPreF3 group and 9.3% of participants in the placebo group. Severe grade three solicited local reactions were rare, reported by 1% and less than 1% of participants in the RSVPreF3 group and placebo groups respectively.

Next slide. This table includes percentages of participants who reported any solicited systemic adverse reaction by maximum severity. The rates of solicited systemic adverse reactions was also higher in the RSVPreF3 group compared to the placebo group at 49.4 and 23.2% respectively. The most frequently reported solicited systemic event was fatigue at 33.6% in the RSVPreF3 group and 16.1% in the placebo group, followed by myalgia, 28.9% in the RSVPreF3 group and 8.2% in the placebo group. And headache 27.2% in the RSVPreF3 group and 16 or 12.6% in the placebo group.

Fever defined as temperature greater than or equal to 38 degrees Celsius was reported in 2% of participants in the RSVPreF3 group and 0.3% in the placebo group. In grade three reactions were low for both groups, ranging from less than 0.1% to 1.7%.

Overall subgroup analyses by age and sex were similar to the overall population. However, solicited reactions were reported more frequently in the younger age, subgroup of 60 through 69 years of age.

Next slide. Unsolicited adverse events were followed in the entire safety population through one month following vaccination by subgroup analyses by age, sex, race, ethnicity, country, or predefined at-risk conditions. There were no specific safety concerns identified.

Of note, the study participants that were not part of the solicited safety subset did not prospectively record solicited reactions on a diary card but reported them as unsolicited adverse reactions.

The most frequent types reported by system organ class were general disorders and administrative site conditions, nervous system disorders, infections, and infestations, and respiratory thoracic and mediastinal disorders. The rates of non-serious AEs in the solicited safety subset were 14.9% and 14.6% of RSVPreF3 recipients and placebo recipients respectively.

The discordant percentages of nervous system disorders in the RSVPreF3 group were primarily due to headaches with 6.4% of vaccine recipients reporting this AE compared to 3.9% in the placebo group. The discordant percentages of the musculoskeletal and connective tissue disorders in the RSVPreF3 group were primarily due to muscle pain with 1.2% of vaccine recipients reporting this AE compared to 0.4% in the placebo group.

Significant imbalance noted in the events characterized as general disorders and administrative site conditions was primarily driven by injection site pain with 15.8% in the RSVPreF3 group and 1.4% in the placebo group and aesthetic conditions with RSVPreF3 group having 3.3% compared to the placebo group of 1.3%.

Additionally, there was a numerical imbalance noted in events of atrial fibrillation with 10 events in the RSVPreF3 group and four events in the placebo group. Eight of these events were also SAEs with three of these SAEs corresponding to new onset atrial fibrillation. Among the 14 participants who experienced events of atrial fibrillation, a medical history of atrial fibrillation was reported by six RSVPreF3 recipients and two placebo recipients.

The remainder of events occurred in participants with relevant predisposing or concurrent medical conditions. Events ranged from one to 30 days after vaccination. Through a data cutoff, an imbalance is no longer seen with atrial fibrillation reported by 14 participants in the RSVPreF3 group and 16 participants in the placebo group.

As mentioned previously, although no anaphylactic reactions occurred in either study group hypersensitivity reactions occurred in 0.2% of RSVPreF3 recipients and less than 0.1% of placebo recipients primarily being driven by rash and injection site were rash.

Next slide. The aggregated safety data presented here includes participants from studies 006, 007, 009, and 004. At the time of the D data lock points, a total of 15,745 participants, RSVPreF3 recipients and 12,499 placebo recipients from four phase three studies were included in the exposed set.

The median durations of follow up from day one to the data lock point across all phase three studies was 7.2 months. SAEs occurring within six months after study intervention were reported in 4% of vaccine recipients and 4.5% of placebo recipients. The SAEs that were most

commonly reported, organized by system oral class, were similar to that of the unsolicited AEs assessed in study 006. The most commonly reported SAEs included infections and infestations most commonly due to COVID-19, cardiac disorders, most commonly due to ischemic coronary artery disorders and nervous system disorders, most commonly due to CNS hemorrhages and cerebral vascular events.

One case of Guillain-Barre Syndrome occurred nine days after RSVPreF3 vaccination and study, 004 was considered by the study investigator and FDA to be an SAE related to RSVPreF3 vaccination. I'll provide the narrative for this case in a few minutes.

Up to the data lock point, deaths were reported for 0.4% of R RSVPreF3 recipients in 0.5% of placebo recipients. Fatal outcomes were categorized most frequently by the SOCs of cardiac disorders and infections and infestations. One participant in Study 007 had an SAE with a fatal outcome secondary to acute disseminated encephalomyelitis that was considered by the FDA to be considered possibly related to the flu or RSVPreF3 vaccination. I will also provide the narrative for this case in subsequent slide.

Next slide. pIMDs, or potential Immune Mediated Diseases, occurring within six months after study intervention were reported in 0.4% of vaccine recipients at 0.3% of placebo recipient. The most commonly reported pIMDs by system organ class were metabolism and nutrition disorders and musculoskeletal and connective tissue disorders, followed by nervous system disorders.

In study 00611 pIMDs were considered by the study investigator to be possibly related to vaccination with six in the RSVPreF3 group, and five in the placebo group. These six events that occurred in the RSVPreF3 group included two episodes of Bell's Palsy, hand Cytopenia, Graves Disease, Gout, and Psoriasis.

In Study 007, two cases of ADEM were considered as possibly related to either RSVPreF3 or Quadri-flu vaccination in the co-administration group, including the one fatal case previously described, which I will go into further details in subsequent slides. And in Study 004, as mentioned previously, one case of GBS was considered as related to RSVPreF3 vaccination. Next slide. Here I'll present the narratives for the two cases of ADEM and one case of GBS. Both cases of ADEM occurred in study 007 in the co-ad group in which participants received RSVPreF3 and flu concomitantly.

The first participant was a 71-year-old male in the co-ad group who developed shaking and shivering and was hospitalized and diagnosed with acute disseminated encephalomyelitis, seven days from the co-administration of study vaccination. He was found by his neighbor lying on the floor, shaking, shivering, was brought to the hospital where he was found to have a blood glucose reading of 1.4 millimoles per liter and was known to have a low Glaxo coma score. A CT scan of the head was performed and reported to previous strokes with Waller demyelinating lesions. Fifteen days after hospital admission, which was 22 days post-vaccination, the participant died with a reported cause of death being acute disseminated encephalomyelitis with a Brighton collaboration level of three.

The second participant was a 71-year-old female in the coadministration group with a medical history of hyperlipidemia and hypertension who developed worsening of tiredness and headaches with intermittent double vision, forgetfulness and confusion twenty-two days after co-administration of study vaccines and was diagnosed with ADEM. She was noted on examination to have an ataxic gait with lower left limb weakness. 16 days after initial evaluation, she still reported feeling forgetful and confused but with improvement in handshaking headaches. The participant demonstrated further improvement in cognition and repeat visits, but the outcome

was reported as not resolved by the time of the receipt of the study report. She had no investigations done and the diagnosis was made only on symptoms and clinical findings. Based on her symptoms, she was diagnosed with ADEM Brighton collaboration level three.

In summary, two cases of ADEM were reported in Study 007 in the co-ad group. No additional episodes were observed in the primary pivotal study 006 or other studies, so overall two cases were reported over approximately 15,000 vaccines. Further, details re regarding these events has been requested. An FDA review is ongoing.

Next slide. One case of GBS occurred in Study 004, the ongoing revaccinated study. The participant was a 78-year-old female who developed lower limb weakness, which started nine days after RSVPreF3 vaccination dose one. She had difficulty walking the next day, developed upper limb and respiratory muscle weakness over the subsequent three days and it was hospitalized for further examination. Cerebral spinal fluid protein was elevated at 146 micrograms per deciliter and ganglia site immunoglobulins were positive. A head MRI was performed and not noted no significant findings. Her hospital course was complicated by respiratory paralysis requiring artificial ventilation. She was started on immunoglobulin treatment for Guillain-Barre syndrome after a two-month hospital course she was transferred to a rehabilitation hospital for an additional six months before being discharged with the total hospital duration of six months without disability regarding her daily life activities.

In summary, one case of GBS was reported in the non-placebo-controlled study 004. No additional episodes were observed in the primary pivotal study 006 or other studies, so overall one case was reported over approximately 15,000 vaccinees.

Next slide. Now we'll discuss the sponsors Proposed pharmacovigilance plan. The applicant will conduct passive and active surveillance activities for continued vaccine safety monitoring,

including routine pharmacovigilance. The applicant has agreed to perform expedited reporting for all cases of GBS and other immune mediated demyelinating conditions. Expedited reporting for all cases of super ventricular arrhythmias in an aggregate analysis and periodic safety reports of these same events.

Note that the following are currently under discussion between FDA and the applicant. Plans for a post-marketing safety study to assess the risk of GBS ADEM and other demyelinating conditions among individuals vaccinated with RSVPreF3, and determination of the inclusion of cardiac disorders as an important potential risk in the pharmacovigilance plan. Next slide. Finally, I will close by summarizing the data from the submission and presenting FDA questions to the committee.

Next slide. To summarize the efficacy data, vaccine efficacy against first occurrence of RT-PCR, confirmed, LRSV LRTD was 82.6% in adults, 60 years of age and older, with the endpoint achieving the lower bounds of the 96.95% competence interval that met study success criterion. Subgroup analyses showed the vaccine efficacy was demonstrated for RSV-A and RSV-B virus subtypes, age groups 60 to 69 years of age and 70 to 79 years of age, and participants with at least one preexisting comorbidity of interest and RSV-ARI.

The number of accrued RSV LRTD cases at the time of analysis were too small to make conclusions about vaccine efficacy and adults at least 80 years of age and by physical frailty in the frail population. Vaccine efficacy against RT-PCR confirmed, RSV severe LRTD based on clinical symptomatology was 94.1%.

The number of RSV severe LRTD cases based on supportive therapy was too small to make conclusions about vaccine efficacy against RT-PCR confirmed RSV severe LRTD based on this definition. After the review of the submission data are not currently available on the

duration of vaccine efficacy and vaccine efficacy in immunocompromised and frail elderly individuals.

Next slide. To summarize the safety data at the time of the DLPs, a total of 15,745 RSVPreF3 recipients from four, phase three studies were included in the exposed set. The median durations of follow up from day one to safety DLP across all phase three studies with 7.2 months. RSVPreF3 is known to have increased reactogenicity when compared to placebo, but the rates of grade three reactions after RSVPreF3 vaccination were low.

Within 30 days post vaccination, a numerical imbalance was observed for all – for events of atrial fibrillation and Study 006 and FDA review of these events is ongoing. The frequency of SAEs reported up to six months post vaccination was 4.0% and 4.5% in the vaccine of placebo groups respectively.

In both study groups, most of the SAEs were events common to the older adult population and or associated with underlying medical conditions. One SAE of Guillain-Barre Syndrome that occurred nine days after RSVPreF3 vaccination, also categorized as a pIMD was considered by the study investigator and FDA to be related to the study vaccination.

One death due to acute disseminated encephalomyelitis occurred in a participant 22 days after receiving concomitant RSVPreF3 and seasonal influenza vaccine was considered by the FDA as possibly related to flu or RSVPreF3 vaccination.

Up to the time of the data lock point, at least one pIMD was reported by 0.4% and 0.3% of vaccine and placebo recipients respectively. Two pIMDs, the two cases of ADEM in concomitant vaccine study 007 were considered by FDA to be possibly related to flu or RSVPreF3 vaccination. A safety update was submitted for extended safety follow up at month

six through twelve continuing SAE and pIMD data, and FDA review of these data are ongoing at the time of this presentation.

Next slide. Today we will be asking for your vote on the following questions. Are the available data adequate to support the safety of AREXVY when administered to individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV? Please vote yes or no.

Are the available data adequate to support the effectiveness of AREXVY for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older? Please vote yes or no. Thank you.

Q & A

Dr. El Sahly: Dr. Geagan thank you for the presentation. I invite the committee members to raise the hand to ask questions to Dr. Geagan.

Give it a minute to get everyone going when we will start with Dr. Bernstein.

Dr. Bernstein: Thank you for sharing all of that data with us. One quick question the data lock point goes back till April of 2022 for certain outcomes or data, how often is that refreshed or added information included?

Dr. Geagan: So the data log point is at which point the vaccine efficacy analysis one occurred. So the data from that endpoint is what is being used to describe the primary efficacy endpoint and is what the question two is being based off of. So the data presented at that data lock point is what's presented in this presentation.

Dr. Bernstein: And when does it get updated with subsequent data or –

Dr. Geagan: So I would refer to GSK my colleagues at GSK to provide answers to that if they have that information available.

