Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

181st Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

Zoom Video Conference

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

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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
	Capt. Amanda Cohn, M.D.	Director, Division of Birth Defects & Infant Disorders, CDC	Atlanta, GA
	Holly Janes, Ph.D.	Professor, Fred Hutchinson Cancer Center	Seattle, WA
	Capt. David Kim, M.D.	Director, Division of Vaccines, HHS	Washington, DC
	Arnold Monto, M.D.	Professor, University of Michigan	Ann Arbor, MI
	Paul Offit, M.D.	Professor, Children's Hospital of Philadelphia	Philadelphia, PA
	Steven Pergam, M.D.	Professor, Fred Hutchinson Cancer Center	Seattle, WA
Consumer Representative	Jay Portnoy, M.D.	Professor, Children's Mercy Hospital	Kansas City, MO
Alt. Industry Representative	Gregg Sylvester, M.D., M.P.H.	Chief Health Officer & VP Medical Affairs, CSL Seqirus Inc.	Summit, NJ
Temporary Voting Members	Kevin Ault, M.D.	Professor, Western Michigan University Homer Stryker M.D. School of Medicine	Kalamazoo, MI
	Daniel Feikin, M.D., M.S.P.H.	Scientific Advisor and Respiratory Diseases Consultant	Coppet, Switzerland
	Capt. Meredith McMorrow, M.D., M.P.H., FAAP	Acting Branch Chief, Surveillance and Prevention Branch, Coronavirus and Other Respiratory Viruses Division, NCIRD, CDC	Atlanta, GA
	Saad B. Omer, M.B.B.S., M.P.H., Ph.D., FIDSA	Director, Yale Institute for Global Health; Yale School of Medicine	New Haven, CT
Speakers	Natalie J. Thornburg, Ph.D.	Acting Chief, Laboratory Branch, Coronavirus and Other Respiratory Viruses Division, NCIRD, CDC	Atlanta, GA
	Katherine E. Fleming-Dutra, M.D.	Acting Team Lead, Vaccine Effectiveness and Policy Team, Surveillance and Prevention Branch,	Atlanta, GA

		Coronavirus and Other Respiratory Viruses Division, NCIRD, CDC	
	Helen Chu, M.D., M.P.H.	Associate Professor, University of Washington	Seattle, WA
FDA Participants	Peter Marks M.D., Ph.D.	Director, CBER, FDA	Silver Spring, MD
	David C. Kaslow, M.D.	Director, Office of Vaccines Research and Review (OVRR), CBER, FDA	Silver Spring, MD
	Joseph Toerner, M.D., M.P.H.	Acting Deputy Director, OVRR, CBER, FDA	Silver Spring, MD
	Sudhakar Agnihothram, B.Pharm., Ph.D.	Acting Senior Advisor to Office Director, OVRR, CBER, FDA	Silver Spring, MD
	Yugenia Hong-Nguyen, M.D.	Medical Officer, Division of Vaccines and Related Products Applications (DVRPA), OVRR, CBER, FDA	Silver Spring, MD
	Goutam Sen, Ph.D.	Microbiologist, DVRPA, OVRR, CBER, FDA	Silver Spring, MD
Designated Federal Officer (DFO)	Prabhakara Atreya, Ph.D.	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
DFO	Valerie Vashio, B. Pharm, R.Ph., RAC	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 Officer	Joanne Lipkind, M.S.	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
Open Public Hearing Speakers	David Allely	Icahn School of Medicine at Mt. Sinai	New York, NY
	Jester Jersey	Vaccinate Your Family	Washington, DC
	Martha Nolan	Healthy Women	Middletown, NJ
	Karen Crowley	Association of Women's Health, Obstetrics and Neonatal Nurses	Washington, DC
	Yoko Allen	Black Women's Health Imperative	Washington, DC

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Call to Order and Welcome

Dr. El Sahly: Good morning. I would like to welcome the members of the VRBPAC, the participants, and the public to the 181st meeting of the Vaccines and Related Biological Products Advisory Committee meeting. During this meeting, which occurs in open session, we will be discussing and making recommendations on the safety and effectiveness of ABRYSVO RSV vaccine, manufactured by Pfizer, with a requested indication in BLA 125768 for the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by RSV in infants from birth through six months of age by active immunization of pregnant individuals.

I would like to remind the committee members and participants to use the raise the hand function in your in your zoom and turn your camera on if you have a question or comment to make, and then I would be able to see it and call upon you to speak. To start us off, I would like to welcome Dr. Prabhakara Atreya as the Designated Federal Officer for today's meeting. Dr. Atreya.

Dr. Atreya: Good morning, everyone. Thank you, Dr. El Sahly. It is my great honor to serve as the Designated Federal Officer, DFO, for today's 181st Vaccines and Related Biological Products Advisory Committee. On behalf of the FDA, the Center for Biologics Evaluation and Research, CBER, and the Committee, I am very happy to welcome everyone for today's meeting. As Dr. El Sahly mentioned, the committee will meet in open session today to discuss and make recommendations on the safety and effectiveness of ABRYSVO respiratory syncytial virus vaccine manufactured by Pfizer with a requested indication in Biologics License Application 125768 for the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by RSV in infants from birth to six months of age by active immunization of

pregnant individuals. Today's meeting and the topic were announced in the Federal Register Notice published on April 11th, 2023.

I feel compelled to take just a few seconds to share that when I first started my public health career at NIH, especially with National Institute of Allergy and Infectious Diseases in Dr. Chanock's lab 30 years ago as a fellow. My very first project that I worked on was to study respiratory virus molecular virology with a goal to develop vaccines for pediatric population. So after spending 30 years in public health at both NIH and FDA, I feel my professional life came to you full circle. And now I feel very honored, and it is very gratifying to me personally, to serve in this capacity as the Designated Federal Officer for this prestigious committee's meeting focused on discussing RSV vaccines to protect pediatric populations.

With that note, I would like to introduce and acknowledge the excellent work of my team whose contributions have been critical for preparing today's meeting. Ms. Valerie Vashio, who is serving as my backup DFO, and Ms. Joanne Lipkind, and Ms. Lisa Johnson, our committee management staff, who provided excellent support.

Next, I would like to introduce our leadership, Dr. Peter Marks, Director of CBER, and Dr. David Kaslow, Director of Office of Vaccines Research and Review, OVRR, and Dr. Sudhakar Agnihothram, Acting Senior Advisor in the Office of Vaccines Research and Review. Dr. Marks, Dr. Kaslow, and Dr. Sudhakar may make remarks to the committee during the course of the meeting. Dr. Marks, do you want to make any comment at this time? Otherwise, you can address the committee later.

Also, I would like to express our sincere appreciation to Mr. Joseph Eley, Ms. Gretchen Carter, and Mr. Derek Bonner in facilitating the technical aspects of this virtual meeting today. Also, our sincere gratitude goes to all 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 and media questions for today's meeting to FDA's Office of Media Affairs at fdaoma@fda.hhs.gov. The transcriptionists for today's meeting are Deborah Dellacroce and Catherine Diaz from Translation Excellence.

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 state your first and last name, your institution, and areas of expertise. When finished, you can turn off your camera so we can proceed to the next person. Please see the member roster slides, in which we will begin with the chair, Dr. Hana El Sahly.

Committee Introductions

Dr. El Sahly: Good morning. Hana El Sahly. I'm at Baylor College of Medicine, a professor of molecular virology and microbiology, adult infectious diseases. My research work centers around clinical vaccine development.

Dr. Atreya: Thank you, Dr. El Sahly. Next, Dr. Adam Berger.

Dr. Berger: Hi, I'm Adam Berger. I'm the Director of the Division of Clinical and Healthcare Research Policy at the NIH. My background, geneticist by training, further training in immunology. Thank you.

Dr. Atreya: Thank you, Dr. Berger. Next, Dr. Hank Bernstein. Can you show the slides please?

Dr. Bernstein: Good morning. I'm Hank Bernstein. I'm a professor of pediatrics at the Zucker School of Medicine at Hofstra Northwell. My expertise is as a general pediatrician, and vaccines. Thank you.

Dr. Atreya: Thank you so much. Next is Captain Amanda Cohn. Dr. Cohn.

Dr. Cohn: Good morning. I'm Dr. Amanda Cohn. I am the Director of the Division of Birth Defects and Infant Disorders at the Centers for Disease Control and Prevention with expertise in vaccine policy and maternal and child health.

Dr. Atreya: Thank you, Dr. Cohn. Next, Dr. Holly Janes.

Dr. Janes: Good morning. My name is Holly Janes. I'm a professor at the Fred Hutchinson Cancer Center. My discipline is biostatistics, and I specialize in vaccine trial design and evaluation.

Dr. Atreya: Thank you. Next, Captain David Kim.

Capt. Kim: Good morning. My name is David Kim with the National Vaccine Program in the Office of the Infectious Disease and HIV/AIDS Policy, which is under the Office of the Assistant Secretary for Health at HHS. And my interest is in vaccine policy and immunization.

Dr. Atreya: Thank you. Next, Dr. Arnold Monto.

Dr. Monto: I'm Arnold Monto. I am Professor Emeritus of Epidemiology at the University of Michigan School of Public Health, and my area of interest is vaccines and epidemiology of viral infections.

Dr. Atreya: Thank you, Dr. Monto. Next, Dr. Paul Offit.

Dr. Offit: Yes. Good morning. I'm Paul Offit. I am an attending physician in the Division of Infectious Diseases at Children's Hospital of Philadelphia and a professor of pediatrics at the University of Pennsylvania School of Medicine. And my interest is in vaccines, specifically mucosal vaccines. Thank you.

Dr. Atreya: Thank you, Dr. Offit. Next, Dr. Steven Pergam.

Dr. Pergam: Thanks, Dr. Atreya. I'm Steve Pergam. I'm a professor at Fred Hutchinson Cancer Center, and my area of focus and research is infections and immunocompromised.

Dr. Atreya: Thank you, Dr. Pergam. Next, our consumer representative, Dr. Jay Portnoy.

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 attending physician in allergy immunology at Children's Mercy Hospital in Kansas City.

Dr. Atreya: Thank you. Next, Dr. Gregg Sylvester, our alternate industry representative.

Dr. Sylvester: Yes. Good morning. My name is Gregg Sylvester. I'm the Chief Health Officer for CSL Seqirus, a pharmaceutical company. I am a pediatrician and preventive medicine physician, and as already pointed out, I'm the alternative industry representative today.

Dr. Atreya: Thank you, Dr. Sylvester. Next slide please. Next, I would like to introduce our temporary voting members. Dr. Kevin Ault. My name is Kevin Ault, and I'm a professor and Chair of Obstetrics Gynecology at Western Michigan University, Homer Stryker M.D. School of Medicine. I have an interest in maternal immunization as well as being a practicing OBGYN.

Dr. Atreya: Thank you, Dr. Ault. Next is Dr. Daniel Feikin.

Dr. Feikin: Hello, I'm Daniel Feikin. I trained in internal medicine, and I spent my career working at the US CDC as a medical epidemiologist. For the last few years, I've worked on a temporary basis for the World Health Organization. My areas of focus have been immunization and respiratory diseases. And I just want to add that today I'm not representing an official position of the WHO, just my own. Thank you.

Dr. Atreya: Thank you, Dr. Feikin. Next is Captain Meredith McMorrow.

Capt. McMorrow: Good morning. I am the Acting Branch Chief for the Surveillance and Prevention Branch and the Coronavirus and Other Respiratory Viruses Division at the US

Centers for Disease Control and Prevention. And I'm a pediatrician and epidemiologist with a focus in respiratory viral diseases.

Dr. Atreya: Thank you, Dr. McMorrow. Next is Dr. Saad B. Omer.

Dr. Omer: Hi, I'm Saad Omer. I'm the Director of the Yale Institute for Global Health. I'm also a professor of internal medicine as well as epidemiology of microbial diseases at Yale School of Medicine and Yale School of Public Health. My interests and focus have included maternal immunization epidemiology of vaccine preventable diseases as well as vaccine safety.

Dr. Atreya: Thank you, Dr. Omer. Thank you everyone for making your introductions, and as you can see, we have great expertise in the committee today. For the topic, we have a total of 15 meeting participants, 14 voting members, and one non-voting member. Now I will hand the meeting to Ms. Valerie Vashio to read the FDA conflicts of interest disclosure statement for the public record. Valerie, can you take it away please?

Conflict of Interest Statement

Ms. Vashio: Thank you. The Food and Drug Administration, FDA, is convening virtually today, May 18, 2023, the 181st 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 May 18th, 2023. The committee will meet in open session to discuss and make recommendations on the safety and effectiveness of ABRYSVO respiratory syncytial virus vaccine manufactured by Pfizer Incorporated with a requested indication in Biologics License Application number 125768 for the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by respiratory syncytial virus in infants from birth through six months of age by active

immunization of pregnant individuals. This topic is determined to be a particular matter involving specific parties, 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 conflicts of interest laws and regulations. The following information on the status of this committee's compliance with federal ethics and conflicts of interest laws including but not limited to 18 US Code Section 208 is being provided to the participants in today's meeting and to the public. Related to the discussions at this meeting, all members, SGE and RGE consultants of this committee have been screened for potential conflicts of interests of their own as well as those imputed to them, including those of their spouse or minor children, and, for the purposes of 18 US Code Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, 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 the federal ethics and conflicts of interest laws under 18 US Code Section 208. Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts of interests when it is determined that the Agency's need for a special government employee services outweighs the potential for conflicts 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 are no conflicts of interest waivers issued under 18 US Code Section 208 in connection with this meeting.

We have the following consultants serving as temporary voting members: Dr. Kevin Ault, Dr. Daniel Feikin, Dr. Meredith McMorrow, and Dr. Saad Omer. 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.

The guest speakers for today's meeting are as follows: Dr. Natalie Thornburg from CDC; Dr. Katherine Fleming-Dutra, also from CDC; Dr. Helen Chu from University of Washington. Disclosure of conflicts of interest for speakers follows applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including Open Public Hearing speakers, to advise the committee of any financial 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 Designated Federal Officer 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. Thank you.

Dr. El Sahly: Thank you, Valerie. To introduce the meeting, I would like to welcome now Dr. David Kaslow. Dr. Kaslow is the Director at the Office of Vaccines Research and Review at CBER, FDA. Dr. Kaslow.

FDA Introduction

Welcome — Dr. David Kaslow

Dr. Kaslow: Thank you very much, Dr. El Sahly, and welcome all to this 181st convening of VRBPAC for an open session to discuss the available evidence and advise FDA on the safety and effectiveness of ABRYSVO RSV vaccine candidate, which was previously reviewed by VRBPAC on the 28th of February of this year, but now for a proposed indication for use during pregnancy. This is the third day that VRBPAC will have discussed specific RSV vaccine in as many months. And as noted when we met in February, these RSV vaccines are based on 21st century science and technology designed to overcome the shortcomings of previous efforts six decades ago. These vaccines represent structural immunology and molecular engineering over empiric vaccinology against a respiratory virus that execs its heaviest disease burden in the youngest and in older adults.

In a previous two-day meeting of VRBPAC, we focused on RSV disease in older adults. This convening of VRBPAC focuses on respiratory syncytial virus disease in the early months of childhood, as will be reviewed by presentations during this this morning's sessions. Following those presentations, VRBPAC will consider BLA 125768, submitted by Pfizer. While the vaccine is the same product as discussed previously, now the focus is on active immunization during pregnancy to provide passive immunity in infants over several months after birth.

This VRBPAC is scheduled at an important point in the BLA review cycle. The FDA specifically seeks the committee's advice on the available evidence submitted by the applicant in this Biologics License Application. As noted in the FDA briefing document, we are asking the VRBPAC members today to discuss and vote on whether the results of the vaccine efficacy trial demonstrates evidence of vaccine effectiveness, and to discuss and vote on whether or not the safety data support a favorable risk analysis considering the discussion of the safety data, for example, premature deliveries, and births.

Let me conclude this brief welcome by thanking the committee members, including the four temporary voting members, for their time today, by thanking those from the FDA who have reviewed this BLA and helped organize this meeting, by thanking today's presenters, and by thanking those who have joined this public open meeting virtually. We look forward to a productive meeting today. Back to you, Dr. El Sahly.

Dr. El Sahly: Thank you, Dr. Kaslow. Next, I would like to welcome Dr. Goutam Sen. Dr. Goutam Sen is the review committee chair at the Division of Vaccines and Related Products Applications at the Office of Vaccine Research at CBER, Dr. Goutam Sen.

BLA for ABRYSVO Immunization During Pregnancy: Pfizer Inc — Dr. Goutam Sen

Dr. Sen: Good morning, everybody. Thank you, Dr. El Sahly, for the introduction. My name is Goutam Sen from Office of Vaccines at CBER, FDA. It's my pleasure to introduce you to the topic for today's discussion, which is Biologics License Application for respiratory syncytial virus vaccine, ABRYSVO, immunization during pregnancy to prevent RSV lower respiratory tract disease and severe RSV LRTD in infants. And the applicant is Pfizer. Next slide please.

So this is the outline of my talk. I'll briefly discuss about the RSV disease, ABRYSVO's vaccine composition, dosage, administration, and proposed indication by the applicant. Overview of the ABRYSVO's clinical package, overview of today's agenda, and questions for the advisory committee members. Next slide, please.

RSV is the leading cause of bronchiolitis and viral pneumonia in infants worldwide. The peak of hospitalization due to RSV disease in infants occurs at one to two months after birth. Palivizumab, a monoclonal antibody, is approved by FDA for the prevention of serious lower respiratory tract disease caused by RSV in certain pediatric patients who are at high risk of RSV disease. Nirsevimab, another monoclonal antibody specific for prefusion A, antigen is under review at FDA with the applicant's proposed indication for the prevention of RSV LRTD in newborns and infants entering or during their first RSV season and for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. GSK's RSV vaccine AREXVY was recently approved by FDA for prevention of LRTD caused by RSV in individuals 60 years of age and older. Next slide please.

Among infants less than six months of age, RSV is associated with around 1.4 million hospital admissions and around 13,000 in-hospital days globally each year. In the US, RSV is the leading cause of infant hospitalization with approximately 1 to 3% of all children in the first 12 months of life hospitalized due to RSV lower respiratory tract disease. Treatment of RSV disease for infants is primarily supportive care, and there is no vaccine available to prevent RSV disease in infants. Next slide please.

So, Pfizer's RSVpreF contains the recommended stabilized prefusion A protein from RSV A subtype and RSV B subtype, 60 microgram each, a total 120 microgram antigen, without any adjuvant. Dosing and administration: a single 0.5 mL dose administered intramuscularly during

the second and third trimester of pregnancy, 24 to 36 weeks gestation. Applicant's proposed indication is prevention of LRTD and severe LRTD caused by RSV in infants from birth through six months of age by active immunization of pregnant individuals. Next slide please.

ABRYSVO's clinical package which was submitted to FDA for our review contains safety immunogenicity and efficacy data from an ongoing phase three study, C3671008, conducted globally in the Northern and Southern Hemispheres, which includes 18 countries and 197 clinical sites with 7,357 pregnant participants and 7,128 infants. Pfizer also submitted additional safety data for our review from approximately 3,638 participants, of which 1,248 recipients got the final formulation of ABRYSVO across four clinical studies conducted in the US, Argentina, Chile, and South Africa. 1001 is a dose finding immunogenicity phase 1 study. 1003 is a phase 2B study in pregnant individuals. 1004 is a phase 2B study, but non-pregnant woman with co-administration with Tdap, and 1014 is a lot consistency phase 3 study. Next slide please.

So after my introduction, Dr. Natalie Thornburg from CDC is going to discuss about RSV virology, strain variation, and surveillance measures, followed by Dr. Katherine Fleming-Dutra from CDC will discuss about RSV epidemiology and this disease's burden in infants from birth through six months of age. Next slide, please. Dr. Helen Chu from University of Washington will discuss about the durability of naturally acquired immunity and susceptibility to repeated RSV infections. There will be a 10-minute short break, followed by Pfizer's presentation for safety and efficacy of bivalent RSV prefusion F, a vaccine for maternal immunization to protect infants by Dr. Gruber, Dr. Simoes, Dr. Munjal, and Dr. Wilkins. Next slide please.

My colleague, Dr. Yugenia Hong-Nguyen, the lead medical officer from Office of Vaccines will present the review of efficacy and safety of respiratory syncytial virus vaccine

immunization during the second or third trimester of pregnancy, 24 to 36 weeks of gestational age to prevent RSV, lower respiratory tract disease and severe RSV lower respiratory tract disease in infants from birth through six months of age. There will be a 45-minute lunch break followed by Open Public Hearing, and then additional question and answer session for CDC, FDA, sponsor, and other presenters. There will be a 10-minute break followed by committee discussion and voting, and the meeting will be adjourned. Next slide please.

So here are the two questions for the committee members to vote. Number one, are the available data adequate to support the effectiveness of immunization with ABRYSVO during the second or third trimester of pregnancy, 24 to 36 weeks gestational age, to prevent RSV lower respiratory tract disease and severe RSV LRTD in infants from birth through six months of age? Please vote yes, no, or abstain. Number two, are the available data adequate to support the safety of immunization with ABRYSVO during the second or third trimester of pregnancy, 24 to 36 weeks gestational age, to prevent RSV LRTD and severe RSV LRTD in infants birth through six months of age? Please vote yes, no, or abstain. Next slide please. Thank you for your attention.

Q & A

Dr. El Sahly: Thank you, Dr. Sen. We now have an opportunity to ask Dr. Sen questions. Please raise your hand if you have questions. I see Dr. Portnoy. Dr. Portnoy.

Dr. Portnoy: Great. Thank you. I always have to get the first word in. Now, I appreciate that the voting questions are specifically focused on the safety and efficacy for infants. I'm a pediatrician, and I'm very excited that this product is going to be evaluated. But I'm just wondering, is there any concern about the safety of the mothers, because you haven't asked that question. It's approved for 60 and older. I don't know that we've ever actually discussed the consequences to the mothers of getting this vaccine. And so would it be possible to have a third question asking,

is it safe for the mothers to get this? Efficacy, I guess, isn't really the concern. It's really the concern, is it effective for the infants. But for the mothers, I want it to be safe also as well as safe for the infants. That's my question. Thank you.

Dr. Sen: So I'll request you to wait to hear from Pfizer's as well as AB's presentation. During both the presentations, I think there will be discussion about how safe the RSV vaccine is for the training enrollment, as well as for the mother. So it'll be discussed.

Dr. Portnoy: Okay. But we're not going to vote on it. I'll request Dr. Kaslow to respond to that.

Dr. Kaslow: Thank you, Dr. Portnoy, for your question. I thank you. Certainly want to hear discussion about that, and Q and A, and discussion. And I think you should also have that in your mind as you go to voting question number two around safety. So I would encourage you to think about the totality of the evidence, safety evidence, as it relates to voting question number two. Thank you.

Dr. Portnoy: Okay. Thank you.

Dr. El Sahly: I have a question. And it's more of a general question. Stabilizing the F protein in its prefusion format. As far as we know, between different manufacturers, does it follow the same pattern? Like we saw, for example with SAR-CoV-2, two proline introduction results in the locking into the prefusion format, or are there different ways of locking this protein in its fusion format?

Dr. Sen: I'll request my colleague Dr. Christian Sauder, if you can respond to that, but I know that we have another vaccine [indiscernible]. So Dr. Sauder, please.

Dr. Sauder: Yeah. My name's Christian Sauder. Unfortunately, we cannot go into any detail of the construction of the protein. Just in general, very general, I can say that there's certain common mechanisms that can be applied to stabilize these proteins in the prefusion forms. But

every company chooses their own approach, which really much resides in the, has the same result that this body is fixed in the prefusion form. Does this help you?

Dr. El Sahly: Not quite, but that's fine. Maybe we'll ask Pfizer later. That's fine.

Dr. Sauder: Yes, probably that's the best way to go.

Dr. El Sahly: Okay. We'll do that. Thank you so much.

Dr. Sauder: Thank you.

CDC Presentations

Dr. El Sahly: Any of my colleagues with additional questions? I do not see raised hands. Okay. So I think, thank you Dr. Sen and Dr. Kaslow. So it's my pleasure now to introduce our CDC colleagues. First off, I would like to introduce Dr. Natalie Thornburg. Dr. Natalie Thornburg is the Acting Chief Laboratory Branch, Coronavirus and Other Respiratory Viruses Division, National Center for Immunization and Respiratory Diseases at the CDC. Dr. Thornburg will go over RSV virology, strain, variation, and surveillance measures. Dr. Thornburg.

RSV Virology, Strain Variation, and Surveillance Measures — Dr. Natalie Thornburg

Dr. Thornburg: Good morning. Thank you. Next slide please. So I'll be giving you just a little bit of background about the virus, the variant structure, the genomics of the virus, and our future plans for viral genomic surveillance for RSV.

So RSV is a filamentous virus from the *Orthopneumovirus* family. It has a genome of about 15.2 kilobase pairs. It's a single stranded negative sense RNA virus, and that means that it's the opposite strand of RNA that encodes for protein. It encodes for 11 viral proteins that can be broadly divided into two subgroups, or serotypes, A and B viruses. RSV A and B viruses co-circulate in a season in single locations. Next slide, please.

This is a cartoon of the variant structure. The two proteins I've highlighted on the surface, attachment G protein and the fusion F protein, are targets for neutralizing antibodies. There are several other structural proteins present in the virus that include the phosphoprotein P, which is inside the capsid, matrix protein also inside the capsid, and then large polymerase L protein. And then there is a lipid bilayer and nucleoprotein, which coats viral RNA. Again, G and F proteins are the targets for neutralizing antibodies. There are medical countermeasure products, prophylactic and vaccines, that target F alone, or some in clinical testing that may have both F and G proteins present. Next slide please.

The G protein is the most heterogeneous protein in the virus. It's the gene encoding the G, therefore, is used to define RSV A and B viruses because it's so heterogeneous, which means it is the gene that varies the most in the genome. It has two large mucin-like domains that provide antigenic masking. Again, I mentioned that some neutralizing activity is directed against the G protein, although the majority of neutralizing activity is directed against the F protein. Next slide, please.

So this is a slide showing the RSV protein sequence variability. This is a trimmed figure and doesn't include the three-prime end of the genome that encodes the L polymerase, which is fairly conserved and not a target for neutralizing antibodies. Across the top are listed the gene products in the genome, so NS1, non-structural protein one, NS2. So those are listed towards the top. The percent variability across the entire gene between A and B viruses is shown in parentheses in black. So if you look at the G gene, you can see in parentheses 53%. If you look at the S protein in black, you can see 15%. The y-axis shows substitutions per site. And again, this is at the protein level. So this is a change in amino acids. The percent variability across the entire gene just within the B viruses is shown in red in the top. So in G you can see across the G gene is

between 2 and 12% variability, and the F gene protein product is 1% variability. And, again, the substitutions per site at each amino acid shown in the graph, RSV A viruses in black and RSV B viruses in red. So you can see the areas of those gene products where there are clusters of substitution. Again, you should pay most close attention to G and F, the targets of neutralizing antibodies. The number of substitutions per site for RSV A, in the black bars and RSV B, the red bars, and the protein sequence variability in each RSV B protein were calculated per strain relative to a consensus.

And so for context, so what we're looking at is 2 to 12%, 1% in RSV F, 53% in G gene between A and B viruses, and 15% of differences between A and B viruses in the F gene. So for context, H1 versus H3HA is about 60% divergence. So we're looking at similar divergence in the G gene product, but much, much lower divergence in the F gene product. Omicron spike versus ancestral spike, there were about 3% amino acid changes total across the entire spike. So more concentrated in the receptor binding domain, which contributed to the partial escape from that delta to omicron shift. And that was 15 of about 222, or 7% differences. Next slide please.

I've already covered the sequence diversity of F and G, but there's more than just sequence diversity. The F protein demonstrates structural diversity and exists in two or more structural forms that expose different antigenic regions even when you have the same sequence.

So this is a crystal structure showing the same protein, the same sequence, in two different structures. The left is a demi-stable prefusion F, and the left is less stable than the postfusion F. The right is the postfusion, more stable F. And so you can see different antigenic regions are colored on the surface of these structures, and some new antigenic regions or some different antigenic regions are exposed in different structural forms. So site zero, which is the target of potently neutralizing antibodies, is colored in red. And you can see it is primarily

exposed in the prefusion form. There are other antigenic regions which are exposed in both, like site four is exposed in both prefusion and postfusion. And then the approximate neutralizing potency is shown on the right in different colors, in decreasing potency. So most of the most potent monoclonal antibodies are directed against site zero, the red shaded area. Orange sort of ranking second, and blue ranking the lowest for potency of neutralizing antibodies.

Now, I told you two slides ago that the most potent neutralizing antibodies were not directed against G, but they are directed against F. In those same studies, there have been pre-absorption of sera with prefusion F, and that removed almost all neutralizing activity, consistent with the idea that site zero and site five, which is orange, have the most potent neutralizing antibodies directed against them. Next slide please.

So I'm going back to this slide with RSV sequence variability. And I just want you to look again at the F sequence and remind you that the sequence variability we're seeing against F, which is where most of the potent neutralizing antibodies are, is about 15% between A and B viruses, clustered in a couple of different regions. And just 1% within one serotype of virus within the B viruses. Next slide please.

So I have already shown you that the G protein has the most diverse sequence in the genome, and therefore it's been historically used to identify the genotypes of the viruses. And this is a list from a 2017 study published of RSV genomes, an example of some of the genotypes that have been identified and some of the nomenclature that you might see in the literature. And so you can see as RSV A viruses have nomenclature similar to GA1, GA5. So that's a G gene, A virus, and a number. And then there's some other types of nomenclature that include ON. And RSV B viruses that you might see include GB1, GB4, GB3, and BA. Next slide please.

So I mentioned earlier in the talk that that RSV can be divided into A and B viruses and that they co-circulate. And so this is a study from community transmission of RSV in one location in Kilifi, Kenya between 2003 and 2017. And what you can observe is that in this location, we observe seasonality of the viruses. So you see peaks at very certain times of year. RSV A is the clear peaks in the yellow line. RSV B is shaded in the sort of aqua peaks. So you see seasonality and you often see co-circulation of A and B viruses. But some seasons, not all seasons, one subtype is more dominant than another subtype. But that is not always true. Next slide.

Alright, so this is from that 2017 study that I showed two slides ago, looking at RSV A and B genotypes by year of sample collection. So these authors, Tony Piedra's group, sequenced about a thousand, or looked at a thousand viral sequences that were published between 1961 and 2014. I've already shown you a list of some of the RSV genotypes, and those lists were from this study. So the inset are published sequences between 1961 and 2000, and the y-axis is much smaller in that inset just because of the smaller number of sequences that were available. And so what I want you to observe here, and you can see the A viruses listed on the top and the B viruses listed on the bottom on the right y-axis, is that in some years, there's some genotype dominance. Some of the genotypes increase by year, and they contract. So there seems to be some drift of viruses, but it's not very dramatic, and it sort of changes more slowly over time. Next slide please.

So, genotypes, again, historically defined by the G gene. Most differ in in sequence. So, G and F are targets for neutralizing antibodies, but absorption demonstrates that the most potent neutralizing antibodies are directed against F. I showed you the amino acid sequence variability across the genome and the F gene product. I also showed you the crystal structure of F with maps

of antigenic regions. And the absorption studies have indicated that most potent neutralizing antibodies are directed against site zero and site five. So this is from that same 2017 study looking at published RSV genomes. And these are maps of A and B viruses, with diversity listed across the genomes. And then shaded in boxes across the genome are antigen regions. It's colored by region of the gene map, colored by region of the F gene. And on the above the x-axis are non-synonymous new substitutions, meaning they do results in a substitution change and an amino acid change. And then below the x-axis are synonymous mutations. So it's more important to pay attention to the bars above the graph because those substitutions result in changes in the amino acid change.

And if you can look, it's a little bit difficult to see the antigenic regions, but you can see there's more substitutions that result in amino acid changes in RSV B viruses than RSV A viruses. RSV A viruses are more conserved. You can sort of see it's very small, but you can see two regions with site zero. It's the sort of second gray area to the left. And then the fifth area to the left. And there are some substitutions and B viruses in site zero, but not many substitutions. There are no substitutions identified in site zero in A viruses that are published. Of course, the limitations of this are the number of sequences. The depths that we have of RSV sequences is much lower than say what we have for SARS-2. And therefore if there are rare substitutions, it may not be detected in the limited genomic data that's available currently. Next slide, please.

So CDC is planning viral surveillance, genomic surveillance, and we have already started efforts to collect specimens and have them and do genomic sequencing to monitor substitutions in targets for neutralizing antibodies. We are relying on a couple of networks for this genomic surveillance. And the first one Dr. Fleming-Dutra will tell you more about in the next presentation. But the first one is NVSN, which is an RSV-associated disease burden estimates

from the New Vaccine Surveillance Network. And this network is year-round acute respiratory illness surveillance. It started with three sites from 2000 to 2009, and it expanded to seven sites during 2016 to 2021 and is currently ongoing. Its prospective surveillance includes inpatient ED and outpatient clinics. And it does PCR testing, research testing, for multiple respiratory viruses, including RSV. And it has a population denominator and market share used to estimate disease burden. And enrollment is children; this is a pediatric network, children under five. Next slide please.

So for RSV-positive specimens, our sites have done RSV A and B typing. And this is the results of those typing from between the 2016-2017 season up to 2020. The share of RSV A specimens is shown in gray, and RSV B is blue. And what you can see is different predominance of A and B viruses in locations, and it changes from year to year. So there are some years that are very dominant, one virus. So if you look at 2019-2020 across all of the sites, RSV B was very dominant. The previous year it was sort of more evenly distributed. And then 2017 and 2018, it was primarily an A dominant year, with the exception of Kansas City, which is B dominant. Next slide please.

We have specimens from all of these cases at CDC, so dating back to 2016, and we will continue to have those going forward. And we're beginning sequencing efforts on historic specimens. And we'll plan on working on getting sort of real time whole genome sequencing up and running so that they will be able to generate genomic data in real time. And this is just example of some of the genomic sequencing that was performed on some 15 and 16 season specimens. And we identified that ON1 and BA9 were the dominant genotypes during those seasons. And that was true across all sites and was not site-specific. So the genotypes that were circulating at our different sites were the same genotypes. Next slide please.

In addition to our pediatric network, NVSN, we're doing our RSV surveillance within IVY network. IVY network includes 25 hospitals and within 20 US states. The population are adults age equal to or greater than 18 years that are hospitalized with acute respiratory illness. The participants that we are enrolling for RSV have tested positive for RSV either by RT-PCR or antigen tests and are within 10 days of illness onset. So we collect upper respiratory specimens for central RT-qPCR testing and whole genome sequences. We just started this effort in the IVY network in the 22-23 season, and we have 225 RSV sequences available for this network thus far. Next slide.

And wrapping up. So in summary, F and G are targets for neutralizing antibodies, with most potent antibodies directed against F. RSV G is the most heterogeneous gene and is used to define the genotypes. There's less heterogeneity in RSV F, but more is observed in B viruses in comparison to A. RSV A and B viruses co-circulate. And we are utilizing NVSN as well as IVY for surveillance and collecting specimens to identify A and B viruses. And we'll be using that for viral genomics surveillance as well. And that is all. Thank you.

Dr. El Sahly: Thank you Dr. Thornburg. I see Dr. Offit has raised his hand. We will have an opportunity to ask questions for both Dr. Thornburg and Fleming-Dutra at the end, after Dr. Fleming-Dutra's presentation. So write down your question. I would like to introduce now, Dr. Fleming-Dutra, Katherine Fleming-Dutra. Also from the National Center for Immunization and Respiratory Diseases at the CDC, she is the Team Lead for the Vaccine Effectiveness and Policy Team, Surveillance and Prevention Branch. Dr. Fleming-Dutra.

RSV Epidemiology and Disease Burden in Infants from Birth Through 6 Months of Age — Dr. Katherine Fleming-Dutra

Dr. Fleming-Dutra: Thank you. Good morning. Next slide. So, today we'll talk about the burden of RSV and US children and then in pregnant people, and then we'll discuss RSV seasonality in the United States. Next slide.

RSV infection is the leading cause of hospitalization in US infants. Most infants are infected in the first year of life, and nearly all by age two years, and 2 to 3% of young infants will be hospitalized for RSV. RSV is a common cause of lower respiratory tract infection in infants, which is what leads infants to be hospitalized. Infants with RSV can have difficulty breathing and eating, and they sometimes need oxygen or other respiratory support and hydration. Next slide.

Prematurity is a risk factor for hospitalization with RSV. Premature infants born at less than 30 weeks' gestation have hospitalization rates three times higher than term infants. And additionally, children with chronic lung disease, prematurity, and congenital heart disease are also at increased risk of severe RSV disease. However, RSV can also cause hospitalization in healthy term infants. An estimated 79% of children hospitalized with RSV aged less than two years had no underlying medical conditions. So, in short, all young infants are at risk of severe disease with RSV. Next slide.

Palivizumab, also known by the trade name Synagis, is the only RSV prevention product currently licensed in the United States. It's a humanized monoclonal IgG antibody targeting antigenic site two of the F, or fusion, glycoprotein, and it requires monthly administration due to its short half-life. Currently, the American Academy of Pediatrics recommends use of palivizumab for prevention of RSV disease in infants at high risk of severe disease, including

infants with the conditions listed here. Approximately 5% of US infants are eligible for immunoprophylaxis with palivizumab. However, data suggests that only 2% of US infants receive one or more doses. For completeness, I will note that the American Academy of Pediatrics also has criteria for Palivizumab eligibility in the second RSV season. And for more information, please refer to the Red Book. Next slide.

CDC estimates that each year in the United States among children aged less than five years, RSV is associated with 100 to 300 deaths, 58,000 to 80,000 hospitalizations, about 520,000 emergency department visits, and approximately 1.5 million outpatient visits. Next slide.

CDC generates RSV-associated Disease Burden Estimates for the New Vaccine Surveillance Network, or NVSN, which you've already heard about this morning. As a reminder, NVSN conducted year-round surveillance for acute respiratory illness with a broad case definition at three sites during 2000 through 2009 and expanded to seven sites in 2016. These seven sites have continued prospective surveillance in inpatient, ED, and outpatient clinics. Following enrollment, respiratory samples are collected and undergo PCR testing for multiple respiratory viruses, including RSV, and population denominators and market share are used to estimate disease burden, including hospitalization rates per 1000 population. Next slide.

This graph shows NVSN RSV-associated hospitalization rates by age group from 2000 through 2004, in red, and 2016 through 2020, in yellow, and in 2021, in gray. RSV-associated hospitalization rates are highest in young infants aged zero through five months and decreased with increasing age in childhood. RSV-associated hospitalization rates in infants age zero through five months are more than double than those among infants six through eleven months

of age. This pattern of seeing the highest rates in infants ages zero through five months is true across different time periods in which NVSN has conducted surveillance. Next slide.

So now we can zoom in and take a closer look at RSV hospitalization rates in children aged zero through eleven months, which demonstrates why passive immunization has been pursued for this age group. Here, the red bars represent NVSN hospitalization rates from 2000 through 2005, while the yellow bars represent rates from the surveillance period from 2016 through 20. The highest rates, again, occur in the first few months of life, peaking at age one month, and then decrease with increasing age, indicating that the older an infant is when they get RSV, the less likely they are to be hospitalized. For RSV A passive immunization strategy needs principally to protect infants until they are old enough that RSV infection is less likely to be severe. Next slide.

We can also examine data on RSV hospitalizations using CDC's respiratory syncytial virus associated hospitalization surveillance network, or RSV-NET, which is a component of the RESP-NET surveillance platform. RSV-NET conducts active, population-based surveillance of laboratory confirmed RSV-associated hospitalizations at sites in 12 states that account for about 8% of the US population. RSV-NET includes patients with positive RSV tests within 14 days prior to or during hospitalization during October through April during the 2018 to 19 and 19 to 20 RSV seasons and nearly year-round in the 2020 to 21 and 21 to 22 seasons. It is important to note that RSV testing is clinician driven and is not systematic. Next slide.

A major advantage to RSV-NET is that it is large and thus can be used for stratified analyses. Here are the seasonal population-based rates of RSV-associated hospitalization among US infants less than six months of age by race and ethnicity during the 2018 to 19 through 2021 to 2022 seasons. You can see that there were differences in hospitalization rates among infants

aged less than six months old by race and ethnicity across these seasons, but the differences varied by season. Of note, these rates have not been adjusted for RSV testing practices and thus may under-represent RSV hospitalization rates. However, this should not affect distribution of rates by race and ethnicity. Next slide.

Here are the rates of RSV-associated ICU admissions among US infants less than six months old by race and ethnicity during those same seasons in RSV-NET. Again, these rates have not been adjusted for RSV testing practices. You can see that population-based ICU admission rates for non-Hispanic black infants in RSV-NET were 1.2 to 1.6 times higher than for non-Hispanic white infants across the four seasons. Next slide.

Additionally, multiple studies have shown increased rates of RSV hospitalization among children who are American Indian and Alaska Native. Shown here is a recent study from the RSV surveillance in Native American children and adults, or SuNA. Highlighted are the seasonal rates of RSV-associated hospitalizations per 1000 children among four American Indian and Alaska Native communities. In these communities, RSV hospitalization rates in infants range from 19 to 112 hospitalizations per 1000 infants. And these rates were frequently 4 to 10 times higher than the rate in the general population as measured in NVSN. This disparity is thought to be due to social determinants of health, such as increased rates of poverty and crowding. Next slide.

So now let's briefly talk about what we know about the burden of RSV in pregnant people. But I will note that the data on RSV and pregnant people are very limited. Next slide. So to start, we can look at the annual rate of RSV-associated hospitalizations per 1000 people across the age spectrum in green, our data from 2016 through 2020 from NVSN, which you've already seen. And in blue, our data from the 2018 to 19 and 2019 to 20 seasons from RSV-NET. And you

can see that among all age groups, the RSV hospitalization rate is lowest among reproductive age adults ages 18 to 49 years. Next slide.

Data from RSV-NET also indicate that RSV's severity appears to be similar in pregnant and non-pregnant people. Among 387 women aged 18 to 49 years hospitalized with RSV in RSV-NET during October through April 2014 through 2018, 41, or 12%, were pregnant. Severe outcomes among pregnant women hospitalized with RSV were uncommon, and actually, ICU admission and death were less common among pregnant women than among non-pregnant women. And being pregnant was not a risk factor for a severe outcome with RSV hospitalization in multi-variable analysis. Next slide.

So now let's talk about RSV seasonality in the United States. Next slide. The CDC's National Respiratory and Enteric Virus Surveillance System, or NREVSS, is our primary source for monitoring RSV seasonality in the US. It is a passive, laboratory-based surveillance system that includes commercial, hospital, and state and local public health laboratories. Approximately 300 laboratories routinely report RSV results. They provide weekly reporting of the total tests performed for RSV and RSV positive tests to monitor real-time virus circulation. All test types are reported, and in recent years, the majority of tests are PCR assays. Testing is primarily clinician directed, and NREVSS includes tests from persons of all ages. Next slide.

This graph shows normalized RSV detections in NREVSS by epidemiologic week from before the COVID-19 pandemic during the 2011 through 2020 seasons. During that time, RSV circulation was highly seasonal in the US with predictable peak activity during December through February annually. Next slide.

We also know that there is some variation in the timing of elevated circulation of RSV in the different regions in the US. This image shows the mean of the curves for the four seasons in

NREVSS data in each US region. However, these data exclude Florida, Hawaii, and Alaska, where seasonality of RSV may be different. Increasing levels begin and peak the earliest in the south, shown in the light gray, and latest in the west, shown in the light green. However, in general, in the continental US, RSV activity begins to increase in October and diminishes to low levels in April. Next slide.

However, the COVID-19 pandemic interrupted seasonal circulation of RSV and many other respiratory viruses. This graph is again, NRVESS data showing the percent of RSV PCR tests that were positive pre-pandemic during 2017 through 2020. Again, showing that RSV transmission followed a consistent seasonal pattern with peaks during December to February. Next slide.

Now we can layer on top the pandemic era RSV seasons. During the 2020 to ‘21 season, shown in the orange hash line, there was very limited RSV circulation until late spring of ‘21. Then activity peaked in the late summer of 2021, shown in the yellow line, and transmission continued through the fall into December 2021. The most recent RSV season is shown in red with increasing RSV activities starting in late summer ’22, and RSV transmission peaked in October to November ‘22. So to summarize, the 2022 to ‘23 season began later than the ‘21 to ‘22 season, but earlier than pre-pandemic seasons, suggesting an incremental reversion toward pre-pandemic seasonality with winter peaks. However, we'll have to wait and see how this plays out next season. Next slide.

The following potential considerations will be important to help determine the optimal timing of RSV vaccine dosing during the year to best protect infants during RSV season. RSV vaccine dosing could be implemented for pregnant people as a seasonal campaign or year-round. Cost effectiveness may vary by timing of administration due to RSV seasonality and maternal

antibody decay, which leads to waning of protection. So, CDC will plan to examine cost effectiveness of seasonal RSV vaccine dosing compared to year-round dosing. Year-round dosing would simplify implementation though, and thus potentially increase vaccine uptake. And year-round dosing could also help protect infants in the event of atypical RSV seasonality. Next slide.

Additionally, as we have discussed already, some US jurisdictions have different or less predictable RSV seasonality, and recommendations for RSV vaccine dosing in those jurisdictions would need to account for that. These jurisdictions include those with tropical climates, parts of Florida, Puerto Rico, US Virgin Islands, Hawaii, Guam, and the US-affiliated Pacific Islands, and also Alaska, where RSV seasonality is less predictable and the duration of RSV activity is often longer than the national average. Next slide.

So in conclusion, RSV is the most common cause of hospitalization in US infants. The highest RSV-associated hospitalization rates are in the first months of life. The risk of hospitalization declines with increasing age in early childhood. Prematurity and other chronic diseases increase the risk of RSV-associated hospitalization, but most hospitalizations are in healthy term infants. Next. RSV hospitalizations are not common among reproductive age women, and being pregnant is likely not a risk factor for severe outcomes with RSV-associated hospitalization. Pre-pandemic RSV seasonality is well defined with limited geographic variability in most of the United States, but the COVID-19 pandemic disrupted RSV seasonality. However, the most recent season suggests that RSV may be returning to typical pre-pandemic seasonality. Next.

I'd like to acknowledge the contributions of many colleagues to this presentation, especially the members of the ACIP maternal pediatric RSV work group and many others from my division at CDC. Next. Thank you.

Q & A

Dr. El Sahly: Thank you, Dr. Fleming-Dutra. I would like to invite my committee colleagues to raise their hands should they have a question to Doctor Fleming-Dutra and Dr. Thornburg. And we will begin with Dr. Offit, I think. Right? Dr. Offit.

Dr. Offit: Yeah. Thanks, Hana. So, my question is for Dr. Thornburg. Given that serotype is determined by the G and not F protein, that the F protein is fairly conserved, then, between RSV subtypes A and B, is there any advantage to including the F, the preF protein, for both A and B in a vaccine, as compared to just doing essentially what GSK did for the over 60-year-olds? Just, say, the F protein, preF protein, for subtype A. Is there any advantage to including both as compared to just one? Thank you.

Dr. Thornburg: Yeah, I don't think if we really know that answer yet, because I don't think we have a good idea yet about like if there's a bias in immune responses against A versus B. Because we've really just started. Whenever we test people, we don't know if they've been infected with an A virus or a B virus. And it's just been within the past, you know, year or two that we have really been able to stand up even A versus B surveillance. So if there's any sort of bias to an immune response, cross protection of immune response, I don't think we know that yet.

Dr. Offit: Thank you.