Dr. Bernstein: Thank you.

Dr. Rizkalla: Would you like a response now or? Yep, for season two, the data lock point goes up until the end of April of this year and results from that season after the end of the season two of the Northern Hemisphere will become available in Q2. The same data lock point will be used for the Northern Hemisphere at the end of April next year, which will then generate results from the end of season three which will be available in Q2 next year, hopefully.

Dr. Bernstein: Thank you, Dr. Rizkalla.

Dr. El Sahly: Dr. Perlman.

Dr. Perlman: Yeah. I just had a question about severe disease. So it looks like there's no RSV deaths in either limit that you studied, correct?

Dr. Geagan: Correct.

Dr. Perlman: And the second thing is in the definition of severe disease, the range was, went all the way from additional oxygen presumably to hospitalization. Do you have a breakdown of what was in the different categories of severe disease? Now, if someone was in a nursing home and they got a little more oxygen does that count as a severe disease?

Dr. Geagan: So the participants that met the, that second definition criteria of requiring supportive therapy were only two participants. As far as the breakdown of those participants I don't have that information available currently, but it was just the two participants that met that criteria definition for severe LRTD.

Dr. Perlman: And so what about in the first group? Definition one, how was that broken down? Do you have any –

Dr. Geagan: So that group was broken down by participants that met that severe definition, so they may not have had the supportive therapy. And as far as further breakdowns I do not have that information, that detail information available at this time.

Dr. Perlman: Yeah. Because it certainly, it was impressive, the effect of the vaccine. But it would be nice to know that we are dealing with really more than minor disease. I don't think we were, but it's a little hard to tell.

Dr. El Sahly: I have a follow up question to Dr. Perlman. In that reading the briefing document and listening to the presentation, it was also hard for me to understand what was severe disease. Certainly we have 16 versus two or 16 versus one based on a definition that after your presentation, I understand it was mostly what the investigator called severe.

The patient may not have needed oxygen, they may not have had wheezing, they may not have – If I, as an investigator called it severe, it became severe in the database.

Dr. Geagan: That is correct.

Dr. El Sahly: Okay. All right. So that is that clarifies it. Thank you, Dr. Feikin.

Dr. Feikin: Hi. Thanks for that very extensive presentation. I had a question about the definition of non-inferiority in the co-administration study and how that's defined. My understanding is that if the upper confidence limit does not cross 1.5 in the ratio, that would be considered non-inferior but yet, there were some differences in the ratio between the two.

If I read it right, there was up to a 22% decrease for the flu hemagglutinin and 27% for RSV neutralization which did not include one. So I'm just wondering if that 1.5, is that standard does, is that a statistical decision or is it a clinical decision? Are we, is it felt that if it doesn't go above a 50% difference, then clinically it doesn't matter so much? So if you could clarify. Thank you.

Dr. Geagan: Yeah, so for the predefined definition of being less than or equal to 1.5 was a statistical determination based on like prior agreed endpoints.

Dr. Feikin: Thank you.

Dr. El Sahly: And what's in the numerator is the coadmin, right?

Dr. Geagan: Correct.

Dr. El Sahly: Okay. Dr. Hildreth.

Dr. Hildreth: Thank you, Dr. El Sahly. I actually want to follow up on a question that you asked earlier, and that has to do with effectiveness versus efficacy. I think our colleagues from GSK have provided compelling evidence that the vaccine is highly efficacious, but effectiveness relates to how it's going to perform in the real world. And the real-world purpose of this vaccine is to prevent disease in older individuals and the number of older individuals enrolled in the studies and a number of severe cases and hospitalizations are not sufficient to make that determination. So the question you've asked us to vote on relates to effectiveness, not efficacy. I have a problem with that, I just want you to help me understand this. And we're not voting on an EUA, it's a BLA, for God's sake. So we're going to be licensed here. So I think this is a very important question, but I'll let you comment.

Dr. Geagan: Yes, thank you for the question. So really, our vote today is based on the data provided at this point for the effectiveness. So we, we asked the committee to respond to the question based on the data provided, and we will take your, any comments and any response to that vote in consideration when going forth with licensing.

Dr. Hildreth: Okay. Thank you.

Dr. El Sahly: I wish I asked the question yesterday. Dr. Holly Janes.

Dr. Janes: Thank you. I had another question on the study that established non-inferiority of the humeral immune responses in the co-administration versus the single administration. Were there any cellular immune response data generated from that study? Given, I guess in particular for the RSV vaccine that induces both CD4 and immune responses?

Dr. Geagan: As far as cellular immunities, no, not in study, not in the concomitant administration study. There was not cellular data available that was submitted.

Dr. El Sahly: Thank you, Dr. Griffin.

Dr. Griffin: Yes, I have a question about ADEM, can you tell us what the baseline risk of a is and has it been linked to flu vaccine before and what the risk is for that with flu vaccine?

Dr. Geagan: So I'm not sure if our pharmacovigilance colleagues are on the line yet, but if they are, I would invite them to speak on this question regarding the baseline incidents of ADEM.

Dr. Alimchandani: Hi, this is Dr. Alimchandani from FDA. That's a really good question and let me get back to you with the numbers after the break. Thank you.

Dr. Griffin: Okay, thank you. I did have one other question about the GBS, and I know we're not supposed to consider what we saw yesterday, but I'm just wondering what FDA is thinking about – these are very rare events and I recall with the SARS-CoV-2 vaccine trials. There were, I think there was only one that I saw, one GBS, and that was in the J&J vaccine that was ultimately shown to be associated with GBS. And in the very large MORA studies we didn't see any GBS. It's not something that you routinely see one or two cases. So I'm just, how is FDA thinking about this, that both RSV vaccines have had GBS cases?

Dr. Geagan: Yes. Thank you for that question. We, as an Agency, we do discuss interdepartmentally about these files, especially ones that are similar, are targeting a similar disease process. So we have discussed the concern for our GBS and while GBS is a rare

condition it does seem concerning to have observed these cases in the context of clinical development program. So we are discussing with the sponsor as far as further development of subsequent safety analysis of GBS. So it is a concern on our end as well and we are working together to discuss outcomes.

Dr. Alimchandani: I'm going to chime in, this is Meghna again. Similar to yesterday, yes, the background rate is one to three per hundred thousand person-years, so we are looking at it closely for both products. You heard yesterday that the applicant, yesterday's applicant, had proposed a post-marketing active surveillance study using Medicare beneficiaries. From GSK at this time we don't have a proposal for a post-marketing safety active surveillance study, but we are discussing and as we, reminded of VRBPAC yesterday, we do have the regulatory authority to require a safety post-marketing studies if it meets certain criteria. So all of that is under discussion as well. But I don't know if GSK has any additional comments on their post-marketing surveillance plans for GBS.

Dr. El Sahly: Anyone from GSK, please?

Dr. Webster: Hi, it's Dr. Webster from GSK vaccine Safety. So the proposed pharmacovigilance plan that we have described today includes enhanced surveillance in the post-marketing setting for all pIMDs, including Guillain-Barre Syndrome and ADEM. We will continue to also follow these very closely in our ongoing clinical trials.

Dr. El Sahly: Thank you, Dr. Webster.

Dr. Alimchandani: I just wanted to point out the enhanced surveillances is really referring to passive surveillance, though it's not an active surveillance. Thanks.

Dr. El Sahly: Thank you, Dr. Alimchandani for clarifying. I have a follow up question and I invite additional committee members to raise hand. I'm sure you all have a lot. I want to focus on

ADEM and GBS just for a minute. If I may ask another question unrelated. The prefusion F protein being locked in the, well being locked in the perfusion state, the F protein being locked in the perfusion state is the approach the same between, various manufacturers because these two products and additional products we're reading on and the literature now are utilizing this particular configuration of F, is it largely locked in prefusion using similar biochemical modalities? Like I know for the SARS-CoV-2, addition of two proteins is usually introduced. What about RSV? Is the mechanism similar across multiple manufacturers?

Dr. Geagan: So I can only speak to what was submitted for this application, but I'll refer to our colleagues at GSK if they have any further comments on the development of this brief configuration.

Dr. Pircon: Hello so technical development at GSK effectively, so we use the backbone describe in the literature from Malan and for the profusion stability of the Pre-F. So we perform some genetic mutation as described Faso. We introduce two diesel feed bone to stabilize the Pre-F. We also increased the IRO phobic cavity, and we introduce Fallon to stabilize theorization of the Pre-F.

Dr. El Sahly: Thank you. At least from my reading, at least some of it is similar across products. Okay. So the other question I have, and I want to see if there are additional hands from my community. No. The ADEM, acute demyelinating disease of the central nervous system, two cases in 15,800 persons exposed. This is a disease with incidence of .1 in 100,000, usually the majority being in children, and then a scatter in young adults. So two cases in elders within three to four weeks post vaccine is highly anomalous from a statistical standpoint. And again, so this is demyelinating disease of the central nervous system.

Then there's the GBS, acute demyelinating disease of the peripheral nervous system. Also within two weeks of vaccination incidents, usually one in a hundred thousand here is one in 15,000. So higher much higher than expected. So to what degree can we ignore the pre-marketing data in favor of post-marketing data? Because the studies were done for a reason, and these are high quality studies and the investigators worked hard to gather this information for us. And I just want to have a sense from you and other committee members or other FDA members to what degree – why should we not have confidence in this data and rely on post-marketing?

Dr. Geagan: I think that's an excellent question. From our standpoint I don't think we are, we're saying ignoring these cases is the correct methodology. We are still reviewing the details of the cases and requesting further information to further quantify the cases themselves. And as I had mentioned, we discussed with our pharmacovigilance team in coming up with a plan with the sponsor to make sure that we are assessing these. But I'm open to hear the committee's thoughts and recommendations on these cases as concerning events.

Dr. El Sahly: Thank you. Dr. Pergam.

Dr. Pergam: Yeah. I'm curious, as part of this detail and this might be a question for GSK, but I'm curious, since we have a lot of data over the last season going all way up to essentially now, we're a couple of months from the second portion of the study being done. Does GSK have any information if there have been additional GBS or ADEM cases that have been at least evaluated in the follow up study? I don't know if that's available to review I if they've been adjudicated or not, but it would be interesting for the committee to have additional information if that is available.

Dr. Webster: Hi, so this is Peggy Webster from GSK Safety. I do want to say that we do have that data available and we have reviewed it. We have no further cases of either GBS or ADEM in

any of our studies. So the one case of GBS, the two cases of ADEM I do want to highlight though that those two cases came from – of ADEM came from a single site, they were reported within two weeks of each other and very few details to actually confirm the diagnosis.

Now, we did propose that we are going to do enhanced post-marketing surveillance. We are still in discussion with the agency. We've not excluded any other options at this point.

Dr. Pergam: Thank you.

Dr. El Sahly: Dr. Berger.

Dr. Berger: I just wanted to make sure I was getting this right, at least on the ADEM itself. My understanding, I thought this was in trial 007, which was the co-ad admin group only as opposed to seeing any in 006, which was just the RSV vaccine versus placebo. Dr. Geagan, I see you shaking your head up and down, so I assume that is correct.

Dr. Geagan: That is correct, yes. And both in the co-administration group as well.

Dr. Berger: So I guess my question to the committee then, I guess this is more of a question in terms of like safety risk for co-ad administering with flu as opposed to the RSV on its own, and whether we're supposed to be thinking about it from this standpoint. We had this debate yesterday as well in terms of what is our role in thinking about things that are much more in line with what's the process for actually administration, versus the evaluating the safety and efficacy of this exact vaccine by itself?

So it's I guess it's a question as to how much we're supposed to be taking that into account when we're evaluating this here. I'm not trying to discount the safety signal here at all and the increased ratio that we're – the incidence rate that we're seeing for ADEM at all, nut I'm just trying to get a sense of like the way we're supposed to be thinking about it, because this seems to

be only with co-administration of flu. Or I guess maybe it's up to us to figure its answer. So is that still just – pass it back to the committee to think about?

Dr. Geagan: Yeah, so I think I would again kind of call on my pharmacovigilance colleague.

Dr. El Sahly: I see Dr. Meghna.

Dr. Alimchandani: Yeah, I had raised my hand.

Dr. Geagan: Thank you.

Dr. Alimchandani: Yeah so, I wanted to begin and respond to that comment about the background rates. It is very rare and yes, there are background rates with – sorry, having some technical issues – background rate with influenza vaccines, but it is still, extremely rare. So it's one in 125 to 250 thousand is the incidence rate, and 5% is associated with influenza. So still, extremely rare, but yes, it happened with co-administration, those two cases. Thanks.

Dr. El Sahly: Dr. Feikin.