Dr. El Sahly: Thank you. Please raise your hand in the Zoom should you have a question. I have a question pertaining to what happened in the recent season, the 2022. Peaked early, finished early. Was there a change in the age of infants and children who had medically attended RSV infections or hospitalization due to RSV infection compared to previous or pre-pandemic age averages?

Dr. Fleming-Dutra: Thank you for that question. I will note that the NVSN did collect data on the, both RSV-NET and NVSN have collected data on the 2022 to '23 seasons. For NVSN, those data are still in preparation, but hopefully will be available soon. There may have been, anecdotally, there were certainly lots of reports of older children during the 2022 to '23 season who were hospitalized. I will remind people that that was not the first season since the pandemic started as shown in one of my slides. There was a season, it was atypically timed, but there was a season during '21 to '22, and then there was the large fall viral respiratory surge in '22 to' 23. It may be that there was a bit of a shift in the age of those that were hospitalized.

But what was really different in that '22 to '23 season is one, it was very explosive really. It occurred with a very tight peak. Whereas the season before that was much more prolonged. And then so it really, that '22 fall respiratory virus surge, I think was felt very acutely by hospitals. The other thing is there was many other respiratory viruses circulating at the same time. And so some initial data from NVSN indicates that it may have been partly due to co-infections that there was some shift in age in that season.

Dr. El Sahly: Okay. 'Cause we had the kind of an experiment there on unintentional experiment with the masking and the social distancing. And so we have a whole cohort of infants that were not exposed at the time they should be exposed. And then, anyway. We'll work more on the NVSN data to solidify. I see Dr. Portnoy. Dr. Portnoy.

Dr. Portnoy: Hello. And what a season it was. Our emergency room was completely packed during the fall. I got to walk by it every day, and it was amazing. We had RSV, we had influenza, and we had rhinovirus simultaneously. My question is, it's interesting that hospitalization rates are very high in very young infants, and then they go down. But we know that immunity to RSV is fairly poor, that people keep getting it over and over again. Are these people getting perhaps

asymptomatic RSV infections, and do we have any surveillance information on how frequently people get RSV infections but don't necessarily get hospitalized? And I'm particularly interested in the maternal age, because these are the women who were going to be vaccinated. I'm just wondering if by vaccinating them, we may also be blocking the transmission because of the preventing recurrent infections.

Dr. Thornburg: Dr. Fleming-Dutra, I'm not sure if you'd like me to take it, but I can say a lot of our — there are some human challenge models that have been utilized in RSV in adults. And those challenge models have indicated that half of adults that get challenged with RSV get infected by RT-PCR output. So only 50% get infected even if they've had a recent infection or if they've had a prior infection. And then of those 50% that get infected, about 50% have symptoms. So about 50% of active replicating infections are asymptomatic.

Dr. Portnoy: Okay. So it's possible that these women are having asymptomatic infection even though they're not being hospitalized?

Dr. Thornburg: Absolutely.

Dr. Portnoy: Okay. Thank you.

Dr. El Sahly: I don't see any raised hands. I have a quick question to Dr. Thornburg. You have shown us that in site zero of the RSV F antigen, there are non-synonymous substitutions that do occur. And that's prior to rolling out any vaccines. Is there a way of determining in silico or using, I don't know, certain animals here, et cetera, which ones would result in escape from the responses to the vaccines under development now?

Dr. Thornburg: It's a little bit difficult with RSV F, because we don't know what the cellular receptor is. So there's been a lot of effort into that, and it's not been exactly identified. So with coronavirus, we know that H2 is the receptor. We know the specific residues that spike

binds to in H2 from co-crystallography. We don't have that kind of information, so we don't know the exact residues in the fusion protein or the G protein that contribute to binding or entry or those processes. I think we know sort of the general regions and some residues that are involved that are targets for neutralizing antibodies. And we know those through monoclonal antibodies studies, but those are just that: monoclonal. So every individual has a swarm of antibodies. And I mean literally every individual, and it's driven by their genetics and their prior exposure history. And so each one of those persons has a unique set of antibodies, and so it can differ person to person. So there may be hotspots in the fusion protein, and we can probably identify those. But we can't say with certainty every single person what their antibodies would be targeting on the F protein.

Dr. El Sahly: Okay. Thank you. I guess as we get more, sera from vaccinated individuals, we can potentially begin to answer. Dr. Kim.

Dr. Kim: Thank you. I'd like to ask you, are there any data, any surveillance information, on pregnant people who might have had an RSV infection and that infection might have provided some protection in their newborns?

Dr. Thornburg: Dr. Chu may be talking about this a little bit in her, her talk next. We do know that there is efficient transplacental transfer of antibodies in general during healthy pregnancies during the third trimester. And we know that there is transplacental transfer of neutralizing antibodies against RSV from pregnant persons to infants.

Dr. El Sahly: Yeah, I think there are some epi-data that generally women with higher antibody levels their infants tend to do better during the RSV season, but maybe Dr. Chu will answer better. Dr. Feikin.

Dr. Feikin: Yeah, I have a question. I'm not sure for which one of you. Is there evidence about whether when you have one bottle infection, upper respiratory track [unintelligible].

Dr. El Sahly: Dr. Feikin, your audio is very poor. Do you mind typing the question in the chat?

Dr. Feikin: Can you hear me any better now without the video?

Dr. El Sahly: Yes, we do. Yes.

Dr. Feikin: Okay, good. Because I was having trouble finding the right chat. So my question was whether there is some evidence that if you have an RSV infection in your upper respiratory tract, you're less likely to have a SARS-CoV-2 infection, or vice versa?

Dr. Thornburg: That is a hard answer and I have no idea, Dr. Feikin. Dr. Fleming-Dutra, do you know of any evidence like that?

Dr. Fleming-Dutra: No. I'm also unaware of any evidence to speak to that.

Dr. El Sahly: Okay. I don't see any more raised hands. I would like to thank our CDC colleagues, Dr. Thornburg and Dr. Fleming-Dutra. Next on the agenda I would like to welcome Dr. Helen Chu. Dr. Helen Chu is Associate Professor, Departments of Medicine, Global Health, and Epidemiology at the University of Washington. Dr. Chu will go over the durability of naturally acquired immunity and susceptibility to repeated RSV infections. Dr. Chu.

Durability of Naturally Acquired Immunity and Susceptibility to Repeated RSV Infections — Dr. Helen Chu

Dr. Chu: Great. Thank you, Dr. El Sahly. And thank you to Dr. Kaslow and the committee for inviting me to speak to you today. The title of my talk is Clinical Considerations of RSV in Infants from Birth to Six Months of Age. Next slide. These are my conflicts of interest. And next slide.

So, in this talk, I will describe the characteristics of maternal and infant RSV infection, the risk of infant hospitalization by age, the risk of infant primary and repeated infection by neutralizing antibody, and briefly go over the burden of disease in pregnant persons. And then I will discuss the transplant RSV antibody transfer and kinetics in normal healthy pregnancies, antibody half-life and duration of production, and the impact of gestational age and other factors including maternal HIV and malaria on antibody transfer across the placenta. And finally, other considerations including breast milk antibody, the potential use of a maternal vaccine in conjunction with a monoclonal antibody, and data on concomitant administration with Tdap. Next slide.

So as Dr. Fleming-Dutra covered very nicely, RSV causes bronchiolitis and pneumonia and is the number one cause of hospitalization for infants in the United States. We know that nearly all children are infected at least once by three years of age. However, repeated infections occur throughout their lifetime indicating a lack of sterilizing immunity with the first or subsequent infections. Despite the high numbers of infants who are hospitalized, the burden of disease in infants who are not hospitalized is very, very high. There are impacts on school and work absenteeism, which is quite significant among children under three years of age. In a study, it was shown that the mean duration of illness in these children is 13 days, and parents miss over one day of work in over half of the cases, with a mean duration of 2.6 workdays missed. For RSV, we have supportive treatment only with no RSV-specific treatments currently licensed for use in young children. And palivizumab, a monoclonal antibody against the F protein, provides proof of concept for the protective effect of antibody directed against the F protein in young infants. Next slide.

We know that infants are at high risk of RSV infection under six months of age and that this decreases with older age. However, the risk of hospitalization remains high in older age groups. In this graph, you can see hospitalization rates per thousand infants on the y-axis and age on the x-axis. Next slide.

And what I wanted to point out is compared to the 2016 to 2020 season in 2021, when we had multiple birth cohorts of infants who had not seen RSV for the past several years, we saw increases not only in the zero to five month age group, but also increases in the 6 to 11, 12 to 23, and the older infants as well, or the older children as well. Next slide.

We know that infants have high rates of primary infection in their first year of life. This is a study called the Houston Family Study done by Paul Gleason in Houston, Texas, where he followed infants from birth up until five years of age, and he sampled them with repeated blood draws as well as nasal swabs at times of illness. So the rate of primary infection in these infants was 69 per hundred child years. But what you can see is that over the course of the first five years of life, the rates of reinfection remained quite high. 75.9 in the one-to-two-year age group, 45.3 in the 25 to 36 months, and going down over time. Importantly though the rates of reinfection were high, the rates of lower respiratory disease, which was defined as bronchitis, tracheal bronchitis, croup, or pneumonia remain lower with subsequent, reinfection. Next slide.

We note both from the palivizumab studies as well as from natural history studies, the higher cord blood RSV neutralizing antibody delays disease in infants. This is, again, a study by Paul Gleason's Group in Houston looking at cord serum antibody titers in infants who are hospitalized with RSV infection. And what you can see is that the higher the cord blood antibody titer, the later the age of primary infection. The thing I would like to point out though, looking at this figure and at many studies that have been done since then in more recent cohorts, is that

there's quite a range of neutralizing antibody in those who are hospitalized with their primary RSV infection, indicating the RSV neutralizing antibody is partially protective, but obviously is not the whole picture. Next slide.

We also know from the studies in Houston, the higher levels of neutralizing antibody are protective against repeated infection, in particular lower respiratory tract disease. Here you can see in this table that as the neutralizing antibody titers increase, the rates of reinfection decrease, ranging from 82.6% down to 11.8%. And again, the rates of lower respiratory disease are much lower than the rates of simply RSV reinfection. Next slide.

The data on RSV burden in pregnancy is sparse. However, in the last 5 to 10 years, a couple of studies have been done in countries around the world, including a study in Nepal, in Mongolia, and South Africa. And all three of these studies were community-based studies looking at respiratory illness in pregnant persons either year-round or during the flu season. And across all three of these studies, what you can see is that the prevalence of RSV infection in pregnancy is quite low, ranging from zero.2% in Nepal, up to 2% in HIV-infected pregnant mothers in South Africa. The one study from the United States that has been published is from Houston, Texas in pregnant persons who are presenting for care with respiratory illness between the months of October through May. And here you can see that 10% of those presenting for care had RSV detected. However, this was not the same as the community-based studies that were done in in Nepal, Mongolia, and South Africa. Next slide.

So now I'd like to go over some data on transplacental RSV antibody transfer. Next slide. So what we know is that vaccines that are given during pregnancy increase maternal antibody titers and lead to increases in transplacental antibody transfer. So in the figure on the left, what you can see is what happens during the normal pregnancy. We estimate that antibody transfer

starts primarily in the second trimester but really increases over the course of the second and the third trimester, so that by the time of birth, the infant antibody titers often exceed that of the mother's. What happens is that this decays rapidly after birth, however, leaving a window of vulnerability before infants are able to mount their own immune response to either infection or vaccination. The principle behind maternal vaccination is that you take this antibody titer and you boost it up to a much higher level, thereby closing this window of vulnerability. One of the effects of this boost in antibody titer, however, is the potential decrease in the infant immune response, which we call blunting, to their first vaccine or exposure, which has been seen with both measles and with, Tdap. Next slide. It takes approximately two weeks to mount an antibody response to your vaccine. And then over the course of the pregnancy, this antibody is transferred across the placenta. Next slide.

So there are multiple factors that impact transplacental antibody transfer. This is a figure showing the separation between the maternal and the fetal circulation by the syncytiotrophoblast layer. So of the immunoglobulins that are in the maternal circulation, only IgG is transferred across the placenta. So IgG is taken up in endosomes and in an acidic pH complexes to the neonatal FC gamma receptor. It is then transported over and released a physiologic pH into the fetal circulation. Next slide.

What we know is that vaccine-induced antibody transfer is impacted by multiple factors including IgG subclass, gestational age, maternal HIV and malaria, and hypergammaglobulinemia. We know that IgG1, which is induced primarily by protein antigens, is transferred preferentially compared to IgG2, which is induced by polysaccharide antigens. We know that the more full term the infant is, the more antibody is transferred across the placenta, and that the maternal HIV and malaria impact transplacental antibody transfer either through

placental inflammation or potentially through high levels of nonspecific IgG, which impacts the ability for disease specific IgG to transfer across the placenta at high rates. Next slide.

In a study done in Bangladesh following mother-infant pairs from pregnancy until 72 weeks after birth, we examined RSV neutralizing antibody titers during this time period in both the mothers and the infants. We found that maternal RSV antibody titers were highly correlated with cord blood antibody titers with an antibody half-life estimated at 38 days. And the higher cord blood RSV antibody was associated with decreased risk of infant serologic RSV infection, as well as a longer time for infant RSV antibody titers above a potentially protective threshold, which redefined as log-based two of eight based on studies done by Tony Piedra's group at Baylor University showing that that level was protective against hospitalization and infants. Next slide.

These are side-by-side scatter plots showing that antibody titers are stable across pregnancy and transfer efficiently at the time of delivery. In the panel on the left, what you can see is maternal antibody titers in this third trimester and maternal antibody titers at birth. And what you can see is that they are highly correlated. And in the panel on the right, maternal antibody titers at the time of delivery compared to cord blood antibody titers. Again, highly correlated, with any value falling above the diagonal line indicating greater than 100% antibody transfer. Next slide.

We know that antibodies stay stable throughout pregnancy and declines in infants in the first four to six months after birth. And here in the panel on the left, you can see maternal antibody from third trimester until birth stays stable and then again stable until 72 weeks after birth. In infants, the antibody titers are highest at time of birth and decline over the first six

months of life, and then between 24 to 72 weeks, infants are exposed to RSV and mount their own antibody response to RSV infection or exposure. Next slide.

This is a Kaplan Meier curve showing the median time for RSV antibody to drop below a potential protective titer of log base two of eight, and we estimated this at approximately 17 weeks, so three to four months after birth. Next slide.

We know that transplacental antibody transfer increases with gestational age. It's estimated that 10% of antibody has transferred by the beginning of the second trimester, 50% by the end of the second trimester, and greater than 100% by birth. And you can see that this is the case for measles, mumps, rubella, and varicella vaccine. Next slide.

What we also know though is that preterm infants are at the highest risk for severe RSV infection, making them most likely to benefit from maternal antibody. So as you think about the timing of a potential maternal vaccine to be given during pregnancy, there is the need to give it early enough to protect the preterm infants, but to also optimize transplacental antibody transfer during the third trimester. Next slide. Next slide.

And finally I'll go over a couple of other considerations to think about as we discuss maternal vaccination strategies. Oh, sorry, it is early in the morning. Okay, next slide. Okay, so one of the things that we know is that breast milk antibody is protective against respiratory infections. And from studies of maternal flu vaccine, we know that higher levels of IgA generated by vaccination are protective against respiratory infections in infants. In a natural history study in Nepal, we evaluated breast milk prefusion RSV antibody and found the higher levels of breast milk prefusion IgG were associated with protection from RSV infection in infants. Next slide.

Some of the things to consider when you think about a potential use in combination with a birth dose monoclonal antibody, based on the data that I've shown so far, is that maternal antibody is estimated to last three to four months after birth. The infants that are born preterm have lower levels of transplacentally-acquired antibody and are more likely to benefit from a monoclonal antibody that is administered at birth. However, to date, there is no published data to show the effect of maternal RSV vaccine on birth dose monoclonal antibody titers, though we would not expect interference from the polyclonal response generated from vaccination. Next slide.

One other potential concern is whether or not infants are able to mount an effective immune response to natural RSV infection in the presence of high levels of circulating antibody, either from vaccination or from monoclonal antibody administration. So this was a paper that was published three weeks ago evaluating infants that were enrolled in the nirsevimab trial, I believe it was the Melody trial, where they evaluated infants who did and did not have natural RSV infection. And in this case, they measured post-F antibody levels as a marker of natural RSV infection because nirsevimab is a preF antibody. And what they found was that in infants in both the placebo and the NIV arm, they were able to mount post F response to natural RSV infection and that these, these rises were similar between the two groups, indicating that in the presence of high levels of circulating antibody, infants are still able to mount that response. Next slide.

And the final thing I wanted to discuss is the data on concomitant administration. So most likely what will happen with a maternal RSV vaccine is that it will be administered in the same visit as the Tdap vaccine because the timing of that at the beginning of the third trimester optimizes antibody transfer to the infant. And this is a study that was done in healthy non-

pregnant women aged 18 to 49 years where they compared separate administration of Tdap and RSV compared to concomitant administration of Tdap and RSV. Well, they found that having the two vaccines administered together led to non-inferior immune responses to tetanus, to diphtheria, and to RSV, but they did find inferiority in the responses to anti-PRN, anti-FHA, and anti-pertussis toxin. It is not clear what the clinical significance of this is, but it does demonstrate that there is lower antibody to the pertussis component of the Tdap vaccine when co-administered with RSV in non-pregnant women. And it's also not clear what this will look like in pregnant women, because there will be impacts, obviously, on transplacental antibody transfer, as well, with lower levels. So, next slide.

So in conclusion, RSV causes severe disease in young infants and repeated infections throughout childhood. Serum RSV neutralizing antibody is protective, though not fully, against severe disease and repeated infections. Maternal antibody transfers across the placenta and is impacted by gestational age as well as other factors including total IgG levels as well as maternal HIV and malaria. We estimate the durability of maternal antibody above a potential protective threshold is approximately three to four months, and that factors including concomitant administration with other maternal vaccines such as Tdap, as well as potential blunting of an infant immune response to subsequent infections or vaccines are things that will need to be monitored over time. So thank you.

Q & A

Dr. El Sahly: Thank you, Dr. Chu, for this presentation. I would like to invite my committee colleagues to use their raise your hand function in the Zoom to ask questions to Dr. Chu. I will begin with the Tdap concomitant administration. Somewhere in the 20 to 30% range, reduction in antibody levels against the three tested antigens. And we do know that transfer across the

placenta is a fraction. So if we are decreasing the antibody levels by 20 to 30% on the mother, we expect the child or the infant to have a, you know, a relative similar reduction in their antibodies. What would that look like? Especially with us using acellular pertussis vaccines that are, you know, we do know that they are, they work not as well as cellular, but they do. And we rely so heavily on that vulnerability window you described for pertussis. What would you think the implications would be on childhood mortality if we are to reduce their pertussis antibody levels by a factor of 20 to 30%?

Dr. Chu: Yeah, that is an excellent question and I think a major concern to think about. With actively transported antibody, the levels in the infant are often higher than the mother's by the time of birth. So we do expect those levels to be higher. But of course will be lower when given in combination with the RSV vaccine, assuming that this holds in larger studies. Because this was not done in pregnant women. It was in healthy non-pregnant women. I don't know that we have a clearly established threshold of protection for prevention of hospitalization for pertussis antibody. So I think that is also to be determined. But I agree that this is a concerning finding and should be repeated, particularly in pregnant women with an evaluation of antibody in cord blood.

Dr. El Sahly: Yeah, well, but, you know, generally speaking, pregnant women are young, have the young healthy adult response to most vaccines, so we expect it to be comparable, at least for now. Dr. Bernstein.

Dr. Bernstein: Thank you for that wonderful talk. I just wanted to know whether you had any comments about the window for these current RSV vaccine studies in pregnant women are ranging from 24 to 36 weeks. Given what you know about antibody durability and transfer, would you comment, or could you comment on whether giving it 24 to 29 or 30 weeks would be

advantageous versus 30 to 36? I believe that's the case and when Tdap should be administered. Thank you.

Dr. Chu: Yeah, that's correct. That's also an excellent question. I think that there have been more and more studies showing that earlier vaccine administration is better in pregnancy, that the earlier that you administer the higher the cord blood antibody titers. The studies have really been done with Tdap rather than with other vaccines. We have also done studies with influenza showing non-inferior immune responses with second versus third trimester flu vaccination. I would say that given the risk of disease in preterm infants and the potential to miss that window, it is better to vaccinate earlier. So that would be my recommendation.

Dr. El Sahly: Dr. Monto.

Dr. Monto: That was a great presentation, Helen, at a very early hour. Influenza, as you well know, is known to cause problems in pregnant women, and we're now pushing influenza vaccination of pregnant women. Any information about co-administration?

Dr. Chu: Not that I'm aware of in this particular population. GSK and Pfizer both have co-administration studies in older adults, which shown non-inferiority of antibody titers to flu and RSV when given together. Let me see. I think that if you wanted to pull that up, that is slide 28 in my slide deck.

Dr. El Sahly: The product we're reviewing today from Pfizer. We, you know, Arnold, I know you missed the meeting in February. The co-administration in young healthy adults of the Pfizer product without the adjuvant. We were, you know, the briefing document indicated interference, but the study had a smaller sample size. And a larger study looking at this particular question is underway, but we don't have those data. We didn't have them in the last briefing document, and I

didn't see it with the data now. But yes, that is a major issue that was discussed at length a couple of months ago.

Dr. Monto: Thank you.

Dr. Chu: Right. It'll be Tdap, flu and RSV.

Dr. El Sahly: Yeah. And we have information that, I mean, even if you look at the slide that you showed, so this is the adjuvant product, which is not under discussion today. You can argue that there's a 15 to 20% reduction. We said that we will not live with 50% reduction, but there is 15 to 20% reduction even with that different product.

Dr. Chu: Right, right.

Dr. El Sahly: So anyway. Well, thank you Helen. This was great. And I don't see any more raised questions. So thank you again. On the agenda, we have a 10-minute break. We are on time. So now it's 10:20 Eastern. We will reconvene at 10:30 Eastern.

Dr. El Sahly: Welcome back everyone. The next hour is dedicated to the sponsor presentation and Q and A. The sponsor presentation will be pertaining to bivalent RSV prefusion F vaccine for maternal immunization to protect infants. Doctors William Gruber, Dr. Eric Simoes, Dr. Iona Munjal, and Jamie Wilkins will be going over the sponsor presentation. Dr. Gruber.

Sponsor Presentation: Bivalent RSV Prefusion F Vaccine for Maternal Immunization to Protect Infants

Introduction — Dr. William Gruber

Dr. Gruber: Thank you. Good morning and thank you members of the committee, FDA, and members of the audience for the opportunity to present today. My name is Bill Gruber, and I am a Senior Vice President at Pfizer and Head of Vaccine Clinical Research and Development. My co-presenters and I are pleased to share data from our maternal vaccine program for our bivalent

RSV prefusion F candidate. I will provide an introduction describing the path to maternal immunization against RSV. Dr. Eric Simoes will follow with a description of the unmet medical need. Dr. Iona Munjal will then review the clinical development plan with emphasis on clinical safety analysis and pivotal trial efficacy. Dr. Jamie Wilkins will then describe pharmacovigilance and surveillance plans, and I will conclude with a description of expected benefit risk. We will then be pleased to address any questions.

The road to having an RSV vaccine that could provide protection against RSV in infants has been frustratingly long and difficult. It began with the discovery of the virus as a cause of infant bronchiolitis in 1957. Vaccine development efforts began in earnest leading to an investigational, formal, and inactivated RSV vaccine in the 1960s, which not only failed to protect, but resulted in enhanced RSV illness for some infected infants. This stymied development until in the late 1970s when Dr. Paul Gleason and collaborators demonstrated that RSV's specific antibody following natural infection in women could be passed to their infants and provide protection during infancy. As a medical student, I had an opportunity to help Dr. Gleason identify children with bronchiolitis from whom cord blood sera for antibody testing was available. Thus began my own career-long quest for an effective RSV intervention.