Dr. Feikin: Yeah, I'm continuing with the ADEM theme here, and maybe this is for Dr. Webster. I did notice in your presentation that those two cases occurred in the South African site which makes me, wonder about HIV or other potential co-factors that might be at play here in addition to the co-administration with influenza vaccine. So I wonder if you have any more information that might help elucidate why these were seen in the South-African site.

Dr. Webster: Yeah. Peggy Webster with GSK Vaccine safety. Thank you for your question. We've tried to obtain more information from this particular investigator and unfortunately, despite all of the attempts that we've made, we have not received any further information.

Dr. El Sahly: Okay. I do not see any additional hands. I note in one of the slides presented that the neurologic pIMD between vaccine and placebo. They were slightly higher in the vaccine, but

it was presented at percentages. But what were they specifically, I wonder if after the break that particular breakdown can be shared on a slide if at all possible?

Dr. Geagan: Yes, I should be able to put that together.

Dr. El Sahly: Thank you so much.

Dr. Geagan: You're welcome.

Dr. El Sahly: Okay. Dear committee, thank you for all these engaging questions. Thank you to GSK. Thank you to Dr. Geagan from the FDA and we will take a break. It is 10:41. We are scheduled for a 40-minute break, so we will reconvene at 11:21 Central, or 12:21 Eastern. Thank you.

Point of Clarification from FDA & Sponsors

Dr. El Sahly: Welcome back dear committee members, sponsor representatives, and the FDA to the afternoon session of our meeting. This time slot is reserved for the Open Public Hearing. For today there are no registered speakers for the Open Public Hearing session, so we'll move to the next item on the agenda. The next item on the agenda is the discussion of the Q&A for the FDA and the sponsor. We will kick off this session with the FDA clarifying a couple of points, Dr. Kaslow.

Dr. Kaslow: Great. Yes, thank you Dr. El Sahly, we'd like to maybe touch on a couple of topics. I'm going to turn first to Dr. Geagan, who will provide the breakdown of the nervous system pIMDs, and when he's finished Dr. Turner will clarify what is meant by effectiveness. Thank you.

Dr. Geagan: Can you hear me okay? Let me share my screen. I was able to put together that table. All right, so here is the pIMDs for the system organ class nervous system disorders. I

broke it down subsequently into preferred terms which you'll see below. So overall in the RSVPF-3group, this is again of 15,303. So it included participants of the four phase 3 studies. There were nine participants that reported a pIMD that fit under the SOC nervous system disorders. Three participants reported an episode of Bell's Palsy, one participant reported an episode of facial paralysis. One participant of facial paresis. One participant reported the Guillain-Barre Syndrome, which we had spoken about at length, and one participant of polyneuropathy and malignant disease. And lastly, a participant reported a preferred term of dizziness, which did get categorized under this nervous system disorders, pIMD classification.

Dr. El Sahly: Dr. Cohn has a question?

Dr. Cohn: Yeah, I just have a quick question about the slide. It's, sorry I'm trying to get my video on. It's very helpful. Thank you. I was wondering if you had any sense of the timing of some of these like the Bell's Palsy and the facial paralysis. Do you know if they occurred within a certain, within 42 days of vaccination or after?

Dr. Geagan: Yes. So the, as far as timing of these cases, I don't have that level of detail available on hand. I don't know if the sponsor has any additional detail regarding the timing of these events – the nervous system events.

Dr. El Sahly: I see also that GSK has a comment or answer to some of these questions.

Dr. Webster: Yeah, we can – I can answer the question about the time to onset. For the events of Bell's Palsy, we have one event that occurred within 41 days, one event that occurred within 198 days. I'm sorry, I'm looking at the next slide.

Yeah, I can put my slide up so you can take a look at it. So this is this is just a listing of all of the related pIMDs that have occurred within participants that have reported more than one. Sorry,

not that participants have reported more than one. Let me clarify that, more than one participant for each of these events.

Dr. El Sahly: So that excludes facial paralysis, facial paresis, I guess looks like, I don't want to rush to conclusions, but they seem to fall in that category. And they fell in the pIMD table from the sponsor, but not in this table, right?

Dr. Webster: So let me just clarify that these are the events that are considered related to either the RSV vaccine or the placebo. If those other cases were not considered related, they won't show up in this listing.

Dr. El Sahly: Okay.

Dr. Rizkalla: Dr. El Sahly, I understand the FDA wants to make a comment, but we've also got some clarifying comments as well that we'd like to come back to from the previous conversation. But after the FDA have had the opportunity to comment, we'll come back.

Dr. El Sahly: Okay. Thank you. Dr. Kaslow or Dr. Toerner, I should say.

Dr. Toerner: Hi. Yes, good afternoon. This is Joe Toerner. I'm the acting Deputy Director in the Office of Vaccine Research and review at CBER, FDA. And there were a number of questions this morning about our choice of the word "effectiveness" in the question, and I just wanted to provide a little more context to why we used that word.

As you all know since 1962 FDA's been charged with making sure drugs and vaccines are safe and effective before use. And over the years, the statutory regulations have characterized what is what is the evidence, or what types of evidence can demonstrate that a product is effective, and FDA has issued guidance documents on in the past, but actually had been updated in 2019. There's a draft guidance document describing evidence of effectiveness for NDA and BLA applications. And so it's really in the context of, an adequate and well controlled trial of vaccine

efficacy that we're asking you to comment on evidence of. Is there substantial evidence of effectiveness here that's been demonstrated.

So don't get too distracted by the choice of that word. It's just a reflection of how our statutory guidelines are worded and the demonstration of an adequate and well controlled study is providing substantial evidence of effectiveness for a product. Just wanted to provide that clarification for you all. Thank you.

Dr. El Sahly: Thank you, Dr. Rizkalla, you had a question or a comment?

Dr. Rizkalla: Thank you, Dr. El Sahly. A couple of things that we wanted to come back to from the previous conversation with the FDA. There was a bit of discussion about severe LRTD and how that's been defined. So we want to provide that clarity for you.

This is really an important feature of the design of our study to capture severe LRTD in numerous ways to really bring that clinical perspective, but also looking at supplemental need for additional therapies in that second definition. What we would like to do is give you more context in definition one, that clinical spectrum and that clinical perspective and how that's broken down and how it informs severe LRTD disease.

And my colleague from clinical, Dr. Hulstrom will address that. And I'll come back with two further clarifications from the previous conversations as well. Dr. Hulstrom.

Dr. Hulstrom: Thank you. Hello, Veronica Hulstrom, clinical development lead for the RSV older adult program. As a reminder, we have 18 cases with – 18 severe LRTD cases, one in the RSV group vaccine group, and 17 in the placebo group. Out of these 18, 14 had at least two lower respiratory signs, and I believe that you particularly raised, the question about the severe by the investigator. We had four cases that were severe by the investigator. They had at least one lower respiratory sign as captured by the definition. However, these cases had all a medical

diagnosis consistent with severe disease, such as a pneumonia that was with an x-ray. We had a COPD exacerbation, we had oxygen supplementation, we had emergency room visits. So very importantly, all cases that were included in the analysis were externally adjudicated by an expert in, with a committee of expert – adjudication committee that were experts in infectious and respiratory disease.

Dr. El Sahly: Thank you that, that was not previously clear. So, thank you for clarifying.

Dr. Rizkalla: And maybe just for the second clarification, Dr. El Sahly I'd like to request Ann Falsey, if you are able to come on video. Just wanted to provide some context in terms of GBS in the context of GBS in an older adult population and provide some valuable context here, Ann?

Dr. Falsey: Yeah, thank you. We've had a lot of discussion about GBS, and the incidence is about one in a hundred thousand, but I think it's important to put it into context that older groups have higher rates of GBS it increases about 50% with each decade of life, and you can find a variety of studies that quote different rates. There was a recent article by Shu in neuroepidemiology in people over the age of 65. The rates were 8 to 12 per hundred thousand, other rates are 6. It just helps to interpret one event in the, this type of study with an enrollment of around 15,000.

Dr. El Sahly: Thank you Ann. So Dr. Kaslow, any other items from the FDA before we begin the Q&A?

Dr. Kaslow: Yes. I think we'd like to maybe come back to the question around non-inferiority in the influenza and Dr. Peterson, I think is online to be able to speak to that cross.

Dr. Peterson: Sorry, could you repeat the question? Sorry, can you hear me?

Dr. Kaslow: We can, yeah, we can hear you again. This is the question in terms of how the non-inferiority margins were set and the slight differences that we're seeing in the absolute values in that non-inferiority flu study.

Dr. Peterson: So you're asking like, how was the threshold determined? The 1.5 margin?

Dr. Kaslow: Yeah.

Dr. Peterson: Yeah, historically for non-inferiority, for other infectious deceives is like Covid and so forth, we typically use, 1.5 margin of non-inferiority. So I don't see an issue with using that same threshold here.

Dr. Kaslow: I guess the question goes back to Dr. Feikin as to whether or not you had specific questions that you wanted Dr. –

Dr. Peterson: Oh, specific questions? The, the non-inferior inferiority success criteria was met for, RSV, SVB, as well as four different strains of influenza. And you – I was able to verify the results using the STM dataset, so I don't have any further questions.

Dr. El Sahly: Dr. Feikin, does that clarify your question?

Dr. Feikin: It yes, it does. Partially, I understand that it didn't meet the non-inferiority criteria. I guess I was just trying to understand clinic – if there was any sort of clinical relevance to that 1.5 threshold because there was some difference between the co-administration and the separate administration groups in terms of these immune markers, but it was only in the, like the 20% difference range. And I was just trying to get a sense of whether that –

Dr. Warter: Hi, this is Clinical Team Lead, so the, even though numerically the titer was higher in the control group versus the co-ed group the statistical criteria also taken to consider what's clinically relevant. And even though there were numerical differences the non-inferiority criteria were still met and so we considered that variability clinically acceptable.

Dr. Feikin: Okay. Thank you.

Additional Q & A for FDA and Sponsor Presenters

Dr. El Sahly: I thank the sponsor and the FDA for clarifying some of these lingering questions from the morning. We will begin now the Q&A session. The Sponsor and the FDA team are here to help address these comments and questions. So I invite the committee members to use the raise your hand function and begin asking the questions. Dr. Pergam.

Dr. Pergam: I figured I'd start us off. I had a question for both the Sponsor and FDA. If there really wasn't any discussion about the use of Shingrix and the RSV vaccine together this can sometimes happen where patients go to get a vaccine and they're offered a secondary vaccine. Is there any decision from either the company or the FDA about separating those two vaccines because they don't both use the same adjuvant, one being higher than the other. Has there been any discussion from either about this being a, maybe a delay or a contraindication to be used together?

Dr. El Sahly: Go ahead, GSK.

Dr. Rizkalla: So, no coadministration studies have been performed to assess the coadministration of the Shingrix vaccine with the RSV vaccine. This is a planned study, we do have some evidence that is looking at sequential administration of Shingrix with another ASO 1E investigational vaccine that was being developed for COPD. We can give you some context there, but this is a plan study looking at Shingrix with RSV in future development.

Dr. El Sahly: Okay. Dr. Alimchandani.

Dr. Alimchandani: Hi. Thanks. I think this is a good segue into another point that we wanted to bring up for the committee to consider. So Shingrix, as was just mentioned, has the same

adjuvant as the SO1 adjuvant vaccine. Now, we just wanted to point out that there was a warning for GBS that was added to the Shingrix label. This was a safety label change, and this was based on data from a study using claims data. So, I just wanted to point that out and there are all the detailed information is in the label for the Shingrix. Thanks.

Dr. El Sahly: Thank you. I don't see questions, but I urge the committee to start raising their hands. Dr. Feikin.

Dr. Feikin: Yeah, I wanted to come back to the severe disease definition and thank you for some of the clarification. So, it sounds like for definition one among the 18 that met the case definition, four of them had at least two lower respiratory tract signs, and four were physician diagnosed, and we know that among those two of them were hospitalized.

And you had mentioned that there was a pneumonia and a COPD exacerbation. I'm just wondering if you could unpack this a little more because honestly, just having two lower respiratory signs, such as cough and sputum don't really constitute severe to me. So, I'm just wondering, in addition to the two hospitalizations, do those include the pneumonia and the COPD? How many others besides those two would have some other objective measure of severity besides just having the two signs.

Dr. Rizkalla: Thank you for your question. Dr. Feikin, my colleague from clinical will address that question, Dr. Hulstrom.