Paul's discovery was followed by purified F protein, live attenuated RSV vaccines and vectored vaccine approaches. In tandem, the first successful passive antibody interventions were approved, but only for very high-risk infants. However, neutralizing antibody levels in recipients serve as an important benchmark for vaccine-induced antibody likely to provide protection. Much of the inactivated vaccine effort remain focused on the RSV fusion, or F, protein. RSV F is largely responsible for fusion of the virus membrane to the host cell membrane and entry of virus contents. However, purified first generation versions of the F protein or other derivatives failed

to induce sufficient neutralizing antibody for protection in adults or older seropositive children. No RSV F vaccine has been licensed to date for maternal immunization to protect infants. We now know why.

Structural work by Jason McClellan and collaborators in the NIH Lab of Dr. Barney Graham elucidated that RSV F on the virus exists in an unstable prefusion form. Only prefusion F can bind host cells for RSV to infect. It turns out that prior failed inactivated vaccine attempts were using the postfusion, or spent, form of RSV F shown on the right, a weak inducer of virus neutralizing antibody. In contrast, the prefusion F trimer, shown on the left, which we call RSVpreF, is a very potent inducer of neutralizing antibody and animal models in humans. Jason and colleagues were able to stabilize RSVpreF. Pfizer then further stabilized the protein and developed a bivalent RSVpreF vaccine including both A and B subgroups to maximize protection. This is the same vaccine which we described to you when seeking the older adult indication for prevention of RSV illness.

What was our rationale for a bivalent RSV prefusion F vaccine? Historically, RSV vaccines targeting F have been monovalent with sequence based on the RSV A subgroup. This is largely based on the high level of sequence identity between RSV A and RSV B F proteins, as well as the high level of F-based cross neutralization between the A and B subgroups. However, the sequence variability between RSV A and B F proteins, highlighted in blue on the structure on the slide, localized to the prefusion specific site zero. A bivalent RSV vaccine containing one prefusion F construct each from the RSV A and B subgroups could elicit more balanced immunity to the two subgroups, which we have shown in both preclinical and clinical studies, compared to other monovalent prefusion F vaccine candidates.

A recent analysis of global RSV epidemiology supports the conclusion that Ontario RSV A and Buenos Aires RSV B remain dominant genotypes and are the basis of Pfizer's RSVpreF bivalent vaccine. We also know that RSV A or RSV B viruses can dominate from season to season, and both subgroups are associated with severe disease outcomes. For the rest of the presentation, I will refer to this vaccine candidate as RSVpreF.

As you've heard, RSV is the leading cause of lower respiratory tract illness in infants, responsible for up to 80% of bronchitis. The potential for the vaccine to meet this medical need was recognized and acknowledged by the FDA based on the portfolio of studies and high efficacy and safety profile in Matisse, shown on the right side of this slide. The FDA granted RSVpreF breakthrough therapy designation and priority review for the Biologics License Application for immunization of pregnant individuals for protection of their infants. We are grateful to the FDA for working with us to reach agreement in advance about study design and, importantly, safety and efficacy licensure criteria.

We will share with you results from RSVpreF clinical development, including the pivotal Matisse study meeting these pre-agreed licensure criteria. This investigation demonstrated 82% efficacy at three months and 69% efficacy over six months of age against severe RSV lower respiratory tract illness, with efficacy observed against less severe disease. The vaccine was well tolerated with a satisfactory safety profile. Therefore, having met pre-specified licensure criteria as agreed to by the FDA, we are seeking the following indication for the Bivalent RSV prefusion F vaccine: the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by RSV in infants from birth through six months of age by active immunization of pregnant individuals.

The dose level is 120 micrograms without an adjuvant. Each dose contains 60 micrograms of each prefusion protein antigen, A and B, in a 0.5 milliliter injection. The presentation is a lyophilized vial with water for injection in a prefilled syringe. The vaccine is to be stored at two to eight degrees Celsius. So let's now turn to Dr. Eric Simoes to describe the RSV disease burden in US infants. As you know, Dr. Simoes has also had a longstanding career interest in preventing RSV illness in infants and has made numerous contributions to this effort. Dr. Simoes.

RSV Disease Burden in US Infants — Dr. Eric Simoes

Dr. Simoes: Thank you very much, Bill. Good morning, members of the audience. My name is Eric Simoes and I'm a Professor of Pediatrics and Epidemiology at the University of Colorado at Denver. I'm going to discuss the burden of RSV in US infants. Here are my potential conflicts of interest. Almost all of these relate to RSV. I have been compensated for the time and travel associated with this presentation, and the University has received grant support for the maternal immunization trials being discussed here.

It has long been recognized that RSV has been a leading cause of lower respiratory tract infections in infants. I've seen this unchanged in the last 30 years, be it Black Lion Hospital in Ethiopia 30 years ago or two months ago. The same is true in Colorado, where I have practiced pediatrics for the last 37 years, and around the United States. The walls are full of babies less than six months of age with severe RSV LRTI during the season. It often overwhelms our pediatric practices, emergency rooms, and hospitals during the winter. It causes up to 80% of infant bronchiolitis. There's nothing more distressing for parents than the frightened look of their three-month-old infant struggling to breathe, being unable to feed. RSV left untreated can lead to severe respiratory distress and even death. We have estimated that globally, RSV LRTI sickens

up to 33 million under five years of age annually, one fifth of which occurs in infants under six months of age, and about 120,000 deaths annually, 97% of which are in developing countries. Finally, we also know that RSV-associated with long-term sequelae, specifically recurrent wheezing and some forms of asthma in later childhood.

I will now focus on the US burden. This data is from the late Karen Hall over the 2000 to 2005 RSV winter seasons in the United States. The rates of outpatient visits in children under five years of age are in gray, ED in red, and hospitalization in blue. Up to a quarter of babies have been seen in the office practice for RSV LRTI in the first year of life, with lower rates in the emergency department. The majority of hospitalizations occur in the first year of life, mostly in the first six months of life. RSV hospitalization is the major contributor to the direct and indirect economic burden of RSV LRTI.

Karen's initial active surveillance studies have been expanded over the last 20 years. Rainisch used Dr. Hall and her team's active surveillance data between 2000 and 2010 to estimate the month-wise burden of RSV hospitalization in infancy, represented by orange bars. Colleagues use similar data from seven-year centers from the 2016-17 season, represented by the blue bars. One can see that the RSV hospitalization rates are highest in the first six months of life.

Shown here is population-based data of RSV hospitalization from over a hundred hospitals, collected between 2000 and 2020, presented in part at an RSV meeting in Belfast last year. In gray are the rates of RSV hospitalization. Pediatricians know that not all bronchiolitis is tested for RSV, hence represented by yellow bars are the rates of hospitalization for untested bronchiolitis added to RSV hospitalization. I would like to conclude that regardless of method, 78 to 82% of RSV hospitalizations occur in the first six months of life.

Both our estimates are higher than those found by active surveillance methods, which underestimate the burden of hospitalization. Likewise, the CDC has conducted nationwide studies looking at the emergency department and outpatient clinic visits over the last several years, illustrated in this and the next slide. The upper graph illustrates that by four months of age, almost one in eight children visit an ER for RSV LRTI. And the lower graph shows that about two thirds of all infant emergency room visits occur in the first six months of life. The same is true of outpatient visits. The majority of outpatient visits occur in infants less than six months of age, accounting for 56% of all outpatient visits.

Finally, as a pediatrician working at an academic institution, I would like to point out that the severe RSV appears to disproportionately adversely affect the most vulnerable in our populations. Medicaid recipients are hospitalized at twice the rate of children with private insurance, accounting for 56% of ED visits and almost two thirds of the US burden of hospitalizations, of the aggregate costs, and of all RSV related deaths. Unfortunately, these babies often miss their well-child visits in the first year of life, but fortunately at least 90% of their mothers attend at least one antenatal visit prior to delivery, allowing for an opportunity to provide protection against RSV with maternal immunization.

I'd like to conclude by saying that RSV is the single most important cause of hospitalization in infancy. It causes between 56,000 and more than 70,000 hospitalizations in the US annually, and more than that if one counts undiagnosed seasonal bronchiolitis cases. RSV overwhelms pediatric practices, emergency departments, and hospitals throughout the country during the winter months, especially the last two seasons post-pandemic. Between 50 and 80% of this burden, especially its more severe manifestation of hospitalization and ICU use, occur in the

first six months of life, and Medicaid recipients form a disproportionate share of this burden. Thank you. I will now turn the presentation over to Dr. Munjal from Pfizer.

Clinical Data — Dr. Iona Munjal

Dr. Munjal: Thank you, Dr. Simoes. My name is Iona Munjal, and I'm a Senior Director at Pfizer and Vaccines, the Global Clinical Lead for the Maternal RSV Immunization Program, and a pediatrician. Before I start with the data, I'd like to express my gratitude to the participants and their families who contributed to the trial, particularly as it occurred in the middle of the global COVID-19 pandemic. And we also give thanks to our tremendously dedicated teams, including our investigators and site staff who are so diligent in the conduct of the study and took such care with these participants.

Pfizer's maternal RSVpreF program is comprised of five clinical studies, a large first-in-human study, additional non-pregnant, non-concomitant, lot consistency studies, and two studies in pregnant participants. All of these studies together comprise 5,000 women who are exposed to the active vaccine and are outlined in Pfizer's briefing document for reference. For the presentation today, I will focus on our two studies conducted in maternal participants. The first study we will discuss is the phase 2b trial that was designed to confirm the dose tolerability and safety in pregnant participants and their infants. Key findings were robust maternal immunogenicity at delivery and antibody persistence in infants through six months of age.

To start, we can review the design of the 2b study, which looked at healthy pregnant participants 24 to 36 weeks gestation who met predefined screening criteria. The study enrolled close to 600 maternal participants. If they remained in the study, their infants were also enrolled. The trial was largely performed in the US, which contributed over 500 participants. Most enrollments started in 2019, prior to the COVID-19 pandemic. Each participant was randomized

to two different preF doses, 120 or 240 micrograms, and formulations with and without aluminum hydroxide, or placebo. The study included maternal blood draws of vaccination through the pregnancy and the delivery period and serology in infants for six months after birth. For today's presentation, I will focus on the data from the participants who received the final selected dose of 120 micrograms, as all doses and formulations showed similar responses in infants.

I'd like to draw your attention to the key immunogenicity data from the phase 2b study. These graphs show geometric mean titers from a functional neutralization assay using RSV A and B antigens based on maternal serology samples taken during the phase 2b study. Blue represents the preF vaccinated participants, and gray is the placebo. The neutralizing geometric mean titers are robust at 15-fold higher than baseline one month after vaccination. Moreover, the responses remain high at delivery with a GMR at robust 11.2 on the left and 13.6 on the right for RSV A and B, respectively. The meantime from vaccination to delivery in the study was about two months.

To demonstrate that the high maternal antibodies are passed to the infants during delivery, I'm now showing you the neutralizing geometric mean titers for paired samples of mothers, in blue, and their corresponding infants, in green. RSV A and B responses are combined in this graph. Regardless of the gestational age of the mother at vaccination, from 24 to 36 weeks, the infant titers are consistently higher at birth, likely due to active transplacental transfer during pregnancy. Although there is no correlative protection for RSV, we tested neutralization with palivizumab at a dose of a hundred micrograms per ml, which is the approximate level that demonstrates protection from intensive care admission. This served as a contemporaneous reference for a level that might represent protection and is shown as the red line for

demonstration purposes. The transplacental transfer ratios for each pair are consistently greater than one.

Now, let's take a look at the infant data after birth. You can see here that the kinetics of the antibody responses in infant participants at birth, one, two, four, and six months after birth show geometric mean neutralizing titers for the preF group, in blue, remain higher than the placebo, in gray, at all time points, suggesting protection to at least six months of age. Palivizumab titers are again shown in red for demonstration purposes for a level that might represent protection.

I'll now present data from our pivotal global phase three Matisse study, or the Maternal Immunization Study for Safety and Efficacy. We knew that Matisse was unique and could be the first successful efficacy maternal vaccine trial for RSV, so care and diligence was taken to get key input on trial design prior to initiation. Following the Phase 2b study and prior to the start of phase three, agreement was obtained with the FDA on the study endpoints, safety dataset, definitions, and trial conduct. Specifically, an agreement was reached that vaccine efficacy in either of the primary endpoints of MA LRTI or severe MA LRTI, with a lower bound of greater than 20% for the confidence interval would be sufficient, and that at least 3000 mother infant pairs exposed was a sufficient safety database for licensure. We also worked with key stakeholders to develop a study that was participant centered and integrated into routine care. This was particularly important during the COVID-19 pandemic.

The trial design and conduct were formed by experienced investigators, experts in the field, nurses and coordinators who conduct trials in maternal populations, and most importantly by pregnant persons and their partners from key regions through extensive surveys. Matisse was conducted in 18 countries globally, with over 200 sites. Over 7,000 vaccinated mothers were

enrolled. Their infants were included if born prior to the primary analysis. We did not show the participants by country, but the largest contribution came from the United States, with 45% of the overall participants. And approximately a third of the participants were from low and low-middle income countries, where the burden of RSV disease each year is the highest.

The efficacy surveillance period for the infant participants was designed to cover four RSV seasons, two in the northern and two in the southern hemisphere. Due to disruptions in seasonality during the pandemic, enrollment was targeted year round. Matisse is a double blind, randomized, controlled phase three efficacy trial. Maternal participants were enrolled if they were 49 years or younger. Vaccination occurred when participants were between 24- and 36-weeks gestation. Participants had to meet qualifying criteria, including basic prenatal care, but to assess a larger population, pregnant women with underlying stable conditions, including diabetic conditions and hypertension, were included. Participants were randomized one-to-one with either the study vaccine or placebo, and the participants who were randomized to the preF group received a single dose of the 120-microgram bivalent vaccine.

The study began in June of 2020 with the primary analysis conducted in September of 2022. The average age of the infants at the primary analysis with this nine months, and long-term safety follow-up of the cohort is ongoing until the last infant completes the study in late 2023. Key maternal demographics are highlighted here for the over 7,000 participants and reflect the diverse population in this global study. Demographics were similar between the two groups. The average maternal age of vaccination was 29 years, with participants ranging from 14 to 47 years overall. Data was generated in adolescent participants and in pregnant participants of advanced maternal age, and we proposed to include them in the indication. The average gestational age of vaccination was 31 weeks, with good representation across all gestational ages of vaccination. I

will now show demographic data from our infant participants. Like their mothers, they represented a diverse population. Demographics were similar between the two groups.

Let's take a look at the tolerability and safety of the vaccine in maternal participants and their infants. The primary safety objectives include local reactions and systemic events after vaccination in the maternal participants. All adverse events are collected through one month after vaccination in the maternal participants, and all adverse events through one month after birth in the infant participants. Adverse events of special interest, serious adverse events, and newly diagnosed chronic medical conditions were collected throughout the study. Adverse events of special interest are specific, solicited terms we asked the investigators to report throughout the study period and are defined here. Independent safety oversight is conducted by an external data monitoring committee who continues to periodically review cumulative unblinded data on all participants.

All maternal participants were monitored with an e-diary mobile device, soliciting adverse events for seven days following vaccination. All adverse events were collected for a month. Delivery events were captured as they occurred after vaccination, and in most participants, delivery occurred outside of the adverse event one-month period after vaccination. The average time from vaccination to delivery was 58 days. Adverse events of special interest, or AESIs, including preterm delivery and serious adverse events were collected throughout the study period to capture infants around all deliveries. Surveillance for respiratory illnesses in the maternal participants was conducted through chart reviews, but swabs were not taken.

I will start with the reactogenicity that was solicited in the vaccinated maternal participants in their e-diaries. The graphs represent the solicited local reactions. The events were mostly mild, in green, or moderate, in blue, and higher in the vaccinated group. Most events

resolved quickly in about two to three days. The most commonly reported local reaction was injection site pain. The solicited e-diary systemic events by maximum severity, again for maternal participants following vaccination, are shown in these graphs. The events were mostly mild or moderate and resolved in two to three days. Few fevers were reported overall and were similar between the preF and placebo group. The most commonly reported event, fatigue, was similar between both groups. Headache and muscle pain were the only systemic events reported more frequently in the non-placebo group compared to the placebo group.

Here we see all adverse events by category in the maternal participants. In each subcategory, the events are low and comparable between the preF, in blue, and the placebo group, in gray, including in the categories of serious adverse events, related events, and adverse events of special interest, including preterm delivery. Of the serious adverse events in the second pair, five were assessed as related by the investigators, including four in the preF and one in the placebo group. These are described in both our and the FDA's briefing documents. All the related events that we describe are reported as being resolved, and there were no related SAEs in infant participants. As I'll show in the next slide, most adverse events were related to pregnancy and delivery.

Here's more detail on the types of adverse events reported within one month of vaccination. As you can see, the most common reported events were typically those related to pregnancy or delivery and were comparable between the vaccine and placebo group. Most events occurred in less than 1% of participants. Premature delivery and SARS-CoV-2 positive tests without respiratory symptoms are adverse events of special interest, and they are therefore actively solicited throughout the study.

Let's now review safety in the infant participants. All infants were scheduled to follow for at least one year. 55% of the enrolled infants were stratified to be followed for up to two years, allowing us to characterize safety outcomes long-term. Unsolicited adverse events were collected from birth to one month after birth. Solicited adverse events of special interest, serious adverse events, and newly diagnosed chronic medical conditions were collected throughout the study period.

In this slide, you can see all the adverse events by category in the infant participants. The events were comparable in frequency, and no differences seen between the RSVpreF and placebo groups in all the categories shown. These include serious adverse events, adverse events of special interest, congenital anomalies, and newly diagnosed chronic medical conditions. The most common events reported within the first month after birth were typical of the newborn period and were comparable between the vaccine and placebo group. Some terms were solicited as adverse events of special interest in infants like the mothers, and these include premature baby and low birth weight baby.

I'll now discuss those birth outcomes in more detail. In this slide, we show details on birth outcomes and developmental delay, represented for preF in blue and placebo in gray. The preF and placebo groups were comparable when looking at rates of prematurity, low birth weight, and developmental delay. When looking at infants born less than 37 weeks, nearly all were born late preterm between 34 and 37 weeks. The from vaccination to delivery was comparable in both groups, and most babies were born more than 30 days after vaccination. This was true of both preterm and term births. As shown on the left columns, very few infants were born less than 34 weeks. Confidence intervals overlapped both in the infants less than 34 weeks and in the infants less than 37 weeks.

The overall numerical imbalance in total premature infants that's shown here led to a re-review of all the data, and as we note in the briefing document, it was driven by a difference observed in upper middle-income countries, notably in South Africa. No imbalance in preterm births were observed in high income countries, which includes the United States, or in low and low-middle income countries. When looking at the birth outcomes listed here, I want to point out that the low birth weight is a potentially more objective outcome, which does not have the variability introduced by ultrasound timing for gestational age, and is shown in the paragraphs to the right of prematurity for very low, low, and normal birth weight. The difference between the treatment groups with regard to low birth weight was less than that observed for the preterm birth outcome. And in the lowest birth weight category, events occurred twice as commonly in the placebo group. When comparing the events of prematurity and low birth weight together, less than half the preterm infants were low birth weight. No observed adverse effects, including no increase in mortality, was seen in premature or low birth weight infants.

Now, let's examine the fatal outcomes in the study. This slide summarizes all maternal deaths and fetal losses reported in the trial. All deaths in the study were deemed not related by the investigator and sponsor. There was a single maternal death, which occurred in a woman in the Philippines approximately two months after vaccination. She unfortunately unexpectedly had a home birth and died of hypovolemic shock secondary to postpartum hemorrhage. The majority of the pregnancies in the vaccinated mothers resulted in live, healthy births, so fetal deaths were rare and reported 10 in the preF and 8 in the placebo group. The incidence rate of fetal deaths in maternal participants who received preF was lower than expected background rates.

Overall and by subcategory, the distribution of deaths in infants was not significant enough to indicate an overall benefit, but the numbers were favorable toward the vaccine. There

were 17 infant deaths overall at the time of the analysis, 5 in infants born to RSVpreF vaccinated mothers, and 12 in infants born to placebo recipients. There's only one infant death associated with RSV, and that infant was in Japan and in the placebo group. There were three deaths at any time in premature infants, or those born before 37 weeks gestation. They were distributed one in the vaccine and two in the placebo group, and died at 5, 34, and 72 days of life. There were seven neonatal deaths, or deaths within the first month of life. All were in low-middle income countries.

The only preterm infant death in the preF group was also a neonatal death. This infant was born in South Africa to an 18-year-old primigravid mother who presented with spontaneous labor within two weeks after vaccination. As often is the case, an underlying etiology for the preterm birth was not identified other than the maternal young age. This was considered not related to the vaccine by the investigator. The FDA noted they were unable to exclude the event being related to the investigational product.

In summary, RSVpreF was safe and well tolerated. Local and systemic events were mostly mild to moderate and short in duration. The adverse event profile did not suggest any safety concerns for RSVpreF vaccination in pregnant individuals or in their infants. There was a numerical imbalance in late preterm births in upper-middle income countries, but not in upper income countries and low-middle income countries. Most preterms occurred near term, and most were born more than one month after vaccination. Mortality data were numerically favorable for the vaccine group for overall infant deaths, neonatal deaths, and upper middle income country deaths. Our extensive analysis of the safety data from the two maternal trials and three studies in non-pregnant participants support the overall favorable safety profile. Pharmacovigilance activities will continue to monitor outcomes in both populations.

I'm now going to review the efficacy data and this pivotal phase three study. Let's take a look at the efficacy objectives. All are in infant participants. There were two equal primary objectives of medically attended lower and severe, medically attended lower respiratory tract illness due to RSV through six months of age. For this presentation, I'll distinguish these as LRTI and severe. Secondary objectives extended to one year. They are the prevention of medically attended lower respiratory tract illness due to RSV, an extension of the primary endpoint, the prevention of RSV hospital admissions regardless of the severity of disease, and the prevention of medically attended lower respiratory tract illness due to any cause. RSV cases were verified by an independent adjudication committee.

In order to systematically capture long-term data for the efficacy endpoints, over half the infants were followed for up to two years to approximate their exposure to two RSV seasons. Infant participants were followed closely via parental weekly e-diary responses or phone contacts for six months to determine if they sought medical care for any respiratory track illness. Each time they did, a study swab and vital signs were systematically collected at a study visit. After six months of age, contacts were monthly, and data was still collected for all medically attended respiratory events, but study visits and swabs were only performed if the infant was hospitalized or had severe illness. Any data collected from the physician or hospital visit were combined with the study visit and collated for a review by an independent adjudication committee to determine if it was a case using the definition shown here. The definitions used by the adjudication committee highlight that key criteria included any of the findings of tachypnea, hypoxemia, or chest wall indrawing for RSV LRTI, and worsening tachypnea, worsening hypoxemia, respiratory support, intensive care admission, or unresponsiveness for severe LRTI.

In conjunction with key experts and in agreement with the FDA, criteria were intentionally objective to discriminate worst disease. All cases had to have a positive RT-PCR for RSV, and over 95% of LRTI events had a qualifying Pfizer study swab performed, but missed swabs could be counted when locally performed if the testing platform and the laboratory were validated by the adjudication committee. The trial allowed for efficacy success to be defined by either primary endpoint criteria, meeting a lower bound confidence interval of greater than 20%. The study had always planned going to four RSV seasons, and this is the data from an analysis at the end of that fourth season.

Based on an interim independent look conducted by the data monitoring committee, when the prerequisite case minimum had been achieved, the vaccine was found to be efficacious for the endpoint of severe LRTI at 90 days. The analysis results for LRTI at 90 days did not meet the statistical criterion for success with the lower bound of 20% because the interim analysis required the use of the very stringent 99.5% confidence level. But, as we'll see in the data shown today, clinically meaningful efficacy was seen for the LRTI endpoint at all time points. As agreed upon with the FDA, 90-day interim success triggered the final primary analysis that we will now review.

The full results of the primary analysis have now been published in the New England Journal of Medicine, April 20th edition, and are presented here. The primary efficacy objective for the Matisse study was met for severe, medically attended lower respiratory tract illness within 90 days after birth. There were 33 cases in the placebo and only six cases in the vaccine group for a vaccine efficacy of 81.8%. Efficacy was met for all subsequent time intervals in this primary endpoint, including 81 total adjudicated cases overall, 19 in the RSVpreF group, and 62 in the placebo for 69.4% efficacy at 180 days. The lower bound of the confidence interval was

above 40 at all time points, which is well above the criterion to meet licensure as agreed upon with the FDA. Cases are cumulative at each time interval.

The efficacy against severe cases by month over the six-month period following birth are illustrated here in a cumulative incidence curve. Efficacy is shown based on case accrual in infants while enrolling pregnant participants continuously, regardless of RSV seasonality. You can see a clear separation in the placebo, in gray, and the preF curve, in blue. This separation is sustained throughout a period which mirrors the highest burden of mortality due to RSV in infants, and in each month shown there are more in the placebo compared to the RSVpreF group.

At all time points for medically attended LRTI, analyzed by the pre-specified 97.58% confidence interval after 90 days, are shown here. It's notable that the final confidence intervals at all time points have a lower bound greater than 20%, with point estimates comparable to the 90-day result. LRTI to 180 days included 174 total cases of RSV positive events with 57 adjudicated cases in the RSVpreF group and 117 in the placebo group for an observed vaccine efficacy of 51.3%, which is clinically meaningful with the potential for significant public health benefit. Similar to the severe endpoint, LRTI cases are shown here in a cumulative incidence curve, and they show a clear separation between the preF and the placebo groups with sustained efficacy out to six months following birth.

Let's look at the secondary endpoint, starting with RSV positive LRTIs from 210 to 360 days after birth. Since this was a continuation of the primary endpoint of LRTI, we've also shown the data through 180 days for demonstration purposes, in gray. Note that this is cumulative efficacy, which is primarily driven by the efficacy less than 180 days. The six month to one year secondary endpoint met the statistical criterion for success, or a confidence interval lower bound more than 0% as agreed upon with the FDA, at all time points, corresponding to an observed

vaccine efficacy between 40 and 45%. At one year, there were 92 cases in the preF and 156 cases in the placebo group for a total of 248 cases and an efficacy of 41%. Meaningfully, this shows that infants are still seeing a benefit to vaccination in the period when maternal antibody is waning. As mothers are vaccinated year-round and infants may be born in and out of an RSV season, this endpoint may approximate real world efficacy for those followed throughout their first year.

Let's turn to another secondary endpoint: admission to a hospital with RSV of any severity of disease. With 10 cases in the RSVpreF group and 31 in the placebo, vaccine efficacy of 67.7% was met for the predefined criterion within 90 days. With 19 cases in the RSVpreF group and 44 in the placebo group, the vaccine efficacy of 56.8% was met for the predefined criterion within 180 days. Vaccine efficacy was not met for 360 days. Although severity criteria were not required for hospitalization, almost 80% of these cases were also severe. The secondary endpoint of LRTI due to any pathogen did not meet criteria for success and is included in the briefing document.

I'll now walk through some exploratory and descriptive efficacy endpoints that did not have pre-specified criteria for success but are likely to be clinically relevant to providers and patients. This exploratory endpoint looked at cases of RSV positive, medically attended respiratory tract illness. Ensure an infant went to the physician or sought healthcare, and was confirmed to have a valid RSV test within six months of birth. This endpoint included cases of any severity, including upper respiratory tract infections. Vaccine efficacy was approximately 38 to 39% for the exploratory endpoint of RSV MA RTI at all time points with confidence intervals above zero. Efficacy to this criterion demonstrates the vaccine efficacy we can assume across the spectrum of RSV disease, including milder coughs or colds.

So here we see the overall efficacy by the two primary endpoints and efficacy from the RSV A and B subgroups for each of the primary analyses. Case counts were small for subgroups A and B specific cases at each time point, leading to wider confidence intervals. Nonetheless, efficacy for RSV A and B is largely consistent with the overall analysis. Trials on the same dose and formulation of the maternal vaccine have been used in larger adult studies, with similar efficacy demonstrated against RSV A and B. I'd like to point out here that RSV A was only a third of cases and had lower incidence in each RSV season.

The totality of data demonstrates that efficacy in infants born to mothers vaccinated 24 to 36 weeks was met for the severe endpoint through six months of age, and clinically meaningful efficacy was observed for the LRTI endpoint through six months. And when combined with the secondary endpoint, efficacy was demonstrated through one year. I will now turn the presentation over to Dr. Jamie Wilkins to provide an overview of our pharmacovigilance and post-marketing safety study plans.

Pharmacovigilance and Postmarket Safety — Dr. Jamie Wilkins

Dr. Wilkins: Thank you, Dr. Munjal. My name is Jamie Wilkins, and I'm the Head of the Risk Management Center of Excellence and Worldwide Safety at Pfizer. I'd now like to turn your attention to our proposed plans for pharmacovigilance and post-marketing studies after approval. Pharmacovigilance activities are a critical component to detect safety events rapidly and continually inform the safety profile of our products.

Pfizer has a comprehensive global pharmacovigilance system. For all marketed products, we routinely conduct robust pharmacovigilance in collaboration with regulators, which includes the rapid detection of safety events via collection, active follow-up, and analysis of data from spontaneous case reports, the literature, and other sources. A subsequent assessment and

evaluation of potential signals to determine possible causal associations is performed. Routine pharmacovigilance for this vaccine will include a standard follow-up questionnaire on pregnancy outcomes and case analysis of reports for mother or infant. Additionally, for the proposed indication, planned risk mitigation activities will include appropriate labeling and a rigorous post-marketing safety study in the US.

Based on the currently available data from the clinical trial program, we are aligned with the FDA that the review of the safety data from these studies did not reveal any significant safety concerns. To affirm the safety profile related to birth outcomes from the clinical trial program amongst pregnant individuals in the US, including immunocompromised individuals, we plan to conduct a post-marketing study of RSVpreF under real-world conditions and a large electronic healthcare claims database. The proposed study will include data partners contributing to the FDA Sentinel Initiative, which includes large US commercial claims, databases, and Medicaid. We are confident this approach will allow for collection of a wide spectrum of variables, including racial and socioeconomic diversity, to inform the contextualization of safety endpoints of interest in this population. The currently proposed endpoints for the study are outcomes of interest as shown here, including stillbirth, preterm birth, small for gestational age, low birth weight, and Guillain-Barre syndrome, and other immune mediated demyelinating conditions. Final endpoints will be determined in collaboration with the FDA.

We are confident the combination of our routine pharmacovigilance activities and risk mitigation activities, including this proposed real-world study, will ensure the timely detection of safety events and confirm the known safety profile of RSVpreF in the US. And now I would like to return to Dr. Gruber, who will provide conclusions and overall benefit risk assessment.

Conclusion — Dr. William Gruber

Dr. Gruber: Thank you, Dr. Wilkins. In conclusion, there is a significant RSV disease burden in infants less than six months of age. RSVpreF maternal immunization demonstrated a satisfactory safety profile in mothers and their infants. The phase three pivotal efficacy trial demonstrated high and consistent efficacy across the spectrum of RSV disease. Pharmacovigilance activities will continue to monitor safety outcomes of interest to further inform benefit risk.

When we consider the global impact of RSVpreF vaccine, we see here that it has the potential to annually prevent a large proportion of hospitalizations due to RSV spanning low to high income countries, shown from left to right. Of the over 1,300,000 global hospitalizations shown on the right, universal RSVpreF maternal immunization could prevent over 950,000 hospitalizations annually. In the United States, based on the RSVpreF maternal immunization efficacy results, universally applied RSVpreF maternal immunization has the potential to annually prevent up to 16,000 hospitalizations and over 300,000 sick visits in children less than six months of age.

Therefore, we are seeking the following indication: the prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by RSV in infants from birth through six months of age by active immunization of pregnant individuals. Thank you for the opportunity to present this important advance for the health of children. My colleagues and I will be pleased to answer questions, and perhaps at the discretion of the chair and in response to a prior question, we would be happy to comment on recent data that's become available and presented to the FDA on concomitant use of flu vaccine and RSV.

Q & A

Dr. El Sahly: Thank you all. Yes. I think everyone would be interested in seeing the influenza data. We do have a whole additional hour, should we view — how long would it be to go over these?

Dr. Gruber: Well, what I would recommend is that we can either show it now or later. I do want to get to other questions that the committee members may have that speak to some of the questions that have been asked of the committee by the FDA. So I bow to your discretion.

Dr. El Sahly: Okay. I think we will go back to the flu question in the whole hour dedicated for more Q and A. Now we have only 10 minutes. Dr. Pergam.

Dr. Pergam: Thanks, Dr. El Sahly. This is a question for Dr. Gruber and Dr. Munjal. I'm curious about the incidents of breastfeeding versus formula feeding within the trial and if there were additional studies that are planned or were collected during the primary trial that looked at breast milk antibody levels, both IgG and IgA, secretory IgA. Because it seems like the vaccine could be a major advantage, being that you can produce breast milk antibodies as well in some of these, particularly these high-risk patients in lower income countries. So I'd be curious, what data do you have available within that?

And then as a secondary question to that is, was there any data to suggest that women who breastfed in the trial had a decreased incidence of RSV? I know that may not be possible, but just with the number in the trial, I'm curious if there's anything in this space.

Dr. Gruber: Yeah. So obviously, as you heard from other presentations, breast milk may offer an advantage as far as protection is concerned. But I think one of the challenges that we face in the course of this trial, even though breastfeeding information was collected, is the level of antibody was so high and the protection so high, it might be buried in that circumstance. And so

when looking at the populations that were either breastfed or non-breastfed, we were not able to discern a difference. Now, once we go to post-approval effectiveness evaluations, it might be possible to tease that out. But we did not detect a difference in this trial between breastfed and non-breastfed infants, and we did not collect breast milk as part of this trial.

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

Dr. Cohn: Thank you very much for such a very clear presentation. A couple of questions related to the very end related to post-marketing. In terms of the outcomes listed, you said there were maternal and infant outcomes, except for most of the outcomes listed were just around birth. And so I was wondering if there were also going to be efforts to continue to look at maternal outcomes like hypercoagulation and things like that, as well as infant outcomes. And then if that's the case, can you talk a little bit more about how you would link data in these large data sets, which can be very challenging? Thank you.

Dr. Gruber: Yes. We obviously take our safety our requirements very seriously, and we'll be doing extensive pharmacovigilance. I'm going to ask Dr. Sarah Macdonald to speak to some of the specifics you've asked about.

Dr. Macdonald: Thank you very much. My name is Sarah Macdonald. I'm an epidemiologist within Pfizer Safety Surveillance Research Team, and I'm also the study lead for the planned post-marketing safety study. So in regards to your question for the specific endpoints, as we discussed previously, we are planning to certainly collect information on stillbirth, preterm birth, small for gestational age, low birth weight, and Guillain-Barre syndrome, and other immune mediated demyelinating conditions. These endpoints are not necessarily the final endpoints. We will be having discussions with the FDA around additional endpoints that may need to be evaluated. And so we will have those discussions.

In terms of other safety endpoints, in the maternal clinical trial, there were no additional safety risks. And we will be collecting additional safety information through our routine pharmacovigilance activities as well. If there was an unidentified safety risk identified through our routine pharmacovigilance activities, this post-marketing study is designed to be modified throughout the study to further characterize the risks of those outcomes. So that will also happen. But as I mentioned, the final list of outcomes will be discussed and agreed upon in collaboration with the FDA. Thank you.

Dr. El Sahly: Dr. Omer.

Dr. Omer: Yeah. In terms of birth outcomes data, it's good to hear the comment about reasonable differences in some of these outcomes. I would be interested in knowing a little bit more about some of the other related outcomes, like small for gestational age, which accounts for prematurity in its computation, as well as differences in mean birth weight. As you know, in such a geographically varied study, the baseline birth weight can play a role and has played a role in having differential birth outcome rates under maternal flu immunization trials. So I'd be curious to know any reasonable differences, first of all, overall and by region rates, if you have those available, for SGAs, small for gestational age, and similar rates for differences in mean birth weight. Thank you.

Dr. Gruber: So thank you for the questions. I'm going to ask Dr. Munjal to speak to some of the specifics regarding other parameters like SGA birth weights. Dr. Munjal.

Dr. Munjal: Thank you. So overall in our study, the number of participants with small for gestational age was exceptionally low. And this may have been due to a requirement that maternal participants have pre-screening ultrasounds to show that the babies were developing well. And so we actually look at both outcomes of prematurity and low birth weight. And if I can

have slide one, please. So what we did look at was the birth weight at delivery. Some of these infants are small for gestational age, although that's the vast minority of them. Most of these actually represent smaller babies due to prematurity or other factors. And you can see here we break it down by very low birth weight, of which there were four in the RSVpreF and eight in the placebo group, and low birth weight, or less than 2,500 grams. There were no differences in small for gestational age by region, but again, the numbers were very small.

Dr. Omer: And maybe if we just leave this slide up. I think, just as a follow-up to that question, this is an important observation as we know that the committee has addressed the issue of prematurity. And as Dr. Munjal expressed in her presentation, first of all, there's obviously no difference that's been seen between, in terms of a statistically significant difference as far as total prematurity, less than 37 weeks. And you can see that represented on the left-hand side, and Dr. Munjal blew that up. We obviously take our considerations of safety, potential safety events, very seriously. And so, as Dr. Munjal said, we probe this further, including the breakdowns that she described, as far as high income countries versus upper-middle income countries and low income countries. And I think one of the findings, it was very clear that the difference that was seen that led to the overall numerical difference was driven by the upper-middle income countries as far as prematurity is concerned. And as you can see on the right, that difference narrows when you use the more objective assessment of birth weight. And in particular, and Dr. Munjal highlighted this without showing you the specific numbers, well, when you actually looked at that most vulnerable group of children, less than 1500 grams, the split actually goes the other way. Now, the total numbers are obviously small, but I think that provides reassurance that there's really not a consistent finding to suggest that there is a true risk of prematurity. And it's important to keep in mind that when we looked specifically at high income countries, including the United States,

the actual number of premature infants that we saw in each group was the same, indicating, and this was in a circumstance where we had two and a half times as many premature births.

So I think the balance of evidence supports the conclusion that there is no compelling evidence to support an increased risk of prematurity in those mothers who received the vaccine. But I did want to get that point across in our 10 minutes here because I thought it was a particular topic that the committee is interested in.

Dr. El Sahly: Okay. Thank you. The last question I have before we go to the FDA presentation is also for Dr. Munjal. So looking at slide CC 40, I think that's the one. Yes. So, okay, so if we, I mean these outcomes, they kind of align together, threatened labor, premature labor, pre-eclampsia, premature rupture of membranes. They kind of fly together. So is there a cumulative of those?

Dr. Munjal: Yeah, so what we looked at is both individually and together outcomes that represented a premature delivery event. And that's when you actually have the birth event occurring. These other events are meant to represent women who may have experienced threatened or preterm labor but actually didn't go on to have delivery. And when we look at them either alone or in aggregate, we don't see any imbalance between the two groups. And that's best represented by the sort of total sock of pregnancy and also by the total adverse events.

Dr. El Sahly: Okay.

Dr. Munjal: If you can go to CC 39, slide two, please. So when we look at total adverse events, and what we also have is we have different system organ classes brought broken down by different groups. And when we look at overall, at any of these different groups by severity or by different groups, for example, of the pregnancy sock, there is overlapping confidence intervals. I

will note that the majority of the events in the study, any of these individual events occurred in less than 1% of participants. And so either taken individually or in aggregate, they are similar.

Dr. El Sahly: Okay, so we are out of time, but we will have opportunity to discuss further. And if you can prepare a response to Dr. Omer's question pertaining to mean birth weight data when we come back for the further discussion, rather than the categorical.

Dr. Munjal: Yes, absolutely. I can address that now or later. Thank you so much.

Dr. El Sahly: Later. We don't.

Dr. Munjal: Thank you.

Dr. El Sahly: Thanks. So, and now doc the FDA presentation the review of efficacy and safety of RSV ABRYSVO immunization during the second and/or third trimester of pregnancy, 24 to 36 weeks gestational age, to prevent RSV LRTD and severe RSV LRTD in infants from birth through six months of age. Dr. Yugenia Hong-Nguyen, Medical officer at DVRPA, CBER, FDA will go over this data. Dr. Hong-Nguyen.

Efficacy and Safety of ABRYSVO — Dr. Yugenia Hong-Nguyen

Dr. Hong-Nguyen: Hello, I'm Yugenia Hong-Nguyen from the Office of Vaccines Research and Review, Division of Vaccines and Related Products Applications. I will be presenting the FDA review of the efficacy and safety data submitted to support this Biologics Licensing Application for Pfizer's respiratory syncytial virus vaccine, or ABRYSVO, for the maternal immunization indication for prevention of RSV lower respiratory tract disease and severe RSV lower respiratory tract disease in infants from birth through six months of age. Next slide please.

This is an outline of today's presentation. I'll start with an introduction, then discuss the clinical study submitted to this biologics licensing application, as well as the efficacy and safety data supporting the application. I'll then discuss the applicant's pharmacovigilance plan. And

finally we'll summarize the data and present the questions for the advisory committee voting and discussion. Next slide please.

Starting with an introduction. Next slide. The RSVpreF vaccine, or ABRYSVO, is composed of RSV recombinant stabilized prefusion proteins. Note that this is the same product, as mentioned already, as for the indication in the older adults age 60 and older, which was recently presented at an advisory committee meeting. Each 0.5 mL dose contains 60 micrograms of each stabilized RSV prefusion antigens, subtypes A and B. The total dose RSV drug product is 120 micrograms of RSV prefusion F antigen with no adjuvant. This is to be administered as a single intramuscular dose in the late second or third trimester of pregnancy from 24 through 36 weeks gestation. The applicant's proposed indication listed here is prevention of lower respiratory tract disease and severe lower respiratory tract disease caused by respiratory syncytial virus, or RSV, in infants from birth through six months of age by active immunization of pregnant individuals. Next slide, please.

I will now discuss the clinical studies submitted for this for FDA review. Next slide. The data from five clinical studies of RSVpreF were submitted to support this biologics licensing application. This table shows the safety database that was exposed to the final formulation. The remainder of today's discussion will focus on the first three studies listed here. The first two studies in the blue box included the maternal participants. The summary data to support the safety and efficacy of ABRYSVO in pregnant individuals and their infants is from an ongoing, multi-country, phase three, randomized, double blinded placebo-controlled trial study, C3671008, which I'll be discussing further after this slide. Please note that hereafter, I'll be referring to this study as study 1008, and the subsequent studies listed here as study 1003, study 1004, and so forth.

Study 1003 was a phase two randomized placebo-controlled, observer-blinded trial, and was the first study of the RSVpreF vaccine candidate in pregnant individuals evaluating safety, tolerability, and immunogenicity of the RSVpreF vaccine in pregnant individuals 18 to 49 years of age and their infants. As a result of the findings from the phase two study, the RSVpreF final formulation was brought forward for phase three development. Study 1004 was a phase two study in healthy, non-pregnant individuals, 18 to 49 years of age, who were randomized to one of five vaccine groups for evaluation of safety, tolerability, and immunogenicity of the RSVpreF vaccine when administered concomitantly with Tdap, which contains tetanus, diphtheria, and pertussis antigens.

The following studies will not be discussed in the remainder of today's presentation and were recently discussed or mentioned at a recent advisory committee meeting. However, in brief Study 1004 was a lot consistency study. Lot consistency across three RSVpreF lots was achieved in the evaluable immunogenicity population based on a 1.5-fold equivalence margin for both RSV A and RSV B antigens.

Study 1001 was a phase one-two first in human dose finding study which evaluated six different RSVpreF candidates at three escalating dose levels with or without aluminum hydroxide and administered alone or concomitant with seasonal inactivated influenza vaccine. Across all studies, the safety database included 3,797 maternal participants with 1,773 maternal participants enrolled from US sites who received the final formulation of the RSVpreF vaccine, which is a 120-microgram dose without aluminum hydroxide, adjuvant, or with no adjuvant. The data from maternal participants, as mentioned, came from studies 1008 and 1003. Next slide please.

I'll now discuss the findings from Study 1008, which is an ongoing, phase three, randomized, double blinded, placebo-controlled trial to evaluate the efficacy and safety of RSVpreF in infants born to pregnant individuals. The study was initiated on June 17th, 2020, is currently ongoing, and is a global study being conducted in 18 countries in both the northern and southern hemispheres. Note, RSV positive illness or disease will be referred to hereafter as LRTD due to RSV, or RSV LRTD, throughout, consistent with a proposed indication.

There were two primary efficacy objectives, efficacy of RSVpreF in reducing the incidence of medically attended lower respiratory tract disease, or MA LRTD, due to RSV and efficacy of RSVpreF in reducing the incidence of severe MA LRTD due to RSV at the time points listed here. The study would be declared a success if the statistical criterion for either primary endpoint was met, with a lower bound of a two-sided 95% confidence interval for vaccine efficacy greater than 20%. This was an event-driven study with a target enrollment of approximately 6,900 mother infant pairs in order to accumulate 124 per protocol cases of MA LRTD due to RSV within 90 days. The sample size could have been increased up to 10,000 pregnant individuals given the variable RSV season since the COVID-19 pandemic. Vaccination of maternal participants was planned a time of year such that the infant was likely to be exposed to seasonal RSV during the first six months of life. There would be up to two interim analyses of the primary endpoint.

MA LRTD due to RSV after at least 43 cases within 90 days had accrued. All medically attended respiratory tract disease, or MA RTD cases, meeting the protocol definition for a potential study primary efficacy endpoint, LRTD or severe LRTD due to RSV, were adjudicated by an independent adjudication committee, which was blinded to the maternal participants

vaccine assignments, an external data monitoring committee, or EDMC, monitored for vaccine safety, efficacy, and potential study futility. Next slide please.

The first interim efficacy analysis was conducted in April 2022, when 56 evaluable cases of MA LRTD due to RSV within 90 days after birth had accrued. The second interim efficacy analysis was conducted in October 2022 after 80 evaluable cases of MA LRTD due to RSV within 80 days had accrued, including 39 evaluable cases of severe MA LRTD due to RSV within 90 days. The recommendation of the EDMC was to stop the study for efficacy due to the success criterion for one of the two primary efficacy endpoints being met. The second interim efficacy analysis was considered the final analysis of the study primary efficacy objectives. For this analysis, 174 evaluable cases of RSV positive MA LRTD within 180 days after birth were submitted for adjudication as of the data cutoff of September 30th, 2022. Next slide please.

The two primary endpoints, MA LRTD, and severe MA LRTD due to RSV were to be evaluated in the infants at multiple time intervals, specifically at days 90, 120, 150, and 180 after birth. These two endpoints were to be tested in parallel. Additionally, testing across the time intervals was planned to follow a fixed sequence. Testing at day 120 will occur upon success at day 90, and so forth. Multiplicity adjustment procedures were implemented to account for the multiple hypothesis tests. The study success was defined as demonstrating that the lower bound of the multiplicity adjusted confidence interval of vaccine efficacy is greater than 20% for at least one of the two primary endpoints, controlling the type one error rate at a one-sided 2.5%. Vaccine efficacy was defined as the percentage reduction in the risk of the primary endpoints in the RSVpreF group compared to the placebo group. Next slide please.

There were three secondary efficacy endpoints. These were to be tested upon success on at least one of the two primary endpoints through 180 days. Similar to the primary endpoints,

testing across the time intervals was planned to follow a fixed sequence. The success criterion for the secondary endpoints was specified as demonstrating that the lower bound of the multiplicity-adjusted confidence interval for vaccine efficacy is greater than 0%.

Additionally, there were multiple exploratory endpoints. These were considered descriptive with no hypothesis testing specified. Selected exploratory endpoints of interest are listed here. Next slide please.