Dr. Hulstrom: Thank you. I just wanted to clarify out of the 18 cases that we had, all had – 14 of those had at least two lower respiratory signs. Four were severe by the investigator. And just to give you a little bit more details of the choice of the two different case definitions of severity in the absence of universal definition for severe for LACD or severe. We really wanted to have more granular view on the severity experienced by the participant, but also expressed the burden

on the healthcare system by use of proactive and supportive therapy, we believe that the severity disease should be assessed considering both the number and sign, as you say – number of signs or symptoms, but also importantly the medical diagnosis.

Therefore, we implied two different case definition. We had discussed those with clinicians including geriatricians. So the case definition one was taking into account the clinical severity, where we considered lower respiratory signs, not symptoms, given that the signs identified at a visit on site or confirmed severe biomedically trained professional.

The case definition two, we discussed that was the definition with need of supportive therapy. I don't know if that addresses your question. Then you had a second question, you wanted a little bit more granularity on the 18 cases in total, correct?

Out of the – basically looking into, in addition to the breakdown that I gave you before of the 14 and the 4, when we looked in the totality of data and we looked into on average, the participants, that experience actually, they experience more than – at least they, let me rephrase that. On average, they experienced 10 respiratory signs of symptoms. It was ranging between 6 and 17. The duration of an LRTD episode for the placebo group was an average 25 days. We only had one case for the severe for the placebo. Four of those needed oxygen supplementation as was mentioned before, two were hospitalized.

That was the pneumonia and the COPD exacerbation. And importantly among those 18 cases, on top of the medically attended arrive visit on site, we had 67 additional medical visits to a GP or a specialist. 22 of those 18 were actually visiting the emergency room and 11% were hospitalized. So as a physician, I consider these as being representative of severe disease, and that's why we had framed it as such as well as in the case.

Dr. Feikin: Okay. Did you did you look at all cause respiratory hospitalizations?

Dr. Hulstrom: Yes, we did we collected all cause hospitalizations, including respiratory – for respiratory reasons.

Dr. Feikin: And in addition to the two, were there more respiratory hospitalizations? The two that we know are RSV confirmed, were there others?

Dr. Hulstrom: So we, what we saw is a balanced number hospitalization due to any respiratory disease amongst those two groups, approximately 110 in each group. Thank you,

Dr. El Sahly: Dr. Bernstein.

Dr. Bernstein: Thank you. I just had a curiosity question. The RSV pre F3 antigen is derived from the RSV fusion F surface glycoprotein of an RSV-A strain, and I noticed that the LRTD efficacy was actually higher for the RSV-A than it was for RSV-B. Is that surprising or coincidental? Is there cross protection or assumed cross protection between A and B?

Dr. Rizkalla: Yeah, thank you for your question. We would say that this is consistent efficacy across both RSV-A and B. Just to put into context, two thirds of the cases that were associated with an LRTD were associated with an RSV-B, so we've got more confidence against RSV-B in terms of the point estimate, but there is consistency of the point estimate with overlapping these confidence intervals. So we can be quite confident in the efficacy across both RSV-A and RSV-B.

Dr. Bernstein: Thank you.

Dr. El Sahly: I have a question pertaining to a the second ADEM case. So either the sponsor or the, or Dr. Geagan, whomever can answer.

So did that second patient receive immunosuppressants after presenting with neurologic deficits?

Dr. Webster: This is Peggy Webster with GSK Safety. Yes. That participant was treated with Prednisone.

Dr. El Sahly: Thank you so much.

Dr. Webster: You're welcome.

Dr. El Sahly: Dr. Perlman.

Dr. Perlman: Yes. So I just had a question about the implications of the demyelinating diseases, and so does this, are you in – I don't know if this is a Sponsor or the FDA, but are diseases like multiple sclerosis, going to be a contraindication for getting the vaccine?

Dr. Geagan: I'll open this up to our pharmacovigilance provider, Dr. Chen, if he has any additional comments on this.

Dr. Alimchandani: I don't think we have discussed contraindications at this point. Does GSK have any comments with the demyelinating diseases as contraindications?

Dr. Webster: Hi, Peggy Webster with GSK safety. I – that's a discussion that we would have to have with the Agency.

Dr. El Sahly: Dr. Geagan, if I can ask one more time awaiting my colleagues to raise hands. To pull that table again. I know it was on and then it went off. I just want to wrap my head around some of what was displayed.

Dr. Geagan: Just a second – if I can share that specific table. Should be seeing the slide now.

Dr. El Sahly: Yes. Thank you.

Dr. Geagan: And I think as a reminder cause I think there may have been a little bit of confusion. This is all, this is the aggregated safety data. So I think that's why when we were looking at the slide from GSK, it did not demonstrate all of these cases. Because these cases are the ones that occurred in all the pooled phase three studies, not just study 006.

Dr. El Sahly: Oh, okay. Oh, so that includes the coadmin study, right?

Dr. Geagan: Correct.

Dr. El Sahly: Okay. I don't see the A here.

Dr. Geagan: Sorry. This does not include 07. This is 06004 and 9. My apologies.

Dr. El Sahly: All right. And I take it, but in, in the placebo group, so these are the exposed in the placebo, how many Bells' Palsy facial paralysis, facial paresthesia, did we see for neuropathy. If you need time to pull those data that I understand it's –

Dr. Geagan: Yeah, I'll need a minute just to pull that, but I should be able to have it before the end of the Q&A.

Dr. El Sahly: Thank you, Dr. Cohn.

Dr. Cohn: Thanks. I have another question about the GBS case. Can you tell us if this case was a vaccinated individual from the United States, and then is there variability globally in the incidents and recognition of – or the incidents of GBS?

Dr. Webster: So this is Peggy Webster with GSK Vaccines. The participant who had the diagnosis of GBS came from Japan where there is a higher incidence of GBS.

Dr. El Sahly: Thank you, Dr. Portnoy.

Dr. Portnoy: Great, thank you. I guess I've been quiet this afternoon. My question involves cell mediated immunity because you did measure it and showed that there was cell mediated immunity post vaccine. I was wondering if there was some – did you compare that to cell mediated immunity that would occur after like wild type RSV infection?

And did your vaccine produce a greater CMI response than a, just an infection with RSV itself.

And did you notice a correlation between that and the effectiveness of the vaccine? Did the patients who broke through, for example, perhaps have a lower response T cell mediated immunity?

Dr. Rizkalla: Thank you so much for your question, Dr. Portnoy from GSK. So to answer your question, in our efficacy study, we did not have cell mediated immunity captured. It was only humeral response and neutralizing A and B was assessed in a subset of participants. So we don't have a perspective of CMI in the placebo group to be able to inform your question.

It was just not a feature of the design of that study. It's an interesting question, but as we've heard yesterday from Dr. Havers and other colleagues from the CDC natural immunity is very short lasting, and reinfection is often a consequence in older adults. So, we don't have a perspective to inform that.

In terms of – I think we're getting to we, we've got very few breakthrough cases, so we've only got seven breakthrough cases. So, to really be able to inform of any meaningful correlate that's not possible. High efficacy is the goal of vaccination and protection of older adults is the goal, which we've been able to demonstrate.

Dr. Portnoy: But did those seven breakthrough cases have any distinguishing characteristics that might have suggested that they would break through them?

Dr. Rizkalla: Not as yet. We haven't really analyzed that because we remain blinded. It's an ongoing study and immunogenicity analysis will be forthcoming.

Dr. Portnoy: Thank you.

Dr. El Sahly: Thank you. Thanks Dr. Hildreth.

Dr. Hildreth: Thank you Dr. El Sahly, I have a question for our colleagues at GSK and a follow up to Dr. Bernstein's question.

I'd like to know whether or not the breakthrough cases, as you call them, were they'd characterized to be A or B. If it turns out that they're all B, and you used A as your fusion protein

vaccine, that might indicate we have a problem on our hands. So did you characterize the viruses that caused the breakthrough infections and the patients who had them by any chance?

Dr. Rizkalla: Yeah. I'll invite my colleague, Dr. Warter to address that question. Thank you for the question.

Dr. Warter: Good afternoon, Lucile Warter, lead for the project. So indeed we sequence the virus is isolated from various, we confirmed cases confirming the PCR results, that was distinguishing the subtype. We confirmed that both RSV-A and RSV-B circulated during the season one. And so at the moment, no, we are not concerned.

Dr. Rizkalla: And just to answer your question, maybe Dr. Hildred, if I may, so you asked specifically the seven breakthrough cases, what were they associated with? So I'll answer that question. I'm just referring to my notes. So we had five cases associated with RSV-B and two cases associated with RSV A. But you need to put into context two thirds of the LRTD cases were associated with RSV B, so by proportion there is no difference.

Dr. Hildreth: Thank you so much.

Dr. El Sahly: Thank you. Thank you Dr. Feikin.

Dr. Feikin: Yeah, I wanted to follow up on the cellular immunity question related to the inclusion of the adjuvant. Obviously, you have a lot of experience with the ASO 1 adjuvants. You didn't have time to talk about it, but in the briefing document it was shown that there was an improvement in the CD4 response with the adjuvant, but there was no difference in neutralization.

So, I wanted to ask you clinically, what would you expect that the adjuvant would enhance in terms of a clinical response? Is it – do you feel that's reflected in the efficacy numbers you saw, or would it be in duration in the second and third season or against severity?

And obviously the reason I asked that is because, as expected that the adjuvant does hurt. And so clearly, you've weighed the pros and cons and decided that it's worth including the adjuvant. So maybe you could help us understand what you might expect from the addition of the adjuvant.

Dr. Rizkalla: Maybe I'll address that last part of your statement, Dr. Feikin, and just to put into perspective, the local reactions following vaccination are very mild to moderate. They generally subside between one to two days. Now the question of the adjuvant is an important one, and I think we need to put this into the context of this diverse, older adult population.

This is a population with varying levels of immunosenescence. This is a population with underlying comorbidity that makes them at increased risk. There's frailty, it's multidimensional. So the importance of the adjuvanted vaccine can be displayed by the consistency of the immune response regardless of all of these factors, we're able to restore the T-cell levels consistently by age, by frailty, by comorbidity, and the response also matches consistently across this population. So, to answer your question, efficacy, that is high and consistent in this diverse population is the value of the adjuvant.

Dr. Feikin: Thank you.

Dr. El Sahly: Thank you both. Any additional questions from our committee members?

Dr. Geagan: Dr. El Sahly, I was able to pull that information regarding the nervous system pIMDs for the placebo group from study 006. So there were three cases in the placebo group compared to the RSV Pre-F3 group. These three cases were optic neuritis, trigeminal neuralgia, and a cerebral vascular accident.

Dr. El Sahly: Oh, okay. Thank you. I do not see additional questions or hands, Dr. Pergam.

Dr. Pergam: Yeah, sorry. I had one additional question just about the specific complications that seem to be rather consistent between the two vaccines that have been reviewed. And I'm

curious from the Sponsor, if they're planning on doing any additional work to understand how this F protein might related to neurologic complications or to some of the cardiac complications that are being described. It's an interesting phenomenon and I'm curious if there additional work that they're doing to see if there are receptors in those areas or other complications that might be associated. Certainly these are signals and not definitive, but I'm curious if you're looking into some of the basic biology of why this might be the case.

Dr. Rizkalla: Yeah, if I may, thank you so much for your comments. This is something that we will continue to investigate and look very closely at, we don't have a comment at this time.

Dr. El Sahly: Dr. Holly Janes.

Dr. Janes: I wanted to ask for some additional reflection on the ADEM cases that, that if I've got it right, occurred only in the co-administration arm of that study and were not observed to occur with single administration of the RSV vaccine and the other studies. Was there anything different about the collection and solicitation of safety events across those two studies that ought to inform our interpretation of the occurrence of that event in one study, but not the other?

Dr. Webster: Peggy Webster with GSK vaccines, I think one of the better pieces of information that can come that will help us inform these cases. We are doing additional co-administration studies where we are looking at co-administration with high dose flu, with adjuvanted flu and with other vaccines. And we've not seen any cases of GBS or ADEM in any of those other studies.

Dr. El Sahly: Dr. Griffin.

Dr. Griffin: Yes. Just wanted to ask about – it seemed very unusual to have these two cases of ADEM at one site, but. It was a much smaller study, so I'm wondering how many sites were actually involved in that study.

Dr. Webster: So let me just add a little bit of context. Sorry, Peggy Webster with GSK vaccines at this particular site they enrolled 150 participants, so that would be 75, that would've been in the co-administration arm. I'll ask my colleague, Dr. Hulstrom, to address your second question about how many sites in total for that study.

Dr. Hulstrom: Thank you. You saw in the presentation we had 17 countries. Just to answer your specific question, we had 264 sites across those 17 countries. [multiple speakers] Oh seven – I can get back with that information to you. Just give me two minutes.

Dr. Griffin: Okay, and at the risk of beating a dead horse bout the facial paralysis and GBS. I was a little interested in the facial paralysis, facial paresis and Bell's Palsy, which would add up to five cases of potential Bell's Palsy.