Safety events in infants are captured once the infant takes a live breath. This included adverse events to one month, and then up to six, up to 12 or 24 months of age were recorded adverse events of special interest, serious adverse events, and newly diagnosed chronic medical conditions. NDCMCs, or newly diagnosed chronic medical conditions, were defined per the protocol as a disease or medical condition not previously identified that is expected to be persistent or otherwise long-lasting in its effects. For example, asthma. Analyses of reactogenicity were based on the maternal safety population. Safety events that were associated with a fetus of a maternal participant before or during birth, or before an infant takes a live breath, were reported for the maternal participant. Next slide please.

Maternal participants were generally healthy pregnant individuals less than or equal to 49 years of age, between 24- and 36-weeks gestation at time of planned vaccination, and were randomized one to one to receive a single intramuscular dose of RSVpreF vaccine or placebo. Other important inclusion criteria were a singleton pregnancy and no significant fetal abnormalities observed on ultrasound. Enrollment was monitored to ensure distribution of vaccination with respect to RSV seasonality and gestational age. Maternal participants were followed from vaccination during pregnancy until six months after delivery.

Safety monitoring of the maternal participants included solicited local and systemic adverse reactions within seven days after vaccination, unsolicited, non-serious AEs through 28 days after vaccination, and SAEs through six months post-delivery or completion of the study. Solicited local AEs included pain, redness, swelling at the injection site, solicited systemic AEs included fever, fatigue, headache, muscle pain, joint pain, nausea, vomiting, and diarrhea. And these were based on a grading scale that that was pre-specified. Preterm delivery was reported as an adverse event of special interest for maternal participants. And already mentioned was the fact that concomitant administration of licensed vaccines were permitted starting seven days after study vaccine administration, with the exception of vaccines containing pertussis, which were allowed starting 14 days after study vaccine administration. And this was based on findings from study 1004, in which reduced antibody responses to pertussis vaccine antigens were demonstrated following concomitant administration of RSV PREA vaccines. Next slide please.

As of the safety data cutoff date, which was September 2nd, 2022, the photo of 7,392 maternal participants were randomized to receive RSVpreF or placebo. The safety population included 7,357 maternal participants, which included 3,681 in the RSVpreF group and 3,676 in the placebo group. Most exclusions were due to not being vaccinated. Next slide please.

For baseline characteristics of race or ethnicity, maternal participants were 64.5% White, 19.6% Black or African American, 12.5% Asian, and 28.9% Hispanic Latino, and were balanced between the groups. Next slide, please.

Based on characteristics of the maternal population, including general medical history and obstetric history, were similar between groups. The majority of maternal participants who were in the gestational age stratum of 32 weeks through 36 weeks at the time of vaccination, 44.7%. The median maternal age at the time of study vaccination was 29 years. Most maternal

participants had a history of zero or one pregnancies prior to the study pregnancy. For the infant participants not shown here but mentioned previously, demographics and baseline characteristics were similar between the two groups. Half of the infants were female. And race and ethnicity were generally reflective of the infant's mothers. Next slide, please.

This table shows definitions of the analyses populations. The evaluable efficacy population was the primary population used for the analyses of efficacy. Next slide. For infants, for efficacy monitoring, surveillance for RTI begins 72 hours after delivery until the end of the infant's participation in the study, which is up to 12 or 24 months of age, depending on the year that the infant was enrolled. All infants born during the trial period had nasal swab testing by age relative to their date of birth and therefore were tested during their peak time of risk, regardless of seasonality. This approximates a real world scenario in which infants may be born at variable times before, during, or after the RSV season and also, as mentioned, accounts for changing RSV epidemiology patterns noted since the COVID-19 pandemic. Mid-turbinate nasal swabs will be collected from infant participants following any MA RTD visit during the RSV surveillance period from birth until visit three, which is at six months, and for all hospitalizations due to an RTD and severe cases of MA LRTD from visit three until the end of the study.

For safety monitoring in infants, the active collection period of non-serious AEs begins at birth and continues through a minimum of 28 calendar days after birth. The active collection period for SAEs, AESIs, and NDCMCs continues through the last study visit. The AESIs of preterm birth, or premature birth, low birth weight, and developmental delay were reported for infant participants. AESIs that were reported as SAEs included extremely preterm birth and extremely low birth weight. SAEs included ectopic pregnancy, spontaneous abortion, intrauterine

fetal demise, neonatal death, or congenital anomalies. Congenital anomalies were pre-specified and based on the metropolitan Atlanta Congenital Defects program. Next slide.

MA RTDs are recorded as AEs or SAEs for the first 72 hours of life, but only recorded as such after this time point if assessed as related to maternal vaccination or resulting in death. RTD criteria are met if the infant experiences any of the respiratory signs or symptoms listed here. An RSV positive test is an RSV reverse transcriptase polymerase chain reaction positive test result by a Pfizer Central laboratory or an RSV positive test result by a certified laboratory with an RSV nucleic acid amplification test. Next slide, please.

For the infants, 7,128 were born to mothers randomized to the RSVpreF or the placebo group. The city population for infants included 7,126 infants. The evaluable efficacy population included 6,975 infant participants, and the most common reason for exclusion from the evaluable efficacy population was due to the mother not being vaccinated at least 14 days prior to delivery. As of the safety data cutoff date of September 2nd, 2022, 45.6% of infant participants had completed the 12-month follow-up visit. Note that only three infants in each group had completed the 24-month follow-up visit. The most frequent reasons for withdrawal of infant participants were loss to follow up and withdrawal by parent or guardian. No infant participants were withdrawn due to an adverse event. Next slide, please. The median follow-up duration for the infant safety and efficacy population was approximately nine months. The median follow-up duration for the maternal safety population was approximately eight months. Next slide.

Now I will discuss the efficacy data for study 1008. Next slide. There were a total of 39 severe MA LRTD events due to RSV within 90 days accumulated at the time of the second interim analysis. Of these, 6 were among infants whose mothers received the RSV vaccine, and 33 were among infants whose mothers received placebo. This resulted in vaccine efficacy of

81.8% with a lower bound of the confidence interval of 40.6%. Thus, the success criterion for this time interval was met as the lower bound of the confidence interval was greater than 20%. Following the fixed sequence testing strategy, the success criterion for the other time intervals for this endpoint were also met. Next slide please.

This is a cumulative incidence or efficacy curve. Red is placebo, and blue is the RSVpreF group. And as you can see, there are more cases accumulating, especially notable further out towards six months or 180-day time point in the placebo group. Next slide. For the second primary endpoint of MA LRTD due to RSV, there were a total of 80 events accumulated within 90 days from birth at the time of the second interim analysis. Of these, 24 were among infants whose mothers received the RSVpreF vaccine ,and 56 were among infants whose mothers received placebo. This resulted in vaccine efficacy of 57.1% with a lower bound of confidence interval 14.7%. As a lower bound of the confidence interval was less than 20%, the success criterion for this endpoint in 90 days was not met. Following the fixed sequence testing strategy, testing for the other time intervals for this endpoint technically stops, and the presented vaccine efficacy results for this endpoint are now considered descriptive. Next slide please.

Again, red is placebo, and blue is the RSVpreF group. And you do notice a gap forming, maybe not as impressive as for the severe cases, but further out towards the 180 day time point. Next slide. As of the data cutoff date, there were 10 hospitalizations due to confirmed RSV in infants within 90 days after birth in the RSVpreF group and 31 in the placebo group, corresponding to a vaccine efficacy of 67.7%. There were 19 hospitalizations due to RSV in infants within 180 days after birth in the vaccine group and 44 in the placebo group, corresponding to vaccine efficacy at 56.8%. These results met the statistical criteria for success

for this endpoint, a lower bound of greater than 0% at all time points within 180 days after birth. Statistical criterion for success was not met within 360 days. Next slide.

RSVpreF met the statistical criterion for success for reducing RSV positive MA LRTDs through 360 days after birth. However, note that these analyses were based on cumulative case counts from day zero. During the period from 181 to 360 days after birth, rates of RSV confirmed MA LRTD were noted to be similar between groups, with 35 new cases in the RSVpreF group and 39 new cases in the placebo group. Therefore, vaccine efficacy beyond 180 days appeared to be primarily driven by cases within the first six months. For all cause MA LRTD, results did not meet the statistical criterion for success at any measured time point within 360 days after birth. Next slide please.

Endpoints were met for the following exploratory efficacy objectives, MA RTD due to RSV within 180 days after birth and severe MA LRTD, as well as MA LRTD due to RSV subtype B within 180 days after birth. And just as already mentioned, the majority of RSV MA LRTD cases in the study were due to RSV subtype B. Limited data available as of the data cutoff date showed similar rates of RSV MA LRTD in both treatment groups during the period of 361 to 730 days after birth, with four cases in the RSVpreF group and six in the placebo group. However, as already mentioned, and of note, only six infant participants had completed 24 months of follow-up, which is around 730 days, as of the data cutoff point. Next slide.

Subgroup analyses for selected efficacy endpoints were performed on the variables listed here. In general, clinically meaningful differences between subgroups were not observed. However, these analyses were limited by low numbers of participants and cases in some subgroups. Next slide. Please note that this table of one subgroup analysis, cases of RSV MA LRTD by gestational age and maternal vaccination, was not included in the FDA briefing

document. You'll note that a trend towards lower efficacy was noted in infants of mothers who were vaccinated between 24 to less than 28 weeks gestation, particularly within 180 days after birth. Within 90 days after birth, lower efficacy against RSV, MA LRTD was seen in infants whose mothers were vaccinated between 32 to 36 weeks gestation. However, efficacy appeared more favorable within 180 days. And of note, only a few were vaccinated after 36 weeks gestation. Next slide, please.

This table also was not included in the FDA briefing document. This shows cases of severe RSV MA LRTD by gestational age at vaccination. Here, a more consistent trend is noted, suggestive of a lower efficacy against severe RSV MA LRTD in infants of mothers who were vaccinated between 24 to less than 28 weeks gestation. Please note that this study was not powered to assess each of these endpoints, however this data was felt to be of relevance, so is shown here. Next slide.

I'll now review the safety data for study 1008. Next slide. This is an overview of safety events for the maternal safety population. Prompted reactogenicity events were captured by many participants via e-diary. The proportions of maternal participants with local reactions reported within seven days after vaccination were higher in the RSVpreF group compared to placebo. The proportions of maternal participants who reported systemic events within seven days after vaccination were more similar between groups. Note at the bottom, the cases of premature delivery, which will be discussed later in this presentation and were already briefly mentioned. Next slide please.

Most local reactions were mild or moderate in severity for both groups. Severe local reactions were reported for 0.3% of maternal participants in the vaccine group. The most commonly reported local reaction was pain at the injection site, reported by 40.6% of

participants in the RSVpreF group and 10.1% of participants in the placebo group. The median day of onset for any local reaction for the vaccine group was day two, with a median duration of two to three days. Next slide.

Most solicited systemic events were mild or moderate in severity. Severe systemic events within seven days after vaccination were reported by 2.3% in both groups. The incidence of fever was low and was similar for RSVpreF and placebo groups, less than or equal to 2.9%, and the exact numbers are listed here. Most were low grade. The most frequently reported systemic event was fatigue, reported by 46% of participants in the vaccine group and 44% in the placebo group. Headache and muscle pain, as mentioned, were reported more frequently in the RSVpreF group. Next slide.

The median day of onset for any systemic event for the RSVpreF group was day two, with a median duration of one to three days. Next slide. For unsolicited adverse events, immediate AEs were reported in one maternal participant in each group. There was one immediate AE of dizziness in the RSVpreF group which was considered related to the investigational product. Unsolicited non-serious AEs within one month were reported in approximately 11% in both groups. Severe or life-threatening AEs within one month were reported in 2.2% in the RSVpreF group and 1.5% in the placebo group. The most frequently reported AEs in maternal participants through one month after vaccination were in the system organ class of pregnancy, puerperium, and perinatal conditions, and infections and infestations. By preferred term, the most frequently reported AE in both groups within one month after vaccination was premature delivery, which was solicited as an AESI at 2.1% in the vaccine group and 1.9% in the placebo group. No maternal participants withdrew from the study due to an AE within one month after vaccination. One participant in the placebo group withdrew within six

months. And for your reference, in case you're not aware, system organ class and preferred term are from MedDRA, which is the medical dictionary for regulatory activities. Next slide, please.

AEs from vaccination through the one-month follow-up visit assessed related to study intervention by the investigator were reported in 0.4% in the RSVpreF group and 0.1% in the placebo group and occurred mostly in the SOC of general disorders and administration site conditions. Most related AEs occurred after vaccination but prior to delivery with the exception of two related AEs, which were reported from delivery to one month after delivery and were in the RSVpreF group. This included one SAE of eclampsia and one event of premature delivery. There were, of note, two cases of eclampsia in the placebo group during the same time period. Next slide, please.

AESIs within one month after vaccination were reported at a similar frequency for both groups. Premature delivery was reported in 5.6% in the RSV preF group and 4.7% in the placebo group. One maternal participant in the placebo group withdrew from the study due to the AE of premature delivery. Next slide.

SAE within one month after vaccination were reported in 4.2% in the RSVpreF group and 3.7% in the placebo group. This included the one related SAE of eclampsia in the vaccine group. The proportions of maternal participants with any SAE reported after vaccination of six months after delivery were 16.2% in the vaccine group and 15.2% in the placebo group. Most SAEs were reported from delivery to one month after delivery, and after vaccination but before delivery. Most SAEs were reported in the SOC of pregnancy, puerperium, and perinatal conditions: in the RSVpreF group, 12.1%, and in the placebo group, 11.2%.

SAEs assessed as related by the investigator included the four maternal participants in the RSVpreF group and one in the placebo group, not listed here. One participant with severe pain in

multiple extremities, which started in the vaccinated extremity two days after vaccination. One episode of premature labor with onset two days after vaccination, which did not result in a preterm delivery. The infant was born without complications at 39 weeks gestation. An episode of thrombocytopenia six days after vaccination with a subsequent diagnosis of systemic lupus erythematous, which was felt to be related to the episode of thrombocytopenia. And a case of eclampsia with onset 15 days after vaccination. Next slide please.

The next two tables show SAEs in the maternal safety population within one month after vaccination. Next slide. As mentioned, most SAEs within one month after vaccination were the SOC of pregnancy, puerperium, and perinatal conditions. This did include cases of preeclampsia, 0.8% in the vaccine group and 0.5% in the placebo group, premature delivery 0.4% versus 0.2%, and premature labor, 0.2% versus 0.1%. Next slide.

There was one maternal death in the RSVpreF group, as mentioned, due to postpartum hemorrhage and hypovolemic shock, which was reported from delivery to one month after delivery. Based on the case narrative reviewed, this outcome was considered unlikely to be related to the study intervention. A total of 18 intrauterine deaths were reported for the index pregnancy, 10 in the RSVpreF group, 8 in the placebo group. In addition, 3 spontaneous abortions during subsequent pregnancies were reported during the period of one to six months of follow up, one in the RSVpreF group and two in the placebo group. Next slide.

This is a table showing an overview of safety analyses for the infant safety population. Overall, AEs were fairly balanced between groups. However, I would like to draw your attention to one AESI, which is premature births, which will be discussed further in this presentation. You may notice a slight discrepancy between the numbers reported previously for premature delivery under maternal safety versus preterm or premature births reported here under infant safety.

Premature delivery was reported in 5.7% in the RSVpreF group versus 4.7% in the placebo group. In the response to our inquiry about this apparent discrepancy, Pfizer confirmed that the AESIs of premature delivery in maternal participants and premature birth and infant participants was largely driven by stillbirths. As a reminder, safety events associated with the fetus before an infant takes a live breath were reported for the maternal participant. However, there were a few additional discrepancies noted where preterm birth outcome was reported in infants whose mothers did not have a preterm delivery reported, which should not be the case. Pfizer did state that these minor data discrepancies have been queried to the sites and will be updated for the final analysis. Next slide, please.

Proportions of infants with any AE reported within one month after birth were 37.1% in the RSVpreF group and 34.5% in the placebo group. Unsolicited non-serious AEs within one month were reported at 28.4% versus 26.2%. Severe or life-threatening AEs were reported in about 5% versus 4.5%. No infant participants were withdrawn from the study due to an AE. One event of prematurity in an infant participant in the RSVpreF group was assessed by the investigator as related to maternal vaccination. This was considered to be mild in severity, as the infant was born at 36 weeks and five days gestation on day 86 post-vaccination. Per the case narrative, the 37-year-old maternal participant was hospitalized four days after vaccination with a report of a two-day history of decreased fetal movement. Upon triage and ultrasound imaging, fetal movement was noted to be present. The maternal participant was discharged home the same day, and on day 85 post-vaccination, delivered a healthy infant without complications at 36 weeks and five days gestation. The investigator's rationale was that an alternative cause for the premature delivery was not found, so given the temporal relation associated with the hospitalization event, the event will be handled as related to the investigational product. Next

slide, please. Preterm birth, low birth weight, and developmental delay were reported as AESIs for infant participants. The following AESIs were reported as SAEs, as mentioned. Extremely preterm birth, less than 28 weeks gestation and extremely low birth weight less than or equal to 1000 grams. AESIs within one month after birth were reported in 8.4% versus 7.2%. Low birth weight was reported in 5.1% in the vaccine group versus 4.4% in the placebo group. Premature birth were reported in 5.7% in the vaccine group versus 4.7% in the placebo group. Note that a difference of 1% was noted in premature births, similar to the difference seen in preterm deliveries, though not statistically significant and lower than background incidence rates of the general population.

A subgroup analysis of live birth outcomes by high income and low and middle income countries did not demonstrate a trend towards an increased incidence of preterm births in low income or lower-middle income countries. However, a difference was noted in the preterm birth rate between vaccine recipients in one upper-middle income country, specifically South Africa, with 8.3% of infants in the RSVpreF group and 4% of infants in the placebo group. Next slide, please.

The SAE of extremely preterm birth less than 28 weeks was observed in one participant in each group. Most premature infants were born in the late preterm period. The AESI of developmental delay was reported for 12 participants in the RSVpreF group and 10 in the placebo group. Next slide. Prematurity overall was not temporally associated with vaccination, with a majority of participants delivering outside of the 30 day reporting period. Next slide. NDCMCs within one month after birth were reported in 0.2% of infant participants in both groups. As of the data cutoff, NDCMCs were reported at a similar frequency between groups,

2.4% versus 2.8%. Asthma-related diagnoses were reported in 2.7% for the vaccine group and 3.1% for the placebo group. Next slide.

For both groups, most SAEs reported as of the data cutoff occurred from birth to one month of age, less than or equal to 15.5% in both groups. The proportions of infant participants with any SAE from birth to 24 months of age were balanced, 17.5% in both groups. From birth to 24 months of age, SAEs were most frequently reported in the SOCs of respiratory, thoracic, and mediastinal disorders, as well as pregnancy, puerperium, and perinatal conditions, and infections in infestations. Congenital anomalies were reported in 5% in the RSVpreF group and 6.2% of the placebo group. Next slide.

A total of 17 infant deaths were reported from birth to 24 months of age, 5 in the RSVpreF group, and 12 in the placebo group. Of these, a total of seven infant deaths occurred during the neonatal period, two in the vaccine group, and five in the placebo group. There were three deaths reported in premature infants, one in the RSVpreF group and two in the placebo group. One infant in the RSVpreF group was born to an 18-year-old mother at 10 days after vaccination with extreme prematurity at 27 weeks and three days gestation and died on day of life four. One infant in the placebo group had a cause of death listed as premature baby, as well as bacterial meningitis and sepsis. There was another infant in the placebo group who was born prematurely, but this was not associated with death. One infant death was adjudicated by the EAC with a possible cause of death, acute respiratory illness due to RSV, and this was in the placebo group. Next slide.

Now to show supportive data from the phase two study, which was the first study of the RSVpreF vaccine candidate in pregnant individuals and their infants. Study 1003 was a phase two study evaluating safety, tolerability, and immunogenicity of the vaccine RSVpreF

formulations in maternal participants and their infants. This was a very similar patient population, also with uncomplicated singleton pregnancies. A total of 581 maternal participants were randomized. 579 completed vaccination. All maternal participants who were vaccinated were included in the evaluable immunogenicity population. This study took place from August 7th, 2019 to September 30th, 2021, also including sites in both the northern and southern hemispheres.

Demographic characteristics of maternal participants were similar cross vaccine groups. Maternal participants received one dose of investigational product, either the final formulation of 120 micrograms or 240 micrograms RSV vaccine formulated with or without aluminum hydroxide, or placebo. Pregnant women participated in the study from the enrollment during their pregnancy and for approximately 12 months after delivery. Infant participants participated from the time of birth and for approximately 12 months after birth. Next slide.

The primary endpoint was the safety evaluation of maternal participants experiencing pre-specified local and systemic reactions within seven days after vaccination, unsolicited adverse events within one month after vaccination, and obstetric complications. Infants were assessed for birth outcomes, adverse events to one month of age, or 28 days, SAEs, and medically attended adverse events through 12 months of age. One of the secondary endpoints was maternal to infant placental transfer ratio of RSV A and RSV B neutralizing antibody titers. RSV-positive LRTD in infants was an exploratory objective in this study. Next slide.

Safety and efficacy findings were similar to what followed in the 1008 trial. Local injection site reactions, predominantly pain, were reported more frequently in participants who received RSVpreF formulated with an aluminum hydroxide adjuvant. No maternal or infant deaths were reported during the study. There was one stillbirth which occurred in a maternal

participant who received placebo. Premature births were reported at 5.3% of participants in the vaccine group versus 2.6% in the placebo group. Next slide. Maternal to infant placental transfer ratio of RSV neutralizing titers of RSV A, RSV B, and combined RSV A and B was greater than one for all vaccine groups. Next slide.

Acute respiratory illness surveillance was conducted in infants for an exploratory analysis of efficacy against RSV-associated LRTD. When all vaccine groups were combined and compared to placebo, preliminary efficacy of maternal vaccination against RSV-associated medically attended LRTD and medically attended severe LRTD were 75% and 83%, respectively. Note that this is limited by smaller case counts. Next slide.

Now I will discuss results briefly from study 1004, which is a phase 2b multi-center placebo controlled, randomized, observer blind study in healthy non-pregnant individuals 18 to 49 years of age randomized to evaluate concomitant administration of RSVpreF and Tdap. 713 participants were randomized to one of five vaccine groups. A 0.5 mL dose of study vaccine or comparators was administered intramuscularly. 709 were vaccinated. Participants received two injections at visit one in accordance with a randomization schedule. Study participation is complete at visit two, which is at one-month post-vaccination. The site of vaccination for RSVpreF containing product is in the left deltoid muscle and I'll be focusing on groups in the red boxes, which include the final RSVpreF formulation as well as placebo or comparators. Next slide.

Primary immunogenicity endpoints were demonstration of non-inferiority of antibody responses when RSV vaccine was co-administered with Tdap compared to vaccine antigens in Tdap alone or to RSV vaccine alone. Antibody responses were measured one month after

vaccination, and the statistical criteria for success are listed here. Next slide. Safety outcomes were assessed through one month after vaccination, which is the end of this study. Next slide.

The statistical criteria for the primary endpoints for tetanus and diphtheria as well as the RSV secondary endpoint were met. However, as shown here and mentioned, the non-inferiority criteria for the primary endpoint for anti-pertussis components were not met. Statistical criterion for pertussis was the lower limit of the 95% confidence interval for GMC ratio is greater than 0.67%, which was met. Next slide.

The most frequently reported reaction for all groups was pain at the injection site. Most local reactions were mild to moderate with a median duration of approximately two days. The most commonly reported systemic reactions were fatigue, headache, and muscle pain. Most systemic reactions were mild to moderate with a median duration of one to three days. Severe headache was reported by three participants in the RSVpreF only group, two in the RSVpreF Tdap group, and one in the Tdap only group. Next slide.

There were two cases of severe and related adverse events. One report of severe constipation in the RSVpreF group. One report of severe lymphadenopathy in the RSVpreF combo with Tdap P group. Severe lymphadenopathy for that case was recorded in the case report form as enlarged lymph nodes of the left axilla. Onset was nine hours after the dose, and duration was for one week. RSVpreF, of note, had been administered in the left arm, or deltoid. All related AEs were resolved by the end of the study. For medically attended AEs, there were two in the RSVpreF group, which included one diagnosis of hypothyroidism and one case of a hand fracture. There was one event of spontaneous abortion that occurred after completion of the study on day 42, reported by a participant in the RSVpreF 240 microgram with aluminum hydroxide placebo group, which, of note, is not the final formulation. Next slide.

Now I will discuss the applicant's proposed pharmacovigilance plan. Next slide. The pharmacovigilance plan is intended to include safety specifications for the product based on comprehensive available safety data that encompasses different indications as well as use in different patient populations. FDA has recommended that the sponsor align the pharmacovigilance plan for ABRYSVO, BLA 125769 proposed for older adults indication, with pharmacovigilance plan for ABRYSVO 125768, which is proposed here for the maternal immunization indication. Presented here is the applicant's pharmacovigilance plan, currently under review. As you may be aware, the applicant is seeking approval for the identical product we have discussed at a previous VRBPAC, for an older adult indication. The applicant typically has one pharmacovigilance plan for a product, so in this case, FDA has recommended that Pfizer harmonize pharmacovigilance plans between the two indications. The applicant plans to perform a post-marketing safety study to evaluate pregnancy and neonatal outcomes in individuals exposed to ABRYSVO in the general pregnant population in addition to the immunocompromised pregnant population. Next slide.

Finally, I will provide a summary and questions for the advisory committee. Next slide. The statistical criterion for study success, which was demonstration of vaccine efficacy greater than 20% for at least one of the two primary endpoints, was met. Effectiveness of RSVpreF immunization during pregnancy was demonstrated to prevent severe RSV infant MA LRTD within 180 days. The data suggests that RSVpreF immunization during pregnancy is effective in preventing RSV MA LRTD in infants. However, this endpoint was not met within 90 days after birth. Next slide.

For vaccine efficacy against RSV MA LRTD within, up to, one year after birth, statistical criterion for success was met with a confidence interval lower bound of greater than 0% at all

time points. However, as I mentioned, these analyses represent cumulative RSV cases from day zero. The number of new cases of RSV confirmed MA LRTD after the 180-day time point were noted to be similar between treatment groups, with 35 new cases in the vaccine group and 39 in the placebo group. Interpretation of analyses beyond 360 days was limited by the low numbers of participants as of the data cutoff. Next slide.

Across all studies, the safety database included 3,797 maternal participants who received the final formulation of RSVpreF with 47% from US sites. Severe local and systemic reactions following RSVpreF vaccination were uncommon. The reactogenicity of RSVpreF was comparable between maternal participants enrolled in the US and the overall population. No meaningful differences were observed between treatment groups and the overall rates of unsolicited AEs within one month after vaccination. AEs and SAEs and infant participants were reported at a similar frequency between groups. An imbalance in the rates of prematurity, with more preterm births occurring in the vaccine group compared with the placebo group, though not statistically significant, was observed. A similar finding was also noted in the phase two study. These findings may be of consideration for further safety evaluation through post-marketing studies. Next slide.

I will now present the voting questions for the advisory committee's consideration. Number one, are the available data adequate to support the effectiveness of immunization with ABRYSVO during the second or third trimester of pregnancy, 24 to 36 weeks gestation, to prevent RSV lower respiratory tract disease and severe RSV lower respiratory tract disease in infants from birth through six months of age? Please vote yes, or no, or abstain. Number two, are the available data adequate to support the safety of immunization with ABRYSVO during the

second or third trimester of pregnancy to prevent RSV LRTD and severe RSV LRTD in infants from birth through six months of age? Please vote yes, no, or abstain. Next slide. Thank you.

Q & A

Dr. El Sahly: Thank you, Dr. Hong-Nguyen. The first question comes from Dr. McMorrow.

Dr. McMorrow: Thank you. I just want to appreciate that. That was an excellent presentation and enormous amount of information that you just covered, the preparation here.

Dr. Hong-Nguyen: Thank you.

Dr. McMorrow: My question is about the duration of protection afforded by this vaccine. The primary endpoint of efficacy is presented as VE in zero-to-90 or zero-to-100-day increments. And as you know, seasonality of RSV has been a bit disrupted lately. And certainly even in the US there are areas of the United States where seasonality is not uniform. The duration is longer, et cetera. And so I would say for myself, in terms of trying to evaluate the duration of protection and whether it truly is protective for up to six months, it would be nice to see a stratified analysis of zero-to-90 day, or one-to-90 days of life, versus 91-to-180 days. And I just wondered if that was something that you all have considered or performed. Thank you.

Dr. Hong-Nguyen: Just give me one moment. I'm going to pull up an extra slide that I think you're referring to in terms of what might answer your question. Could you please go to slide 11 for the backup slide? Slide 11. So for within the first 90 days, which is one question I think you were asking about, this is not a powered analysis, but a post hoc analysis kind of stratifying or breaking down within the first 90 days by 30-day time points. And you can see that there is some efficacy, at least within the first 30 days. A little bit questionable at the later time points within the first 90 days. The confidence intervals were very wide and a little bit difficult to interpret this.

And then your other question, I think, or comment was about kind of beyond six months. As I mentioned, we have very limited data here in this study with very limited case counts beyond that time point, but I think because we're talking about passive immunity here, wouldn't necessarily expect a very long duration of protection from this vaccine administered to maternal participants to protect their infants. So I believe that our impression, as of our FDA review as of now, is that there is efficacy demonstrated at least to six months. But as I mentioned, and I could go back to those slides if you would like, but beyond the 180-day time point, a little bit less pronounced. Does that answer your question?

Dr. McMorrow: This is excellent. My specific question was for 91 to 180 days, because I think that's of relevance to the duration of the season in certain locations. So, thanks.

Dr. Hong-Nguyen: I'm sorry, I don't actually have a table of that. I would invite Pfizer to comment more if they can provide any additional information on this.

Dr. Gruber: I am going to ask the team. Again, I assume you're asking us to do this now. We can certainly do that. If we bring up slide one, this represents vaccine efficacy by interval of months. Again, addressing the point that was raised about how can we be confident about the nature of efficacy extending out. Maybe while this slide is up, we've got the one also with severe LRTI, that would be helpful to have as well. But you can see that as you, and again, we're recognizing that the study was not powered to look specifically at these small intervals. And as you've already heard, the confidence intervals are quite broad, but you can see that, working all the way through, that the efficacy persists out to six months. And that this is some of the data that you just heard shared by the FDA.

If we bring up slide number two, please, to the screen. This represents the efficacy for severe disease, again, broken out by intervals. Once again, obviously the confidence intervals

become quite broad, but I think you see compelling evidence that when you look at the intervals, even out to four and five and five-to-six months, that you have 57% efficacy against severe disease, for instance, in that five-to-six-month interval. So I think this is compelling information, obviously made possible by the fact that over that full six-month period, there were children continuing to be exposed so that you could demonstrate that efficacy. That's not true for all cases. There have been other studies that have been done that haven't been able to demonstrate that durability for, potentially for monoclonals or other vaccines. So this is a positive finding in our regard to suggest there is meaningful clinical efficacy out to six months.

Dr. El Sahly: Thank you both. Next question is from Dr. Ault.

Dr. Ault: I think one of, one of the things you could consider in your post-marketing surveillance is looking for pertussis cases in newborns. Maternal Tdap vaccine is very effective at preventing that, and so it would be a safety signal that you could find right away if there really is interference with co-administration. And there's plenty of data, since that's a 10-year recommendation, to base a study on.

Dr. Hong-Nguyen: Excellent point. Thank you.

Dr. El Sahly: Thank you, Dr. Ault. Next question is from me. If you don't mind going back to slide 54. I can say it awaiting the slides being pulled up. Basically 4.7% versus 5.7% in terms of premature birth, which is slightly different than premature delivery. But also here we have the phase 2b where different formulations were tested, but also the placebo invariably had the lowest premature birth. So we have now five different comparisons, and in every comparison the premature birth were more common and individuals who got the preF. Statistically speaking, what is the likelihood of this happening by chance?

Dr. Hong-Nguyen: I don't know if I can comment specifically on statistically speaking and chance in this case. We know that compared to lower background rates, it's less than what is in lower background rates, which is estimated to be 10% both in the US and worldwide. However, we understand that this is a clinical study where we would expect that, due to excellent care and different circumstances, we wouldn't really be okay with something close to that rate, regardless. So you know, the difference is notable, and FDA did note this as well. And this is partly why postmarketing discussions would definitely be focused on this, so if this goes to market. And again, mentioned, this was not found to be statistically significant, but of course should not be dismissed and should be focused on for further discussions and considerations.

Dr. El Sahly: Yeah, and I mean in terms of the background rate, these women were pre-selected to have over them background rate, so that's not surprising. But even in women with low background rate, this was observed. So let alone, you know, once we start talking about twin pregnancies and older, you know. Anyway, we'll, I guess, have more time to discuss later. Dr. Portnoy is next. Dr. Kim after, and then we will break. And there will be opportunity to ask more questions.

Dr. Portnoy: Oh, I hate to be between the group and lunch, but one of the biggest concerns I had about development of RSV was the fact that there was this enhanced disease that occurred in infants in a previous vaccine. We were all, we actually had a meeting a long time ago discussing how you could possibly test a vaccine in infants and make sure that it was safe enough to do it without, inducing enhanced disease. I think this is a brilliant way to do that, vaccinate the moms and then hopefully the passive antibody will do the job. My question is, I'm still concerned about enhanced disease, though. Was there any effort to look for or to evaluate for the possibility of

enhanced disease in infants of mothers who received the vaccine? Did any of them show an unusually, you know, severe case of RSV or was there an effort to look into that?

Dr. Hong-Nguyen: I don't specifically have an answer to your question based on the available data that was provided to us in this Biologics Licensing Application. I definitely validate your concerns that, I think most people are concerned about the possibility of enhanced respiratory disease based on history and all the historical roots of the RSV vaccine program. And my understanding is that I think Pfizer is, I would ask Pfizer to comment a little bit more on anything that they're able to disclose, but in regards to animal studies sort of looking at concerns that regarding enhanced respiratory disease.

Dr. Gruber: Yeah, so thank you, Bill Gruber from Pfizer. I think you're absolutely right. The circumstance where enhanced disease was seen in, was in a very different circumstance where you had naive young children exposed for the first time to an inactivated vaccine with the postfusion form, informal. And we know now or, or have good evidence to believe, that that was due to an enhanced TH2 response and the presence of binding antibody that wasn't neutralizing. We don't have that here. We clearly have high levels of neutralizing antibody that are passively transferred from women who had had prior exposure to natural infection, and we're boosting that type of response. And as we've shown, that passes the placenta, reaches levels that are well above utilizing, levels that would be associated with protection.

But in addition to that, if we can bring up slide number two, I think this helps inform in somewhat of an indirect way a reassurance that we're essentially not leading to enhanced disease farther on. So Dr. Munjal showed you a different version of this slide, but this just represents what was seen over time in terms of continued efficacy. And as has been pointed out, the efficacy is really driven by what's seen in the first 180 days. And you've heard that the split looking

between 180 and 360 is 35/39. So we can't claim that there's additional efficacy there, but there's another reason why that's important. Because it's suggesting we're not kicking the can down the road in that, as antibody declines, those children who receive the vaccine are not worse off. There's not an increased risk for them acquiring disease. So I think that, coupled with the overall efficacy where we're preventing hospitalization, where we're preventing severe LRTI and preventing LRTI, provides real confidence that there is no risk here of enhanced disease.

Dr. Portnoy: Wow. Thank, thank you. I just have to say that I was very concerned about that and the solution you came up with to do passive immunization I think is brilliant and I really appreciate it. Thank you.

Dr. El Sahly: Dr. Kim.

Dr. Kim: Oh, thank you. I wonder if we can go back to slide number 60, please. And a question for Dr. Hong-Nguyen is on slide number 60. If you would review the content of this slide on which you discussed immunogenicity, or the interference of immunogenicity when Tdap is administered, concomitantly with the RSV vaccine. And specifically if you would compare the pertussis component to tetanus and diphtheria and describe for us once more what the difference is with pertussis component.

Dr. Hong-Nguyen: I'm not sure if I understand, but I think you're getting at the difference between looking at the data here for diphtheria and tetanus compared with pertussis. So, I mean, these are all lower than the statistical success criterion, which was greater than 0.67 for the lower bound, but a little bit more on the border for anti-PT. And I would say if there's further details about specifics on this topic, perhaps Pfizer could elaborate.

Dr. Gruber: Yes, thank you. So we recognize the results that were obtained in the non-pregnant population for administration of Tdap. And it is correct that we didn't meet non-

inferiority for the pertussis containing antigens but did for the others. I think there are two ways to look at that. And then I think, as is noted in the FDA briefing document, we're under discussion with the FDA about how this should be handled. This has not been a unique experience. There are other circumstances in which pertussis-containing vaccines have been administered in conjunction with, for instance, meningococcal conjugate vaccines or influenza vaccines, where the pertussis antigens did not meet non-inferiority. And yet those vaccines continue to be recommended to be given together. So that's one possible outcome. And again, we'll be discussing this with the FDA.

On the other hand, I want to be mindful of the fact that particularly in a US population, particularly given the interval that was studied here from 24 to 36 weeks, with women coming in with successive visits for prenatal care, there's the opportunity to actually give the RSV vaccine at a separate time from Tdap or, for that matter, influenza vaccine. So I think we shouldn't see this as constraining, in my view, in terms of the ability to apply this vaccine to a pregnant population. Because there either is the possibility that we could still administer it together, or there's enough spacing during the second and third trimester that we could space the vaccines.

Dr. Kim: Thanks for the elaboration.

Dr. Hong-Nguyen: And one more comment, I just wanted to mention that now, granted, there is clinical concern about, you know, especially since Tdap is a common administered vaccination routinely during pregnancy. So it's a valid concern about this finding. This was done in non-pregnant individuals. So we don't have data on this concomitant administration in pregnant individuals. And we, the FDA, do expect to include the findings of the diminished responses to pertussis antigens with concomitant administration of ABRYSVO and Tdap in the ABRYSVO prescribing information. As per our labeling regulations and longstanding practices for vaccines,

we anticipate including this information in the clinical studies and drug interactions section of the prescribing information.

Dr. Kim: Perfect. Thank you.

Dr. El Sahly: Thank you both. Though I would like to, I mean, in terms of the issue of multiple antenatal visits, that's the best-case scenario. And unfortunately in the last few months, we've all seen data about maternal health in the US that is less than what we had hoped for. So regardless, thank you all. We will have the opportunity to discuss more right after lunch. We are bound by the Open Public Hearing, so this is our anchor. It is going to be at 2:15 PM Eastern Time, so that gives us a little less than 45 minutes for break.

Dr. Atreya: Hana? Hello, Hana. This is Prabha. The Open Public Hearing starts at 1:15 PM Eastern Time.

Dr. El Sahly: Yes. One meeting I'm going to get the Eastern and Central together, y'all. Yes.

Dr. Atreya: Thank you.

Open Public Hearing

Dr. El Sahly: All right. Welcome to the Open Public Hearing session. Please note that both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in this meeting. Likewise, FDA encourages you, at the beginning of your

statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. I turn the meeting now to Valerie Vashio, who will read the guidance and introduce the Open Public Hearing speakers.

Dr. Vashio: Thank you, Dr. El Sahly. Before I begin calling the registered speakers, I would like to add the following guidance: FDA encourages participation from all public stakeholders in its decision-making processes. Every advisory committee meeting includes an Open Public Hearing, OPH, session, during which interested parties and persons may present relevant information or views. Participants during the OPH session are not FDA employees or members of this advisory committee. FDA recognizes that the speakers may present a range of viewpoints. The statements made during this Open Public Hearing session reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate agency agreement with the statements made. With that guidance, I would like to begin. Every speaker will have only four minutes to make their remarks. We request each speaker to stay within their allotted time, and we thank you for understanding. Let's begin with our first OPH speaker, David Allely.

Mr. Allely: Hello. Can you hear me?

Dr. El Sahly: Yes, we can.

Mr. Allely: And I'd like to just confirm, before I get started, that you can see my slides?

Dr. El Sahly: Yes, we can.

Mr. Allely: Okay. Great. Uh, good afternoon. Thank you for the opportunity to speak. My name is David Allely. I'm a medical student at Mount Sinai, and I'm here today to share my thoughts on the questions facing the committee. I don't have any conflicts of interest, just a lot of

debt. Uh, please excuse what may feel like a rushed presentation. I think there are a lot of important things to cover, and my time is limited. Next slide.

I have three arguments that I hope the committee will engage with: First, with respect to efficacy, the Matisse trial did not report all-cause hospitalization, all-cause LRTI hospitalization, or even all-cause severe MA-LRTI. Next slide. Here we see the only all-cause outcome reported in Matisse, all-cause MA-LRTI, in which vaccination unambiguously showed zero benefit at any time point measured. I will direct your attention to the column to the far right, which shows vaccine efficacy. We did not see this data mentioned in Pfizer's presentation today. The FDA presentation did acknowledge it but did not provide the actual point estimates and confidence interval as we can see here. We're left to wonder whether infants of vaccinated mothers had any overall reduction in risk of severe LRTI or hospitalization. Next slide.

In the interest of time, I'll briefly mention that, in the primary analysis, three cases were withheld from each group that met criteria for severe MA-LRTI, and their inclusion would've increased the cases in the vaccinated group by 50%, from six to nine, but only increased cases in the placebo group by 10%, from 33 to 36. This made the point estimate in confidence interval appear more favorable to the vaccine product. When Pfizer's presentation mentioned the lower bound of the CI was above 40% at all time points, that is misleading, as they're using bias data that omitted these other cases. This omission is acknowledged in the results section of the New England Journal of Medicine, April 20th publication. Next slide.

I no longer see the slides. Is everything working?

Dr. El Sahly: Joe, we no longer see the slides.

AV Support Joe: Ah, yes. One second. We'll have him back up.

Mr. Allely: Great. So, furthermore, when we look at the RSV associated hospitalization data, we see that at 90 days, there were 10 hospitalizations in the vaccinated group and 31 in the placebo group. Please direct your attention, again, to the rightmost column and look at the width of these confidence intervals. If this was a primary outcome, it would've failed to meet the 20% minimum for the lower bound of the confidence interval at every single time point. The study had too few events to prove much of anything. I want to mention that these confidence intervals were not included in Pfizer slides this morning showing the same data, and I think it would be helpful in the future if the FDA required consistency in data presentation to prevent this kind of asymmetry in data provided to this committee. Next slide.

With respect to safety, we know about this increase in preterm birth. It's been discussed a lot, and I assume will be more so. So we can jump to the next slide. I want to add this: I haven't heard this mentioned at all, but in February of last year, GSK halted all of their maternal RSV vaccination and their trials following the discovery of an increased rate of preterm births, which they concluded led to the increased rate of neonatal death in their study RSV MAT-009. There's been no mention of this today, and it's obviously of major importance. This data can be readily found in the documents that GSK submitted a few months ago during consideration of their adult RSV vaccine. Next slide.

Here we see the preterm births in Pfizer Matisse trial. In their presentation, they mentioned that this is not statistically significant, which may be true; but, if real, it would be highly clinically significant, and they simply weren't powered to detect this difference. The arguments made about the outcome being limited to certain countries is of limited help, as interpretation of these subgroup analyses is difficult. Next slide. We'll actually move on in the interest of time. Next slide.

And with respect to effectiveness, the study omitted breastfeeding data, as we know is an important potential modifier of vaccine efficacy. We heard earlier that there was no difference detected, but this data should be presented. There was also technically no difference detected in preterm births, and yet the data we do see with respect to that outcome, are highly concerning. Next slide. And in the interest of time, I'll now wrap up. Next slide. So, in summary, this committee is tasked with making recommendations regarding the safety and efficacy of this product based on a single phase three trial. With respect to efficacy, we have only one all-cause outcome reported for which the vaccine had zero effect at any time point measured. Members of the committee and the FDA, please require that Pfizer prove this product can reduce all-cause hospitalizations and severe infections, not just the number of positive RSV swabs. Without all-cause data, we simply do not know whether there was any reduction in hospitalization or even severe LRTI, which is the only reason an RSV vaccine is desirable.

With respect to safety, this is the most important message I would like to emphasize. Today's presentations have not demonstrated the safety of this vaccine. There's a known safety signal of increased preterm births leading to neonatal death with a similar product which led GSK to halt their maternal RSV trials. It's unimaginable to me that anyone could comfortably sign off on this product's safety given this limited data.

To put it simply, a nearly identical product led to this increased rate of preterm births and neonatal deaths. In Matisse, ABRYSVO led to an increase in preterm births, but no signal of neonatal death. The same imbalance was seen in the phase two trial reviewed today. We have every reason to be highly skeptical of the safety profile of this product, and the data provided today does not begin to alleviate my fear that this product may do significant harm. I have more

to say, but I want to be respectful of the time I was allotted. Thank you for your time and consideration.

Dr. Vashio: Thank you, Mr. Allely. Jester Jersey.

Mr. Jersey: I'm present. Can you hear me?

Dr. El Sahly: Yes, we can.

Mr. Jersey: Okay. Wonderful. Thank you. I want to begin by saying that I have no pharmaceutical conflicts nor financial conflicts to disclose. Good afternoon to the FDA and the VRBPAC advisory committee. Thank you for allowing me to present again. Today I will be talking about increasing vaccination rates, addressing gaps in immunization through policy advocacy and collaboration. Next slide, please.

First, assessing our current situation is in order. Next slide, please. After three years since the pandemic, COVID is currently on the decline once more. Also, we've just come out of one of the most severe flu seasons in the last decade. Lastly, we have a new tool in the fight against RSV, the vaccine ABRYSVO being considered today. Things may appear to be heading on the right track; however, according to the International Federation of Red Cross and Red Crescent Societies, or IFRC, the world is dangerously unprepared for the next pandemic. This assessment came just four days after I initially addressed VRBPAC earlier this year. Next slide, please.

The IFRC Secretary General Jagan Chapagain went further stating that the pandemic should be a wake-up call to prepare for the next crisis. Next slide, please. Secretary General Chapagain recommended that world leaders center strategy around building trust with local communities but acknowledge that tackling health inequality and leveraging community members in lifesaving work is also important, echoing my comments in January. Next slide, please. While the IFRC and I have mentioned this, this is nothing new. US Surgeon General

Vivek Murthy advocated a similar strategy two years ago this month regarding working with local community members. Next slide, please.

As we address RSV in the future, there are things we should keep in mind. First, coverage from the pandemic health emergency has just ended. We need to learn the lessons from addressing COVID and build upon the strategies that work. Second, vaccine rates for flu and COVID boosters were low. Next slide, please. Third, routine vaccine rates for non-seasonal vaccine preventable diseases have reached a 30-year low. This last point connects with the previous two points. Vaccine fatigue could play a significant role in what the future vaccine rates for an RSV vaccine would look like. Next slide, please. Vaccines will always be necessary. Therefore, we have to make routine vaccines routine again because they work and still save lives. Next slide, please.

What's next? I have three suggestions, and that's through policy, advocacy, and collaboration. Next slide, please. First, invest more in vaccine programs that save lives from COVID, such as Section 317. People think hesitancy is the biggest issue, but access could be playing an even larger role than most realized, just as important as to work with policy advocates who support equitable vaccine access. Next slide, please. Support community vaccine advocates, this includes social media influencers, to reach online audiences nationwide. Next slide, please. Finally, collaborate with allies on the ground, especially those that are community based and have experience working on a national scale to build trust and ensure equitable access. Next slide, please. Don’t just work for those you serve, but work with them too because often the best vaccine advocates are the people you're helping. Next slide, please.