And given what we've seen with some of the Covid vaccines and signals there, I think it would be beneficial to have a – to look at the timing, to have that information on the timing and to investigate whether those other two cases were also Bell's Palsy.

Dr. Webster: Yes, Peggy Webster, GSK Vaccines, I don't have that specific information together on a slide for you, but again, like Dr. Hulstrom, if you give me two minutes, I think we can pull that together.

Dr. Griffin: Great. Thank you

Dr. El Sahly: Dr. Kim.

Dr. Kim: Thank you. We've been talking a lot about rare events and population groups that are put fairly small. For example, people with immunocompromising conditions in the grand scheme of the protocol for this study as well as the study from yesterday. And I pose this question to the FDA specifically perhaps Dr. Turner or Dr. Kaslow. The, basically both the GSK and Pfizer, our Pfizer colleagues have indicated that the study didn't – was not powered enough

to identify certain questions that we have been asking. Yesterday we heard that the study was empowered enough to assess the impact of the – for older population people who are 80 or older or people who are hospitalized. And today we are hearing that those with comorbid conditions not be – their vaccine effectiveness could not be assessed because of the power of this study. But however, we did – the two studies from yesterday and today they were large studies, obviously, but there – the case definition the time of study period and other methodologies.

I think there's a lot of similarities between these between these studies. So what if we are to do a beta analysis? Meaning this would be right up right up FDA's alley – beta analysis of the two studies that were presented yesterday and today to see if we can get a better sense of what syndrome or any other safety issues that have come up can be assessed perhaps with a larger base number and a – as well as the impact that the of the investing effectiveness of the subpopulations or specific other situations. And I say that because we have two studies now that – but we also know that there are other RSV vaccines coming down the pipeline. And I suspect the timing and case definition and things like that will not be all that different. With some tweaks understanding the caveats, perhaps with these two studies and perhaps down the line, that we might have a beta-analysis that might inform us of some additional thing – a additional questions that we have been asking.

Dr. Rizkalla: So, I'll let the FDA respond, but just one clarification Dr. Kim, about the population in the study. 38% were considered pre-frail in our study, and 39% were considered as having comorbidities of interest, which we know increased the risk of severe complications associated with RSV infection.

In terms of the frail population and the 80 plus, this study was done in the context of an ongoing pandemic and site access to long-term care facilities, aged care facilities was

compromised in that setting. So this was a challenge and a consequence of the pandemic and the environment in which we operated to conduct this study.

But we have a very representative population that reflects the US census population, and we are quite sure of the profile of the vaccine and the benefit that this potentially can have for the US public health.

Dr. Toerner: Yeah. Hi, this is Joe Toerner acting deputy director OVRR CBER FDA, Dr. Kim thanks for that question, our obligation is to review each BLA application independently. We would not be in a position to review these applications together, and it will be up to academicians to perhaps consider conducting meta-analysis based upon aggregates of data submitted for publication for example. But at FDA, we're considering these two applications independently. Thank you.

Dr. Kim: I – to be sure I wasn't suggesting that any of what I said would be considered for the application for BLA concerns of the day.

Dr. El Sahly: Dr. Berger.

Dr. Berger: Thanks, I appreciate the additional information on the GBS case, and I wanted to dive into it a little bit more to make sure I fully understood the potential ramifications from this. It's helpful to know that this occurred in a patient from Japan, but that also raised the question of how many patients in the study were actually from Japan?

And the second part of that then is, what is the increased incidence rate in Japan for GBS? I think I just want to make sure I'm not comparing this to what we're used to thinking about from a generalized standpoint, one to two across the board. If we're talking here – we're looking at 1 in 15,000, patients overall, but if it's actually only 500 patients in Japan, that is a significant difference.

But also, based on the incidence rate there, maybe not. So, I'd like some additional information as to how many patients actually were participating from Japan and what is the incidence rate. And if it, if you know that from an age standardized or age adjusted risk, that would be really helpful.

Dr. Webster: Thank you for that. Peggy Webster with GSK Vaccines, we're getting quite a number of slides here that we're going to have to give us five minutes to pull together, but we will come back to you with all of that information. Thank you.

Dr. Rizkalla: And maybe Dr. El Sahly, there was a question before about the sites. I'll get my clinical colleague, Dr. Hulstrom to respond the number of sites that were involved and the countries that were involved in the flu coadministration study.

Dr. El Sahly: Sure.

Dr. Hulstrum: Hello, Veronica Hulstrom, so we had three countries in study of seven, 14 sites and two sites were in South African.

Dr. El Sahly: Thank you. Does that answer your question, Holly?

Dr. Janes: That was my question. Thank you. Yes.

Dr. El Sahly: Great. Dr. Cohn.

Dr. Cohn: Thank you. I was wondering if FDA could speak a little bit more about the excess cases that require, or that led to FDA adding the Shingrix warning label. I think it was three per to six excess cases per million, but can you talk a little bit more about whether or not that has persisted since that study occurred?

And any more information about the ages or anything about – related to that, of those cases?

Dr. Geagan: Thank you for the question. Yes, I was going to offer Meghna to respond.

Dr. Alimchandani: Thanks, hi, this is Meghna, So now thank you for this question. So again it's the same adjuvant as Shingrix a as an RXV. So the Shingrix study – the association between vaccination with Shingrix and GBS was evaluated among Medicare beneficiaries, And the primary analysis, which was all doses, found an increased risk of GBS during the 42 days following vaccination with three excess cases per million, which is I think what you said, Dr. Cohn.

And there was a secondary analysis that looked at dose by dose and there was an increased risk of GBS in the 42 days following the first dose of Shingrix with an estimated six excess cases per million doses, and no increased risk of GBS was observed following the second dose of Shingrix. So I hope that helps.

Dr. Cohn: That's very helpful. Thank you.

Dr. Webster: This is Peggy Webster from GSK Vaccines. If I could just add a little bit of context to this as well. The study did not take into account a confounding factor, which is that participants who, after they have a shingles episode, are likely to get a Shingrix vaccine. And we've done a subsequent analysis to account for that confounding factor, and it reduces the estimated excess risk to about two cases per million doses.

And I also want to clarify that for Shingrix GBS was added to the label as a precaution and not a warning. Thank you.

Dr. El Sahly: Thank you all for these clarifications.

I have a question pertaining to the rashes from table 10.8 in the briefing document. The vaccinees were more likely to get rash. Some of it was due to injection site redness because it wasn't captured for everyone as a reactogenicity. But is that – is that all what we're talking about because I understood it to be more like generalized rash?

Dr. Webster: No, the, those cases were rash at the injection site, not generalized rashes.

Dr. El Sahly: Okay. That's stable. 10.8 in the briefing document?

Dr. Webster: I don't see it there. Let me pull up a slide, oh, I have a slide here. So of those cases of hypersensitivity that were identified, when we did the specific searches in our safety database, we found 11 cases of injection site rash and five – sorry, 11 in the RSV vaccine group, 5 in the placebo.

Dr. El Sahly: Okay. So, it's mostly injection site?

Dr. Webster: It is mostly injection site. There were some cases of rash reported in there as well. but the overall incidence is relatively balanced.

Dr. El Sahly: Okay. I don't see any additional questions. Any final words or comments from the FDA before we move to the next agenda item?

Dr. Alimchandani: I just had one clarifying comment if that's okay?

Dr. El Sahly: Absolutely.

Dr. Alimchandani: It's just for Shingrix and GBS, it's in the warnings, and for questions section, it was a required safety labeling change that FDA did. I think there was a comment that it's a precaution and not a warning, but we consider – it's in the warnings and precaution section of the label. Thanks.

Dr. El Sahly: Dr. Cohn.

Dr. Cohn: I just have one more clarifying question. Is there any language related to persons with a previous history of GBS in that label or in other labels that have had a slight increase in risk but not necessarily associated with individuals who have had previous disease?

Dr. Alimchandani: I am not sure, Dr. Cohn, I'm going to look it up a little bit and get back to you. There is an increased risk with the private history of GBS, but I am not sure if it's in the label.

Dr. El Sahly: Dr. Pergam.

Dr. Pergam: Yeah, thanks. Dr. El Sahly, I sort – this is maybe an impossible question to answer, but I thought I would ask it anyways. I do know that the Shingrix vaccine can co-administered with flu vaccine. And I was curious, is there been any reports that either GSK or FDA is aware of ADEM cases happening in co-administration with Shingrix and flu vaccine that have been reported in the pharmacovigilance and post licensure studies?

Dr. Webster: Yes. So, Peggy Webster with GSK Vaccines. With Shingrix, we have seen among the 80 million doses that have been distributed since its launch in 2017, we have six reports in our safety database for ADEM.

Dr. Pergam: Thank you Peggy.

Dr. El Sahly: Okay. Going once, going twice. Before we move to the next session. Dr. Alimchandani?

Dr. Alimchandani: Yeah, I just wanted to respond to the question from Dr. Cohn that we do not have any language in the Shingrix label about the risk of GBS, in somebody who has previously had GBS. Thank you.

Dr. El Sahly: Dr. Kaslow.

Dr. Kaslow: Yep. Great. I was just going to say, I think we are ready to move on to the next session where the committee has discussion and voting. Thank you.

Dr. El Sahly: Dr. Paydar, do you want to get us into the next session? The next session on our agenda will be discussion and voting on the two questions as delineated earlier this morning. We

will try to dedicate half the time to the safety and half the time to the efficacy questions to allow, robust discussion around these two issues.

And I invite everyone to gather their thoughts as Dr. Paydar now pulls the question number.

Dr. Paydar: Derek, if you don't mind, put up the voting question number one. We have a little bit of discussion on this one. This is where Dr. El Sahly is talking about – we discussed this a little bit before we go into the voting.

Dr. El Sahly: Okay. Dr. Paydar, so I read, and we begin now?

Dr. Paydar: Yeah, actually I take this back for just a second. Why don't I read my script and then I'll have you read the questions for –

Dr. El Sahly: Yes. I knew there were the scripts on this.

Dr. Paydar: Yes, yes, there is always the script. Okay, only our non-regular members and three temporary voting members. A total of 12 will be voting in today's meeting. With regards to the voting process, Dr. El Sahly will read the voting question for the record and afterwards all regular voting members and temporary voting members will cast your vote by selecting one of the voting options, which include yes, no, or abstain.

You'll have one minute to cast your vote after the question is read. Please note that once you have cast your vote, you may change your vote within the one-minute frame. However, once the poll has closed, all votes will be considered final. Once all the votes have been placed, we'll broadcast the result and read the individual votes allowed for the public record.

Does anyone have any questions related to the voting process before we begin? If not, Dr. El Sahly please go ahead and read the voting question number one for the record.

Dr. El Sahly: Voting question number one, are the available data adequate to support the safety of AREXVY (RXVpreF3+ASO1e) when administered to individual 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV?

So the way the flow is going to be, just like yesterday, I will invite the committee members to raise their hands, but if they don't, everyone will get an opportunity to weigh in on this question – their viewpoints. We will vote, and after that, everyone will explain briefly their vote. And Dr. Berger volunteered to begin.

Dr. Berger: I actually, I'm wondering if GSK is going to be able to provide the information related to the number of individuals who are participating from Japan in the study prior to voting, at least on the safety question.

Dr. El Sahly: Are they – Dr. Paydar are they in the room still?

Dr. Webster: Yeah, this is Peggy Webster. We're still here. I'd like to invite my colleague, Dr. Pircon to address the background rate of GBS in Japan.

Dr. Pircon: Hello. Good afternoon I am Jean Pircon, Epidemiologist for GSK. So we – there is a global and national burden of Guillain-Barre syndrome in Rome that has been studied and we could see in this paper that in Japan it was one of the highest prevalence rate that was reported. So, this was a literary review that was done with data from 1990 to 2019.

Dr. El Sahly: What was the rate?

Dr. Pircon: Yes. So, the prevalence rate was four per 100,000, and also increasing by age with a factor of 20% every 10 years of age.

Dr. Rizkalla: And there was another question, Dr. Berger, about the number of participants recruited from Japan. We've got that response for you as well. Just give us one moment, Dr. Hulstrom will address your question.

Dr. Berger: Thank you. And that's the Bergazi paper from Journal of Neuro Inflammation that you're quoting.

Dr. Hulstrom: So let me give you the number while Dr. Pisano is coming up. The answer was yes. So now to the numbers of participants that were vaccinated in Japan, we had two studies that included participants in Japan over four included 150 participants, and over six included 1043 vaccinated.

Dr. Berger: Thank you.

Voting Question #1 Discussion

Dr. El Sahly: We will now begin the discussion session where everyone gets to weigh in on question number one. And I think just because Dr. Berger had his question last, his name appears first. So it's to you, Dr. Berger.

Dr. Berger: I should have just got my video and mute undone it would've been faster. Thank you for starting here, I definitely appreciate all the information that's been provided. Certainly, this was a 25,000-patient study and the safety part of that looked at 15,800 individuals.

I do have some concern around the incidents of GBS including – based on the numbers that you just presented here. That Bergazi paper, I think puts it out with an age adjusted or age standardized rate of 6.4 per hundred thousand. And clearly, we're looking at 1200 patients and seeing one in there. So it seems to be above even the rate within Japan.

I do think that there's going to be a lot that's going to have to rely on the post-marketing surveillance, just like we heard yesterday. I'm going to come back to that concept here. I don't think this is something that's probably going to be answerable, in, in additional clinical trials or

additional information that's going to come out necessarily here, so I do think a lot of this is going to rely there.

On the age, I do I do share the concern there, but I think this is really an administration issue as opposed to, or it seems to be an administration, a co-administration issue as opposed to individually with the RSV vaccine. So that gives me a little bit more willingness to go down the safety route for this.

Again, I think we are – I do want to say, I suggest heavier reliance on the post-marketing surveillance, and not only just reliance, but like making sure that there's an enforcement around the requirement for actually conducting these. So at the moment, I think the profiles seem to be within the acceptable range, and I'm probably going to vote yes. Thank you.

Dr. El Sahly: Thanks, Dr. Berger. Dr. Griffin?

Dr. Griffin: Yeah. Okay. Sorry. Yeah, I'm, I have to note that in Japan, Guillain-Barre Syndrome is still very rare, and that FDA does consider this related to the vaccine. So I think we don't know how common it is, but it's – I remain very concerned about GBS, and I do feel confident that post-marketing surveillance could pick it up, but I think it could be very bad for the adult vaccine program.

I think these cases were very notable. The one woman spent six months in the hospital these are very devastating events. The ADEM, I don't know I think I would feel more confident if we had more data on co-administration. I'm not sure what's going on, but I just don't see why the rush for getting this vaccine approved now.

Dr. El Sahly: Thank you, Dr. Griffin. Oh, I'm sorry, did you have one more comment to say?

Dr. Griffin: No, I just noticed I never got my video started.

Dr. El Sahly: It’s okay. Thank you, Dr. Griffin. Dr. Cohn.

Dr. Cohn: Thank you. I would vote yes to this question similarly to yesterday. I'm also extremely worried about the GBS. I do appreciate that the population that was, the data – the demographics of the population today were much more – there were many more comorbidities and I feel like the Sponsor did a really nice job of trying to have a representative population and that can also maybe more real in terms of what we may see when a vaccine program is implemented.

It's hard to say, I worry about these adverse events too, in the context of our adult immunization program. And I'm very worried, frankly, about these vaccines being used this year in particular, because I do think that we still have a lot going on with Covid vaccines and sorting through potential cases, GBS this fall will be very complicated.

But that being said, I do feel like this study meets the – I feel like this study gives me the data to be as confident as I was yesterday, for example about the safety of this vaccine.

Dr. El Sahly: Thank you, Dr. Cohn. Dr. Pergam.

Dr. Pergam: Yeah, I would just echo comments made by my prior committee members. I feel very similar to how I felt yesterday. I think the cases of GBS are concerning for vaccine, the vaccine platforms in general as but we're talking about a single case, which it doesn't feel like a lot to the public but can be reflective and so we need to be cautious about that.

But I think the GSK has demonstrated in the past a pharmacovigilance program has looked at this pretty carefully with the Shingrix vaccine and has made label changes in the past. So, I think there's a good precedent set that this is – this will be well tracked in this particular vaccine.

The ADEM, I'm less convinced. It's a strange situation where it's one singular site within a two-week period to have two ADEM cases, which seems almost statistically impossible. And so it's a – it's an odd cluster that I don't quite understand. The fact that there's been six cases with all of

the adjuvant prior in the data from Shingrix, which uses a higher dose of the adjuvant, does suggest that that's about the range you would expect in normal rates within the public. So I'm not totally convinced of the ADEM, but I think it'll just be important to continue to monitor neurologic side effects in general with these vaccines.

I would just say I find it fascinating that both of these vaccines, and I'll reiterate what I said earlier, both have neurologic and cardiac manifestations with atrial fibrillation, and so it does suggest maybe a mechanism that needs to be further evaluated because I don't typically think of neurologic complications with RSV, nor do I usually associate cardiovascular complications with RSV. So there must be something about this fusion protein that's mimicking something in these areas that these are truly related. So, I'd be really curious to, to know how this is going to be pursued in the future. But I feel comfortable voting yes.

Dr. El Sahly: Dr. Feikin, if I may clarify first. This is asking your viewpoint or comments on the question, not necessarily how you will vote. That is something you will I guess perform after the discussion. And then explaining the vote, of course, by then we would have known how everyone voted when Dr. Paydar reads the list.

But the purpose of this part of the program is just to understand where everyone is, what everyone's thoughts are, and give everyone an opportunity to weigh in on the question. So, with that Dr. Feikin I think is next.

Dr. Feikin: Yeah, I agree with what Dr. Pergam just said. I think it's hard. I think our charge is to look at this vaccine and the data that we were presented with individually. That's the way that FDA will evaluate the BLA. So, I think we need to try and, in some ways, to put aside what we heard yesterday. I think our discussion about GBS might be different if we hadn't heard yesterday's presentation because it would've been one case. I don't – I'd like to get Dr. Jane's

opinion on this. I don't think it's actually right to draw your circle around the Japanese participants to get a rate. I think that's a little bit of the cancer cluster fallacy is that you draw your circle around where you find your case. I think we need to look at that in the context of the total population. And I also I can't quite figure out the ADEM signal. I think it is odd that it's from one site out of all the sites in one study. So I have questions about, about that one. I'm not, it's not fitting together with the others for me. Thank you.

Dr. El Sahly: Thank you Dr. Feikin. Dr. Kim.

Dr. Kim: I think everything that we've been talking today, I like what Dr. Feikin just said stems from – regarding GBS, actually stems from the discussion we had yesterday. But that aside I think in addition to the GBS concern the GSK vaccine actually, we haven't discussed this much, but atrial fibrillation, a-fib is not something – is something that that GSK identified and that they deemed worthy of continued follow up.

And I think no matter what we discussed today regarding a-fib, we're only going to need more information on that with post-marketing surveillance. And so GBS, a-fib, anaphylaxis and whatnot. I think we'll rely on post-marketing surveillance to give – to keep us in informed. But on the – what Dr. Cohn mentioned earlier about the complexity in implementing something this fall. Of course, there's a lot of things going on and it seems things don't get any easier even if you get over one hurdle because something will always show up for the next challenge. But I think I think I'd like to say that despite the challenges, despite the additional hurdles our obligation is to do what's right for the public. And in this case, we have a bad disease. We have a good vaccine, so far anyway, given clinical trials, that it's a safe vaccine and that it could be – and that the vaccine could be used to prevent disease. Yeah, given that, I think that that sways how I would vote for – on the safety as well as effectiveness for this vaccine. Thank you.

Dr. El Sahly: Thank you, Dr. Kim. Dr. Bernstein.

Dr. Bernstein: Thank you. I agree with my colleagues' sentiments around this vaccine. Personally, I feel more comfortable with the organized, thorough and detailed amount of data presented today.

Today's Sponsor, I thought did an impressive job in addressing the unmet needs of the vulnerable populations and included co-administration. Again, it's not like yesterday, it's not clear to me whether or not there's a true safety signal, especially around inflammatory neuropathies and atrial fibrillation. So I do think post-marketing surveillance will be most helpful in monitoring these possible safety signals.

And I also agree with Dr. Cohn. There's no reason to – we've been working on a RSV vaccine for decades. I don't know that there's a rush to get this to market if we're going to take two steps forward and three steps back as far as public health and optimizing vaccination rates.

Dr. El Sahly: Thank you, Dr. Bernstein. Dr. Janes.

Dr. Janes: Thanks, I think I don't have much to add to the comments that have been raised around, the signals that have been seen here but the necessity for post-marketing surveillance to rally help us understand if these are real or statistical artifacts.

In response to the question that Dr. Feikin raised about how do we even estimate the rate of these safety events in this population? I would agree with him that it is very challenging to figure out what is the denominator, what is the exposed population that we're talking about here? And per the design, I would argue that the exposed population is all vaccine recipients in the trial.

It is potentially misleading to begin to narrow that denominator to – based on the characteristics of the participants that were observed to have adverse events. And so really, I think it

necessitates a larger study to definitively establish if this actually is an increased risk associated with this vaccine or not.

But I find it hard to disentangle the safety and efficacy, as others have said in yesterday's discussion, it's really about benefit risk. And to me, I was really swayed and assured by the data that was presented here for this vaccine in terms of high efficacy against severe disease outcomes associated with RSV infection and estimated 94% reduction in the incidence of those outcomes, which to me, is a strong argument against a potential increased risk of these other adverse effects associated with the vaccine.

Dr. El Sahly: Thank you, Dr. James, Dr. Hildreth.

Dr. Hildreth: Thank you, I don't have much to add to what my colleagues have said. I think that the sponsor's done a great job of presenting data in a way that makes me comfortable assessing that the benefits of this vaccine outweigh the risk, and especially in severe disease across all of the age groups, regardless of whether or not they're comorbidities.

I was also very impressed at every single question raised, they answered. So they're clearly very meticulous in the work that they've done. I feel comfortable if this were to be given a thumbs up, so thank you.

Dr El Sahly: Thank you, Dr. Portnoy.

Dr. Portnoy: Thank you. One of the disadvantages of going later is that most of what I was going to say has already been said. I agree pretty much with Dr. Bernstein and Dr. Cohn. They hit what my thoughts are precisely. When I think about safety of a vaccine, I have to – I can't disentangle it from the thing that it's being used to prevent.

The RSV has serious harmful effects. It's prevalent, and it's a bad disease. And so a certain amount of safety can be compromised in a vaccine in order to prevent those adverse outcomes. I took on comfort in this vaccine noting that it seems to be relatively safe.

The number of acute adverse events are pretty low. It's slightly higher than yesterday, but I attribute a lot of that to the adjuvant. And it, in terms of the adjuvant, I take comfort in the fact that it was used in the Shingrix also. So we actually have quite a bit of experience with this adjuvant. We know how it works and what the adverse profile of the adjuvant is.

That has given me some comfort. I do expect to see a little bit more adverse effects when you use an adjuvant like this. But on the other hand, to me, it indicated that the vaccine is working and that there's a good immune response.

The question of low frequency events like BBS, that'll come out in the wash later on as more people are enrolled in the trials and as well as receive the vaccine and have post approval surveillance.

There's no way – we can beat our heads against each other now, but there's no way we're going to know what the outcome of the GBS surveillance is until the drug is approved and we see what happens. So I take pretty good comfort.

I do think that Glaxo did a wonderful job of presenting the data. It was very clear the co-administration issue was taken care of. The populations were more representative of those who were going to get it. So all of those things give me a lot of comfort in this vaccine. Thank you.

Dr. El Sahly: Thank you, Dr. Portnoy. Dr. Perlman.

Dr. Perlman: Yeah, I just want to agree with what everyone else has set up till now. I think that, like yesterday, there's a low signal with GBS and maybe there's low signals with atrial fib that goes away after a few months. But in terms of actually knowing whether this matters or as

common, I don't think until we do post-market surveillance we'll really know. So I think it's the – I think this vaccine is safe.

I think it's the – to answer the question, I think the available data supported the safety of the vaccine. And of course, we'd all like to have more information about GBS. Thank you.

Dr. El Sahly: Thank you, Dr. Perlman. I will also wrap up by expressing my viewpoint regarding the safety question. I will go back to the GBS, but I also may want to put it in the inflammatory neurologic complaints. Whether we're going to call it ADEM or not is a different story. The investigator called it as such, there was doubt cast around the diagnosis, but then again, one was investigated and one got better with steroids, so it's hard to dismiss I would think unless there's a background outbreak of Zika or Campylobacter or a disorder that results inflammatory neuropathies, which I haven't heard of then these rates are above the background. And whether or not post-marketing is the way to go I am struggling with this question as much as I struggled to – y'all can see how much I try to get more answers and more tables to see for anything that can provide a concluding answer.

But I'm left with a higher than background incidence of significant inflammatory neurologic complaints of sort. So this is where I'm coming from and I put that in the context that Dr. Cohn eloquently described, which is we have a vaccine program to worry about, not just a pathogen, which we should worry about RSV, nothing exists in a vacuum. And this is where I stand on the issue of the safety and how I view the data presented today.

Dr. Paydar, anything else we need to do before we move to the voting portion?

Dr. Paydar: No. We are ready to go ahead and vote. I've already read the script we're just going to take off at this point if Derek would be kind to go ahead, move all the non-voting members out of the main room. And for those of you who are not voting, please just be patient

with us. Don't log out of Zoom. We'll be back in a few minutes, and we'll start the voting immediately. Thank you.

Voting Question #1 Results and Explanations

Bonner: We are ready to display results.

Dr. Paydar: Great, thank you Derek. We have a total of 10 out of 12 for voted who have voted Yes, that's 83%. 2 out of 12 have voted no, that's 17%. And no one has abstained this time from voting. There are 12 total voting members, and I'm going to read them for the public record. Dr. Marie Griffin, no. Dr. Jay Portnoy, yes. Dr. Steven Pergam, yes. Dr. Amanda Cohn, yes. Dr. Stanley Perlman, yes. Dr. Henry Bernstein, yes. Dr. David Kim, yes. Dr. Holly Janes, yes. Dr. Daniel Feikin, yes. Dr. Hana El Sahly, no. Dr. James Hildreth, yes. Dr. Adam Berger, yes. Thank you so much. We can move on to the voting question number two discussion Dr. El Sahly.

Dr. El Sahly: Dr. Paydar, do you want me to go – do a round table to explain the vote or not?

Dr. Paydar: Yes. Please Go ahead. Pardon? [multiple speakers] Go ahead for vote explanation for voting question number one before we go on to two.

Dr. El Sahly: Okay. And your dear colleagues, this is not to put you on the spot or anything. If you have minimal or no comments to say, that's perfectly fine. I'm just going to invite everyone to explain their vote as briefly or as expansively as they wish. Dr. Griffin.

Dr. Griffin: Yes. I think for a vaccine that could be potentially recommended every year for everyone, 60 or 65 and older, we should have more safety data. And there are some big safety concerns that I have in the study population there was one GBS, two potential, ADEMs with one

death versus two hospitalizations and a lot of other significant disease, but not requiring hospitalizations in the placebo group.

So I think even in the study population, it's hard to weigh the risk and benefits. So we're all – we just think it's going to be much more beneficial in this other population that we didn't study.

So I'm – two, I think we should have more data on co-administration with flu and Covid, because that's definitely going to happen, if it's recommended.

And third, I think we don't have any data on revaccination and safety of revaccination, so I think this is our chance to get more information on these vaccines before they're licensed.

Dr. El Sahly: Thank you Dr. Griffin. Dr. Portnoy.

Dr. Portnoy: Yeah. Yes, I don't really have too much to add to what I did before. I voted yes, because I felt that while there were some adverse effects, they were justified by the harm that the disease causes. I thought they were acceptable, and the low frequency events, we'll find out with the post-marketing surveillance. Thank you.

Dr. El Sahly: Thank you, Dr. Pergam.

Dr. Pergam: Yeah, I don't have anything to add to my prior comments. I feel like the safety data was okay. Made me feel like a good one for yes.

Dr. El Sahly: Dr. Cohn.

Dr. Cohn: I'll just add that – I'll just say that. I voted yes because in isolation I felt like the adverse events that were seen in this population were similar to other vaccines that have met this threshold for safety data.

I still completely concur with Dr. Griffin's perspective that from an overall program and risk benefit. I don't think that this – in the question wasn't this, but I do very much think that the risk benefit still needs to be understood better before we embark on what could be an annual

vaccination program, but I did feel like the company did a very good job with this first single dose safety data.

Dr. El Sahly: Thank you, Dr. Perlman.

Dr. Perlman: Yeah, I don't have much to add to that. Yesterday I voted – I abstained, today I was a little more convinced, partly because there was only one case of GBS, which of course is silly to compare two to one, so I recognize that.

I think the ADEM is – I don't know what that is, but to have two cases in one site out of 150 people, just is so extraordinarily high I don't really know whether to count that as an adverse event, and we'll find out.

Dr. El Sahly: Okay. Dr. Bernstein.

Dr. Bernstein: Yes, I voted yesterday because I feel that today that the data, the sponsor's done an impressive job, as I mentioned earlier, in being organized and thorough and detailing a lot of data. I do have concerns about whether or not – it's just not clear whether or not there's a true safety signal or not here with the inflammatory neuropathies of the atrial fibrillation, but I'm optimistic that post-marketing surveillance will be helpful in monitoring for that safety signal. And as I mentioned a few minutes ago, I absolutely don't feel that we need to rush to get this necessarily to market if in fact, at it's at the expense of those 60 and older being up to date with other vaccines like flu and Covid, et cetera, so thank you.

Dr. El Sahly: Thank you. Dr. Kim.

Dr. Kim: Thank you. I don't have anything more to add than what's already been said. Thank you.

Dr. El Sahly: Thank you. Dr. Janes.

Dr. Janes: I don't have any more to what I've said in terms of my rational for the vote, thank you.

Dr. El Sahly: Dr. Feikin,

Dr. Feikin: I agree that post-marketing, a post-marketing study would really – and surveillance would be the only way to get the numbers to really clarify these potentially rare events.

Dr. El Sahly: Thank you, Dr. Hildreth.

Dr. Hildreth: Thank you. I don't have anything to add to what I said. I think the data presented to us – there are some challenges and possible safety signals, but I think the data weren't – a voted yes. And so, I voted yes. Thank you.

Dr. El Sahly: Thank you, Dr. Berger.

Dr. Berger: Likewise. I don't have much to add here. I just want to, again, stress, I voted yes cause I think it did meet the bar for voting yes. But I do think this relies on making sure that those post-marketing surveillance studies are done. It's the way that we're going to be able to parse out whether these are real safety signals or not and what kind of information we want to make sure that patients are aware of before they actually take the vaccine. Thank you.

Dr. El Sahly: Okay. And then the last item is from me. I voted no for this question for the previously stated reason in which what seems to be inflammatory neurologic diagnoses of sorts whether we agree it's ADEM or not. We definitely saw Guillain-Barre maybe other less minor complaints do rise above the average seen. The post-marketing surveillance can help answer I would agree with that, however – once a vaccine is licensed, it is really hard to collect data given our decentralized healthcare delivery system.

It will take a huge effort to answer the question when we already have indication that there may be a safety issue. We saw that, for example, in the Covid effort, the CDC so beautifully helped us mitigate some of the safety concerns. But I don't know that's going to happen with every vaccine. So, pre-licensure is probably where most of the effort should go when feasible. Thank you all.

So, Dr. Paydar, will display question number two and will read a script for us.

Dr. Paydar: Dr. El Sahly, this is when we will have a discussion of this question. So, if you don't mind reading the question, we'll have a discussion before we go into voting. Thank you.

Voting Question #2 Discussion

Dr. El Sahly: Okay. Question number two. Are the available data adequate to support the effectiveness of AREXVY (RSVPreF3+ASO1e) for the prevention of low respiratory tract disease caused by RSV in individuals 60 years of age and older.

We will be discussing this question. You can either raise your hand and I will ask you to weigh in, or I will just go around the virtual table and invite you to weigh in. And remember, don't, you don't need to tell us how you're going to vote, you just tell us your viewpoint of the data presented when it pertains to this question. Okay, I will invite Dr. Berger again.

Dr. Berger: Going to start twice, much appreciated. In looking at the data that's been presented, I think we're looking at fairly robust vaccine efficacy numbers coming out. Obviously, I think we'd all like to have more data and I did hear specifically that the sponsor expects to get through year two in quarter two of this year.

There is more data that's going to be available not that far off into the future, which would be really helpful in better understanding the efficacy rates, especially since it'll now be parsed over those two seasons. I think we did hear, there is at least some higher inclusion numbers for those

with comorbidities, age, and differences in age that we're seeing. I did think that those gave me a little bit more support for thinking through the efficacy here.

Obviously, again, though, we'd love to see more in those spaces especially with the, with those, with increasing numbers of comorbidities, but overall I think I'm looking at some significant potential benefit from this vaccine. I'll just end there.

Dr. El Sahly: Thank you, Dr. Cohn.

Dr. Cohn: I was, sorry, got my camera off. Okay, great. Thanks. I similarly agree that these data are robust and demonstrate potentially very high effectiveness against lower respiratory tract disease. I also believe that understanding – I wish that we had another season of data in for many reasons, but in part because it is a hard risk benefit when you do look at just this population that there really was not a substantial amount of severe disease in those that were studied, makes me gives me pause about expecting the potential benefits to be – applying this to the general population of which we do see a high burden of disease. But overall I think that the data are very supportive of effectiveness.

Dr. El Sahly: Thanks, Dr. Cohn. Dr. Pergam.

Dr. Pergam: Yeah, I think looking at the totality of data, I think the sponsors did an excellent job presenting the data in a way that was both informative and clear. And I think that they really, as one of my colleagues had mentioned, did a really good job of answering particular questions we had about subsequent follow-up studies or concern.

It's really, I struggle with this because again, this is a BLA and it feels like a major undertaking to say yes to a study that is planned for three years, that we're looking at the first year of data, to make decisions particularly when we know in another month, two months, we'll have additional data for that second year and that always is challenging. We're making decisions

about a yes vote in the situation, so I'm again torn as I was yesterday. But I think one – the two pieces that really strengthen the argument with this population is, it felt like significantly more patients with comorbidities that were included in the data. The efficacy did also appear, and I would expect the same if you were included more patients with high comorbidities, to be more protective in those with higher risk because of the incidence of disease, which I think is important.

I really would love to see more severe cases and I think we all appreciate that this year was really a big RSV season and that this upcoming data that will be coming in April will be very informative because there will be more cases likely, and more potentially severe cases within that group that would be highly informative for us. That's the way I'm looking at this one. I'm going to be putting my vote together.

Dr. El Sahly: Thank you, Dr. Pergam. Dr. Feikin.

Dr. Feikin: I think the data presented certainly answers this question that's posed to us about efficacy or effectiveness. And it did show some robustness in the results among 60-year-olds, 70-year-olds with those comorbidities, RSV-A and RSV B. However, there's two gaps that I see, the first is there was not sufficient numbers to assess the efficacy in 80 plus year olds. And we saw from the epidemiology that's an age group that has a real sharp increase in severe disease and hospitalization. There were only two cases versus three cases in the placebo we certainly need to look at that.

The second is, I'm not convinced that first severe definition is really severe disease. To me it's more of a moderate disease. So, I don't think we have the answer about efficacy in a truly severe disease group. There were only two hospitalizations and part of that is because of the low incidence, but I don't think that we can say we have the answer to that.

I suspect that the trend will be the same in 80-year-olds and for severe disease, but I don't think the data that we saw today shows that. Thank you.

Dr. El Sahly: Thank you, Dr. Feikin. Dr. Kim.

Dr. Kim: Looking at the question the primary endpoint has been met although there were some questions and that we have all tried to poke holes at the data to see to see what might come of those holes that might help us be better informed. But I think our collective thirst for additional data has no grounds. As GSK is want to do, they will continue to collect additional data and that gives me additional comfort in supporting the conclusion that the vaccine – that the effectiveness of the of the GSK vaccine is indeed very favorable for use for adults 60 and over.

Dr. El Sahly: Thank you, Dr. Kim. Dr. Bernstein.

Dr. Bernstein: Yes. As far as this question is concerned, I do think there is limited data regarding the severe disease, but one can make an assumption that if we have a such a positive impact on decreasing lower respiratory tract disease, that in turn, that would decrease hospitalization and the amount of severe disease.

I was impressed, and whether that's the use of an adjuvant or not, but I was impressed with the apparent duration of neutralizing antibodies and cell mediated immunity going out 360 days. And I certainly look forward to years two and three data, and also continued study in vulnerable populations like the 80 plus year olds as my colleague just mentioned, as well as immunocompromised individuals, because I think they are certainly at high risk and can benefit greatly from such an effective vaccine, thanks.

Dr. El Sahly: Thank you Dr. Bernstein. Dr. Janes.

Dr. Janes: Thank you. In terms of the question around efficacy, and I have little doubt in my mind that these data have established efficacy in individual 60 years in age over, quite high and

precise estimates of vaccine efficacy well above the bar that was set out in multiple subgroups against RSV-A and B.

I take my clinical colleagues concern about the severe disease endpoint. But it was, but against – I guess against a bit more severe endpoint than what we saw yesterday. It was informative to see a very high efficacy against the severe disease endpoint as defined for this study.

I thought it was very helpful to see, from the sponsor, the plans in terms of continued follow up these participants, which will allow robust, independent of answers in terms of durability of vaccine efficacy, as well as advocacy with a booster which are key questions. So I thought in all, the data were well presented and a bit more representative of the population that, that's really at risk of this disease, as was mentioned by others. And so I felt to this question is yes, in my view.

Dr. El Sahly: Thank you, Dr. Janes, Dr. Hildreth.

Dr. Hildreth: Thank you, Dr. El Sahly, I think that the sponsors have done a great job of presenting data that favorably supports the effectiveness or efficacy of this vaccine. I'm particularly pleased that they paid attention to the CD4 T-cell response, which I think is contributing to the durability of the response. I think that they've met the bar more than adequately, so thank you.

Dr. El Sahly: Thank you, Dr. Hildreth. Dr. Portnoy.

Dr. Portnoy: Thank you. Yeah, I was comparing, I know I'm not supposed to, but I was comparing today's data with yesterday's, and the number of patients enrolled really isn't that much different. And I was concerned about that yesterday, but somehow, I take more comfort in the data today. The efficacy is pretty similar, it's robust, but the confidence intervals were narrower and back of the envelope.

It appears to me that adding a few patients or flipping a few to the other direction probably would not change the results of this outcome, which gives me more confidence in the results and in the efficacy.

As Dr. Bernstein mentioned, I also appreciate that cell mediated immunity was measured along with humeral immunity and that it was persistent over a full year that I thought was very encouraging and suggested to me that there is a mechanism of action that might be more robust than perhaps a non-adjuvanted vaccine might have had.

The fact that the adjuvant is there, we've seen it with work with Shingrix, that also gives me comfort in in the effectiveness of this vaccine. So, guess those are my thoughts. Thank you.

Dr. Eh Sahly: Thank you. Dr. Griffin.

Dr. Griffin: Yeah, I agree that the data supports the effectiveness for prevention of lower respiratory tract disease. So, they – but I think I would like to see more data on – since the vaccine will be used for many years. I think we should have additional years of data.

Dr. El Sahly: Dr. Perlman, I don't know why, but the Zoom always puts your name last .

Dr. Perlman: I was wondering, it’s the last letter of the alphabet. Yeah, I agree with my colleagues. I think that it would've been nice to have more data for severe disease for immunocompromised populations. I think we've had so much – we've learned a lot from using the COVID 19 vaccines and we know they're really hard to protect. So that may be something that would be good information, but may not actually be that helpful, because we may need other ways to prevent disease in those populations. So I think the sponsor put together a very good program and they have good data.

I'm a little surprised, I guess maybe it's the selection of who was put in these trials, but I'm surprised that there wasn't more severe disease with RSV in this population. They usually –

people often get sick with this and it's hard to know more than the two people who went into the hospital really had severe disease. But all in all, I think at this point, the data supports the effectiveness.

Dr. El Sahly: Thank you, Dr. Perlman. I think everyone got to way in. Now is my turn. And I will begin actually with a comment I had that sort of answers, maybe answers, I don't know what Dr. Perlman asked, which is why there were so few cases. These data were collected in the prior RSV season, and as we have known from other data in our country that elders were much better than younger individuals at social distancing and taking their precautions to avoid Covid. So, it is possible that the force of infection during the season in which we collected this data, or the sponsor collected this data is not the steady state force of infection that we will see.

Which brings up the issue of the importance of the season that just passed, the data of the season that just passed, especially that the CMI and the [indiscernible] that were generated by this vaccine that the volunteers put up with all this reactor for that particular durability and strength of immune response. So we can see the fruits of it in an efficacy of sort. Regardless, as asked here, the data does support the efficacy as defined a priority for this trial. And the individuals who are at higher risk of disease were represented.

Dr. Paydar, the next item on the agenda is the voting.

Dr. Paydar: Yes. So, I'm just going to give a very quick – we have done this two seconds ago, so I'm just going to repeat this. Again, we have, for the public record, nine regular members, three vote temporary voting members and a total of 12, who will be voting today.

Dr. El Sahly will read the voting question number two for the record. You have one minute to vote. Voting options are yes, no, or abstained.

So, Dr. El Sahly, would you be so kind to read the voting question number two.

Dr. El Sahly: Are the available data adequate to support the effectiveness of AREXVY (RSVPreF3+ASO1e) for the prevention of low respiratory tract disease caused by RSV in individuals 60 years of age and older.

Dr. Paydar: Great. Thank you. Derek if you would be kind to let us know when all the voting members are present. For those who are non-voting, please don't leave the Zoom platform. We'll be back in a few minutes.

Voting Question #2 Results and Explanations

Mr. Bonner: We are ready to display.

Dr. Paydar: Great. Thank you so much Derek. So, there are 12 total voting members for today's meeting. We have a unanimous vote yes. And I'm going to read the voting responses of each of the voting members, for the public record.

Dr. Marie Griffin, yes. Dr. Jay Portnoy, yes. Dr. Hana El Sahly, yes. Dr. Stanley Perlman, yes. Dr. Henry Bernstein, yes. Dr. Holly Janes, yes. Dr. Amanda Cohn, yes. Dr. James Hildreth, yes. Dr. David Kim, yes. Dr. Daniel Feikin, yes. Yes. Dr. Adam Berger, yes. Dr. Steven Pergam, yes. So, this concludes the voting portion for today's meeting. I'll now hand over the meeting back to Dr. El Sahly, to conduct the voting explanation for voting question number two GSK case. Thank you so much, Dr. El Sahly.

Dr. El Sahly: Thank you. Dr. Paydar. Dr. Griffin.

Dr. Griffin: Yes. I just want to say that I think our votes will be considered, these yes votes as supporting licensure, and I don't think necessarily everyone who voted yes thinks that the vaccine should be licensed at this point. So, I just want to say that. Yeah, I think it's a great

study. I think the sponsor did a great job, I would be more comfortable with more data, more years of data.

Dr. El Sahly: Thank you, Dr. Portnoy.

Dr. Portnoy: Yeah, I don't have a whole lot more to add other than to say that this has been a terrible disease, I've been treating it for many decades. The prospect of a vaccine is very exciting to me. I can't wait to see how it works, and I'm looking forward to the post surveillance study results, thank you.

Dr. El Sahly: Thank you, Dr. Perlman.

Dr. Perlman: Yeah so, I agree with the previous comments. I really hope that the vaccine, just as Dr. Griffin said, the vaccine is actually not licensed for a year or two and we get more data. So we have more comfort with both its safety and its efficacy, and then it'll be an easier sell to the general population.

Dr. El Sahly: Thank you, Dr. Bernstein.

Dr. Bernstein: Yeah, I don't have a lot more to say with what I've already said. I think an RSV vaccine could have an immense impact on this very common respiratory pathogen. I would love to see more data, which it sounds like will be available from GSK in April and then the following year. I do think ongoing monitoring and data collection and evaluation will be incredibly important. Thanks.

Dr. El Sahly: Thank you, Dr. Bernstein. Dr. Janes.

Dr. Janes: Nothing further to add in terms of my rationale for the vote but just along the themes of others, just to highlight, I think that one of the comments that's been made repeatedly is in terms of the difficulty of answering these questions with separating out the safety and effectiveness or efficacy considerations. And so, to reiterate that again here. Thank you.

Dr. El Sahly: Thank you, Dr. Cohn.

Dr. Cohn: Thanks. Nothing more to add in terms of my rationale for the vote. I agree with the other comments. The impact of this vaccine will only be seen when we achieve high uptake. And I think if you look over – if you think about this over many years, it may be that having more robust data that we will be getting soon may in the long run actually be better for public health than getting this vaccine out during this season.

I think we are seeing what happens with adult vaccines, which are really hard to disentangle the risks and benefits in a population that's not all uniformly healthy like we see in most children in infants.

I think this whole meeting has given me pause and hope that people really come together and think about how in the future, these vaccine studies can be done so that we can disentangle some of this stuff early and make sure that we do maintain high vaccine confidence in the population.

Dr. El Sahly: Thank you, Dr. Cohn. Dr. Hildreth.

Dr. El Sahly: Thank you Dr. El Sahly. I have nothing more to add to what was said previously. I agree with my colleagues and the real test – the real-world benefit of this we'll see when the vaccine is out there being used in the public.

Dr. El Sahly: Thank you Dr. Kim.

Dr. Kim: All in all from this protocol the vaccine is effective. The vaccine met the primary endpoint requirement, and the vaccine did indeed address the question that was posed, question number two regarding effectiveness. So it was an easy answer, but there are obviously additional comments made with made by other committee members that should be taken into consideration. Thank you.

Dr. El Sahly: Thank you. Dr. Feikin.

Dr. Feikin: I vote yes, also I do think there – the data was convincing. I think there are a lot of questions that still remain about implementation, optimal use. I think the optimal age group needs to be clarified. I think the effectiveness in the very elderly against severe disease persistence into the protection in the second season.

These are all important policy questions that I think need to be answered. I think personally that these answers will probably come post introduction. I'm not sure how much more we're going to get by waiting for a second season. We might get a little bit more, but I do think having well designed post introduction, effectiveness, impact studies will be crucial for the policymakers. Thank you.

Dr. El Sahly: Thank you, Dr. Berger.

Dr. Berger: Thanks, I don't think I could add much to what everybody else has stated before. I think it met the bar for answering yes to the question of whether the data that's been presented meets the effectiveness query here.

But I just want to stress, I do think there is the public interest to serve here as well. And just recognizing that the data is available shortly, I think it would behoove FDA to wait until they've actually had a chance to see that data before they make this a final decision on licensure.

As Dr. Feikin just mentioned, it may or may not address any additional questions, but just in terms of making sure that there isn't any change in signals, I think it would serve the public's interest by doing so.

Dr. El Sahly: Thank you Dr. Pergam.

Dr. Pergam: Thanks, Dr. El Sahly, just to comment, thanks Dr. El Sahly for running a really tight two days. I appreciate how you kept us on task, and this has gone very smoothly. So, kudos to you for great leadership.

And I don't have much else to add other than what I previously stated, but I do have to echo what a lot of folks have said, is that the year two data is going to be quite interesting, particularly because of the RSV season we had this year. It may be very informative. It may provide some more data about severe cases, which could help us to strengthen the argument to the public. But I think the take home for me is that the public should understand how carefully we're looking at this data and how cautiously this is a large, randomized trial, the top mark that you could get for a clinical trial. And yet we're being cautious about improving that vaccine in the situation. I think all of us have some hesitation, but I'm very excited about the possibility of an RSV vaccine being available and the efficacy data that was presented is robust and included populations that I think are interesting.

I would just say, my last comment is I really would love to see GSK put together trials in immunosuppressed patients because that population has not been studied in any way at this point. So I'd really encourage the FDA to pursue having additional studies in those groups. Thank you.

Dr. El Sahly: Thank you, Dr. Pergam, and I will explain my vote. The vaccine did meet the primary endpoint as previously stated. Especially when it comes to lower respiratory tract, the disease – what was deemed severe was probably not so severe. So that remains an outstanding question.

These trials are two and three years long for a scientific and a public health reason. And while the study did meet its final primary endpoint, there's a bigger picture that needs to be understood so we have a better idea. I agree with some of the comments that second year may inform more durability than necessarily efficacy for this vaccine where the CMIS are really high towards the end of the one year, it may inform a bit about this efficacy. But regardless it's

important to see the big picture and allow studies to go to completion in order to make critical determinations about products especially if we are not faced with the public health emergency like COVID 19 three years ago. With that, I turn it over to Dr. Paydar, but before that, usually we ask if the FDA has any final comments to the committee.

Closing Comments

Dr. Kaslow: No, no final comments to the committee at this time, although maybe I'll just go ahead and do my concluding remarks now. Which is, again, I'd really like to thank the advisory committee for your critical and probing questions and the subsequent voting discussions on the second day as with yesterday. And it's really quite helpful to hear the discourse on safety topics, including your discussions on and GBS and other neurologic disorders, concomitant vaccine use, atrial fibrillation, and the importance of robustness of the post-marketing studies and surveillance. And then also on the efficacy topics, including disease severity, endpoints at risk populations, additional vaccine effectiveness, and correlates of protection.

So let me conclude by thanking the advisory committee and technical staff that ran another flawless virtual meeting today. Let me also thank the FDA BLA review team and today's speakers, and then finally to thank you, the advisory committee and chair Dr. El Sahly for yet another productive day, be well.

Dr. El Sahly: Thank you so much. Dr. Paydar.

Adjournment

Dr. Paydar: Thank you so much Dr. El Sahly for closing comments. I wanted to thank the committee and the CBER staff for working so hard to make this meeting a successful meeting. I am now calling the meeting officially adjourned at 2:42 PM Eastern Time. Thank you so very much. Have a nice rest of your day.