To summarize: Vaccines still matter. To get them to those who need them, enact helpful vaccine policies, support health advocates, and partner with fellow collaborators to increase

vaccination rates. Next slide, please. Thank you for your time and consideration. Stay safe and have a nice day.

Dr. Vashio: Thank you, Mr. Jersey. Martha Nolan.

Ms. Nolan: Hi. You can hear me, right?

Dr. El Sahly: Yes, we can.

Ms. Nolan: Good afternoon. My name is Martha Nolan, and I am the Senior Policy Advisor for Healthy Women, an advocacy organization dedicated to educating women so they can make informed health decisions and advocate for themselves and prioritize their health and wellness. Healthy Women believes vaccines are an essential tool to protect against serious disease across our entire lifespan, and we routinely share information and updates on what is available to keep women and their families informed. We are often the caretaker. Women are often the caretakers of both the young and the older generations in their family and are making the routine healthcare decisions needed to keep the family healthy.

The intergenerational nature of our society lends itself to an environment in which the viruses can spread among those most vulnerable, from the youngest to the oldest. The dramatic rise of respiratory syncytial virus, RSV, cases in the United States during the fall of 2022 served as an important reminder of how those types of respiratory viruses can aggressively cross that generational gap. Particularly, we saw RSV leaves pregnant women and their infants vulnerable to serious illness. According to the CDC, an estimated 58 to 80,000 children younger than five years old are hospitalized due to RSV infection each year in the US, and those infants six months and younger are at a greater risk of severe illness.

We are incredibly encouraged by the promise of potential availability of maternal RSV vaccines this year, and, if approved, we'll do our part to ensure women are informed about the

value and availability of these preventive measures. While today's conversations are important in terms of ensuring the safety and efficacy of these new vaccines, it is just the beginning of the efforts to ensure that those most vulnerable are truly protected from this virus. Following FDA action regarding approval, it is critical to ensure the value of these vaccines is accurately represented within all communities, and that we prioritize equitable and broad access to them. This is especially important given that we know maternal vaccination rates remain dangerously low.

According to the CDC, the receipt of both flu and Tdap vaccines among pregnant women decreased from about 30% in 2020 to 2021 flu season to just over 22% in the ’21-‘22 flu season. As you know, these tools are incredibly valuable in ensuring the health of both the mother and the baby, but only if we are doing our part to educate on their value and ensure all communities have equal access to them. We appreciate this committee's role in ensuring that safe, effective, and innovative new vaccines are made available to all of those who would benefit from them. With so many looming threats to our respiratory health, including COVID, influenza, pneumonia, and RSV facing us this fall, we are hopeful that all pregnant women will have access to this critical protection. Thank you for the opportunity to speak.

Dr. Vashio: Thank you, Ms. Nolan. Karen Crowley.

Ms. Crowley: Good afternoon. Can you hear me?

Dr. El Sahly: Yes, we can.

Ms. Crowley: Thank you very much. I have no disclosures or financial relationships to disclose. The Association of Women's Health Obstetrics and Neonatal Nurses supports initiatives to reduce infant mortality and improve the health status of newborns, advocates for health equity to improve outcomes and access to high, equitable, and necessary services for marginalized

populations, including women and birthing people, and advocates for unrestricted access to preventative healthcare service. Through empowering and supporting nurses caring for women and newborns and their families through research, education, and advocacy, AWHONN represents over 350,000 nurses who provide care in these specialty units and are committed to the health of their patients and infants.

As the vice president of Nursing at AWHONN, I would like to provide supporting comments on the RSV vaccine candidacy for approval, illustrating the health and economic burden of the respiratory syncytial virus, which currently has no prophylaxis or treatment available. In the United States, RSV accounts for 500,000 emergency room visits, 80,000 hospitalizations, and 2.1 million outpatient visits, and as many as 500 deaths in children less than five years of age. RSV induced pneumonia in infants less than one year of age is the most common cause of pneumonia in the United States, with those less than six months of age, born premature, with chronic lung disease or congenital heart defects, weak immune systems, or neuromuscular disorders being at the highest risk.

Data collected from states that participate in the RSV net surveillance system, which captures data on hospitalization rate of individuals who tested positive across various demographics, indicated worsening trend in the most vulnerable infant population. When comparing hospitalization trends from 2021 through 2023 RSV seasons, the number of hospitalizations for zero to six month and six to twelve month old infants increased exponentially. With only half of the current RSV season completed, there has been a 62% and a 58% increase in admission in those two age brackets between the seasons. This number will continue to climb as we head into the next RSV season.

Globally in 2019, RSV resulted in 33 million cases in children, 3.6 million hospitalizations, and over 101,000 deaths in children, with 45% of those occurring in infants less than six months of age. RSV related emergency visits surpass those of the flu and COVID-19 in infants less than one, and at times reached as 12 times as high as those previous respiratory illnesses. Most childhood deaths caused by RSV occur in developing countries, 97% occurring in low to middle income countries, and of those 4% occurring in hospitals with 80% occurring in the community.

There are disparities in the prevalence of RSV with Black, Alaskan Native, American Indian and Hispanic infants affected two to five more times higher than white infants. Approval of the RSV vaccine with maternal immunization protocol will be a critical step forward in combating the most prevalent respiratory virus seen across the globe that results in the most morbidity and mortality in healthcare system costs of all respiratory viruses. Primary prevention through use of vaccines has been well documented as safe, effective, and a cost saving approach to combat the prevalence, incidence, morbidity, and mortality associated with communicable diseases.

In addition, the success of passive immunity to newborns through maternal Tdap and COVID-19 vaccine should be considered in the development of an approval of vaccinations when safety data is evident to help reduce negative health outcomes. The Matisse trial demonstrate high efficacy and safety data in a multinational study over several RSV seasons in vaccinated individuals and their newborns up to two years post-birth. The statistics on RSV hospitalization and death in infants are concerning, and we have no way to combat the virus without prophylaxis or treatment. Protecting infants against RSV through maternal vaccination

can help turn that turnaround of hospitalization rate and deaths. AWHONN supports the approval of a primary prevention mechanism with the approval of the RSV vaccine. Thank you.

Dr. Vashio: Thank you, Ms. Crowley. Yoko Allen, MPH (She/Her) Black Women's Health Imperative.

Ms. Allen: Good afternoon. The Black Women's Health Imperative is the first and only national nonprofit organization solely dedicated to achieving health equity for black women in America. This year marks 40 years of advocating for the health and wellness of black women and girls. We understand that the risk of contracting RSV is higher for premature babies and that African American women are more likely to give birth to a premature baby as compared to white women. According to CDC, in 2021, the rate of preterm births among black women was nearly 15%, which is about 50% higher than the rate of preterm birth among white women at 9 1/2 %.

According to the National Institutes of Health, results of a birth cohort study from 1999 to 2018 showed the infant mortality, RSV mortality burden was greatest in white women infants at nearly 45%. Nearly 26% of infant RSV deaths were black, which is a 54% difference. We understand that on March 2nd, 2022, Pfizer announced that its vaccine candidate received a breakthrough therapy designation from the FDA for prevention of RSV associated lower respiratory tract disease in infants up to six months of age by active immunization of pregnant women. The FDA designation was informed by the results of the phase two-B proof of concept study, which evaluated the safety, tolerability and immunogenicity of RSVpreF in vaccinated pregnant women ages 18 through 49 and their infants. 80% of maternal participants were white, and only 16% were black, which is 133% difference, not reflected in the rate of RSV infant mortality at 54%.

The Black Women's Health Imperative supports a proven, safe, and high efficacious prenatal vaccine for RSV that will result in healthier lives, therefore, recommending ingredient transparency and more transparent study results across race, ethnicity for making informed decisions, as well as clinical trial recruitment rates that reflect the rate of infant RSV mortality. This level of transparency matters to families and their advocates. With distrust in clinical trials among black and brown populations, these recommendations would yield balanced perspectives and help increase future treatment, study participation, and support from black and brown community stakeholders. Thank you for this opportunity.

Dr. Vashio: Thank you, Ms. Allen. I also want to thank all of the participants today for sharing their perspective. This concludes the Open Public Hearing session for today. Now I hand over the meeting back to our chair, Dr. El Sahly, could you please start the next session?

Q & A for CDC, FDA, Sponsor, and Other Presenters

Dr. El Sahly: Thank you, Valerie. And welcome back to the committee members, the sponsor, FDA, CDC, and other presenters. We have now the opportunity to ask questions to everyone who was represented today. So I'm going to ask, first, we have two holdouts from this morning. So we're going to try and address those. And in the meantime, please raise your hand. So after those two questions, we can begin new questions. The first one is for Dr. Omer. He asked about the mean birth weight and not just the categorical, and then the co-admin data with influenza vaccines. And I think Pfizer should be addressing those two questions.

Dr. Munjal: Thank you very much. Iona Munjal from Pfizer. If I could have slide one up, please. And I think that your question was regarding a mean, rather than looking at the categorical, birth weight. So if I can orient you on the graph, the placebo is in gray and the RSVpreF is in blue. As you see for the total participants in the study, the mean birth weight, it

was the same at 3.3 overall. And so when we saw the difference in low birth weight, it was specifically driven in, in those in upper middle income countries in those under 37 weeks. If we look at high upper middle income, lower middle income, and low income, we see that similar rates are seen across all of the income categories by region.

In regard to your additional question that you had regarding SGA, I said the numbers were low, and I'd like to specifically tell you that there were 32 in the RSVpreF group, or 0.9%, and 38 in the placebo group, or 1.1%. These adverse events were all reported in the first one month after vaccination. We didn't have any other additional events of SGA reported in the rest of the trial. In regards to the non-inferiority with flu code administration, I'd like to refer to Dr. Gruber please.

Dr. Gruber: Yeah, if it's okay, we'll go ahead and go to that. If we bring up slide number two. So the question was asked about the nature of data that we have regarding concomitant administration of influenza and RSV vaccine. We have done a study, and these results just recently became available, and we provided them to the FDA, so they're not in either briefing document. This is in an older adult population in which Flu-ad was administered with 120 microgram dose of concomitant RSVpreF and is represented here. You can see on the slide forest plots that speak to the nature of the geometric titer ratio, with one being an equal ratio. The requirement was that these were, essentially, above 0.67, the lower bound being above 0.67. I think you can see across the board, whether we're talking about the influenza antigens or the RSV antigens, that non-inferiority was met in this population, again, non-pregnant, older adult population, but I think provides some reassurance about the potential to be able to administer the two vaccines together.

Dr. El Sahly: So we will, with that in mind, I mean, this data are very much in line with the slides shared by Dr. Chu earlier this morning in that there is interference, but not to the pre-specified level. So question from Dr. Offit, I think, is next.

Dr. Offit: Yes. Yes. Thank you, Hana. So I actually want to pick up on something that you alluded to, Dr. El Sahly, as well as, actually, the first person who spoke in the Open Public Hearing about GSK's vaccine. So this is something I think we do need to talk about here. So GSK also had a maternal vaccine program. Their vaccine was almost identical to this vaccine, and it was 120 micrograms of a preF protein. In that case, it was just a subtype A, but un-adjuvanted. So unlike the greater than 60 year old vaccine, which did have an adjuvant, this was un-adjuvanted. So it's for 120 micrograms un-adjuvanted given at 24 to 36 weeks. And then they had a problem with premature births.

Now, there was a meeting in Lisbon, an RSV meeting, a two-day RSV meeting, within the past couple weeks, where GSK presented, trying to sort of drill down on those data. And at least what they presented in the 11 or 12 slides that they presented, and it's an open meeting. Anybody can look at these slides. What they found was that, like Pfizer, where they saw this was in low and middle income countries, not high income countries, there was also a temporal association, meaning there was sort of a several month period where you had that increase in statistical association with premature births, but not at other times.

And the third thing, and probably most importantly, it wasn't as much as it was an increase in premature births as during that period of time, when there was clearly an increased risk, there was a decrease in the placebo group. So why would that be? It was like a U-shaped curve. Why would there be a decrease in the placebo group? They argued that when you looked at where there were other vaccines given, it may have been that there were other vaccines given

to that placebo group that weren't given in the RSV F protein group, specifically a COVID vaccine, which then would cause a lower instance of premature birth, say, in that group.

But, in any case, if they were trying to make a case for why it was that this was just a statistical bizarrity and not something real, why have they halted or arguably abandoned that program? Because that is hanging over this program. I mean, if GSK has truly abandoned a program on a similar or almost identical vaccine, that is going to hang over this program. So I think it does, as David Allely said in that first presentation, I think it does need to be addressed. Thank you. And I'd like the FDA to address that, actually. Dr. Hong-Nguyen, if you could address that. I mean, 'cause you obviously have seen the GSK data.

Mr. Toerner: Hi. Good afternoon. My name is Joe Toerner. I'm the acting Deputy Director in the Office of Vaccines Research and Review at CBER, FDA. I'm happy to provide a response to that. You know, we're here today to discuss Pfizer's product. We're not at liberty to provide comment on other vaccines that are not the subject of today's discussion. We hold very close proprietary information, and it just wouldn't be appropriate for us today to comment on another manufacturer's product.

Dr. Offit: Yeah, the only thing I would say is that this, these are not proprietary data. These data have been publicly presented. They're clinical data or safety data. They are not proprietary. And they do, they do impact this. I think it's –

Mr. Toerner: Yeah.

Dr. Offit: As I said, I think we need to have that discussion.

Mr. Toerner: And we very much look forward to your discussion on this topic this afternoon. We very much look forward to it. It's just that you're asking us to comment specifically on another sponsor's information today. And we're just not at liberty to do that in this forum.

But I did, while I have the podium, I did want to draw your attention to a topic that was raised this morning, and it had to do with birth outcomes in different countries. And it was discussed that in upper middle income countries, there was a difference in birth outcomes that was noticed. But I wanted to draw your attention to a slide that's in, or a table that's in our briefing document. It's table 14 on page 35, and we also have it as one of our backup slides. It's slide number four, is our backup slide. And it just describes the data that was observed in South Africa looking at live birth outcomes. But I want to draw your attention to the data in the United States on live birth outcomes. And, again, it's in our briefing document, table 14. Thank you.

Dr. El Sahly: Well, I mean, the trends, the US and South Africa, both are showing in the same direction.

Dr. Gruber: Yeah.

Dr. El Sahly: One is just more than the other.

Dr. Gruber: Yeah. So this is Dr. Gruber from Pfizer. Could I be permitted to respond to Dr. Offit's question?

Dr. El Sahly: Sure.

Dr. Gruber: Yeah. So I certainly agree with the FDA. We're here obviously to discuss, you know, Pfizer's data, and, of course, we don't have privileged information as far as GSK's data is concerned. Dr. Offit had mentioned, you know, at least one potential confounding factor. We don't know about what other factors may have affected their results. I would remind the committee, for those that are familiar with that data, that they actually saw an increased death rate in their study, which may have, of course, prompted, as you might imagine, the DMC to stop the study.

We actually saw just the opposite of that. We've actually seen a lower number of deaths, albeit the total numbers are small, but certainly don't fit with the experience that existed in the other sponsor study. I will take a little bit of an exception to the notion that the vaccines are in some way identical. They're not. True, they both essentially address the RSVpreF protein, but the Pfizer vaccine has been stabilized in different ways than the GSK. The vaccine manufacturing process is different and the excipients are different. I'm not saying that that necessarily explains one way or another, but I do want to dispute the idea that the vaccines are absolutely identical. The target is clearly the same.

Again, we saw, of course, as we've already told you, no overall significant difference in preterm births, although they were numerically higher in the RSVpreF group. And it's already been stated that was driven by upper middle income countries. And we can just bring up slide number two. This recapitulates, to some extent, what you just heard from the FDA, in regards to table 14. We have similar information in our table 25, I believe, within the briefing document, but I'd highlight, again, the nature of where this signal, presumptive or at least possible signal, has occurred. And it was within upper middle income countries driven by South Africa. That's completely discordant with the bookends on either side.

Now, admittedly, the low middle income and the low income countries, small number of preterm births in that setting. But at least we're not seeing a split that favors or indicates a higher rate in the vaccine group. But I really want to draw your attention to high income countries, which includes the United States. And I want to also point out that in the circumstance of the proportion of premature births, it existed in high income and upper middle income countries. They're actually about the same. But the driver here, because there's so many more individuals born in high income countries, consequently they're more premature births. And so there's the

opportunity to have more precision around the potential for whether there truly is a signal. And as you can see here, and as I briefly mentioned in my response this morning, excuse me, there are an identical number of preterm births in high end countries between the RSVpreF group and the placebo group with the denominators only differing by a small amount. So you can see that the overall incidence is basically the same in that circumstance.

If we talk about low birth weight, again, the difference is narrow, which, again, I think is important, as Dr. Munjal described, because birth weight is a more objective measure, I think, of prematurity. And ultrasound has some potential for error. I think, if we can bring up the death piece, because I think this is a particularly important point. So to slide number three, please. And again, I know this was already presented, but I want to make a point about the nature of what we're describing here. So you've seen the total infant death rate already, and, as I already said, this is distinctly different from the other sponsor's study. And in every circumstance where we're looking here, whether it was death due to RSV, where, you know, sadly there was the one child who died in Japan or we're looking at preterm deaths, or in terms of neonatal deaths, you can see that, again, there's, if anything, at least an observed incidence that's lower in the vaccine group compared to the placebo group.

Now, I grant, again, the total numbers are small, but at least we're not seeing sort of a reversal here that would suggest that there's an increased risk. Of those seven neonatal deaths that occurred in the course of this study, two were, of course, in the RSVpreF group and five in the placebo group. And all of those were in low middle income countries. So the nature of, you know, something that might be affecting those particular countries differently than what was happening in the United States, and I think is, at least from a death perspective, is not the case. And so I think we need to place all of this in context.

As you've already heard, the overall results show no statistically significant difference. The results, you know, are driven by the upper and middle income countries, with the high income countries not showing this difference. And as you've heard from us, as well as the FDA, there's the real opportunity then to look at this during the period of pharmacovigilance when we have larger numbers of women being vaccinated to determine whether or not there is, in fact, any sort of a signal.

But the evidence to this point provides no real support when we take the totality of it, based on the Pfizer vaccine, for an increased risk of prematurity. And we can investigate that again, post-approval, in a setting where, I might add, and again, you know, there's an expectation, given what I've already described to you, that we have the potential to keep 16,000 children out of the hospital if the vaccine was universally applied in the United States and over 300,000, you know, medically attended visits. You've heard from a number of people, even on the committee, about the long length of time that people have been waiting for this vaccine. So here's an opportunity.

Dr. Offit: Okay. Just two quick points, 'cause I don't want to spend the whole time, Hana's whole hour doing this, but just two quick points: One is that in that study, in the GSK study, while death was sort of what got everybody's attention, it was associated with severe premature birth. I mean, those weren't two separate things. It was severe premature births leading to deaths. It was the same thing. It was severe prematurity. Secondly is, it's a little hard to imagine why giving 120 micrograms of a preF protein in each case on adjuvant, the difference in whether you see premature births would be solely based on how that protein was stabilized. I mean, I can't imagine what that mechanism would be, but I'm open-minded to –

Dr. Gruber: Well, again, I think that's a key point, right? I mean, obviously, you've said something important, Dr. Offit, obviously it's hard to imagine what that would be. Actually, if I can just take one additional minute of time to show something I showed before to get to that last point that you mentioned. So slide two up, please. And, again, I want you to just focus on that last part. You were talking about the nature of vulnerable infants and extreme prematurity, and I would argue that low birth weight less than 1500 grams, speaks to that very group that you were saying, you know, had the increased death rate. Well, we actually had fewer, again, numbers are small, but certainly nothing to suggest a signal where we had four in the vaccine group and eight in the placebo group amongst low birth weight infants, less than 1500 grams. So, again, taking the totality, the evidence, it's hard to come up with a compelling case for an increased rate of prematurity in the vaccine group.

Dr. El Sahly: Okay. So to stay on that topic, the phase two-B, which was even a smaller study, and which had additional arms with aluminum as an adjuvant, also everything favored, you know, all the preterm birth differences was heading the direction of the vaccine as opposed to placebo. And this particular study began enrolling a year, I think, before the other one. So the temporal association question is different, is, you know, wouldn't apply. So what would be the explanation there? I mean –

Dr. Gruber: Well, I think, again, I'm going to ask Dr. Munjal maybe to describe something more about the respective studies and combine the data. And you've also heard from the FDA, their view on this, the phase three study is sizably larger. The number of total prematures in that phase two study is smaller. So the confidence intervals around any sort of observations there are necessarily much bigger. So I would hesitate to draw too much inference from a small pilot sort of experience, as opposed to what I've described to you where we have, particularly within high

income trajectories, including the United States, a large number of premature births to look at. And in that circumstance, we did not see a statistically significant difference. But, Dr. Munjal, I don't know if you wanted to comment more.

Dr. Munjal: Thank you. So if I can have slide two up, please. Because the very small numbers in the phase two-B study, this study actually, through the inclusion/exclusion criteria, involved mostly healthy moms. But if you look at slide two, what we did, I think, that was helpful is that we combined the phase two-B and the phase three data so that you can see the totality of the preterm infants that we represent in both studies. So when you look at the pooled RSVpreF on the left in the dark blue, that's any amount, any dose or formulation of RSVpreF, you'll see that the total rate of prematurity that we expressed in the Matisse study doesn't change. And when you look at the specific 120 microgram group, it's exactly the same as what we reported in the phase three study. So taken individually in the phase two-B study, there was no difference between the groups, although the numbers were very small. And when you look at the combined group and the overall study, they don't really change the findings that we reported in the phase three study.

If I can have slide one, please. And there was a comment in regard to the timing from the, you know, overall. So to Dr. Offit's questions, there was no timing in terms of seasonality or time of the year. So when you look at different months of the year or when it was occurring, there was no timing there. And then related to the timing from vaccination to birth, the majority of the preterm deliveries were recurring later. And so when you look at poor outcomes like death or poor neonatal outcomes, in our study, we don't see those poor outcomes, death being one of them. And this is probably due to the fact that most of the infants are born very near term and not proximally related to the vaccine. Thank you.

Dr. El Sahly: Okay. Um, next question is from Dr. Cohn, I think.

Dr. Cohn: Thank you. This is a question for Pfizer. Related to the previous discussion, I was wondering, you break down the racial and ethnic background of the population, but I was wondering if you could give a similar type of breakdown just by the population that was enrolled in the US I think sometimes it can be confusing when you have a multi-country study and don't understand quite what the population looked like in the country that you're in. In addition to that, you did allow some women in the study that did have some stable, underlying medical conditions. And I was wondering if you could give us a little bit more information about what proportion of women in the study, especially in the US, had one of those underlying medical conditions.

Dr. Gruber: Yeah. So happy to answer both those questions. I'm going to ask Dr. Munjal to come up again to provide you some of the specifics.

Dr. Munjal: Thank you very much. So if we could have slide one come up, please. So this is the population just specific to the United States. About 45% of the total population of the study did come from the United States. So you can see here the demographic and baseline ethnicity characteristics of those maternal participants. The infant participants are similar, and the numbers between the RSVpreF group and the placebo group are similar. You can see, on the right-hand column, a reference from US data. We made specific efforts throughout the trial to recruit a diverse population both in the US and globally.

And, Dr. Cohn, I think you had referenced it in relationship to the last question, so we did actually look at infant outcomes by race and ethnicity in the United States. And in terms of both preterm delivery less than 37 weeks and low birth weight, there was no difference between non-white or white US participants or Hispanic or non-Hispanic participants between the RSVpreF

and the placebo group. So similar to the overall US population, there was no difference between those subgroups.

Regarding the rates of other background factors, we looked at, for example, age, participants under the age of 18 or under 20, or over the age of 35, 'cause we know age is a risk factor in pregnancy. We did have a substantial number of participants, for example, in advanced maternal age. When we look at background factors though, like hypertension, anemia, and preeclampsia, the background rates of those were actually quite low. And that is likely due to two factors: One is that we had eligibility criteria, and secondly that some of the women in this study actually enrolled prior to the time in which some of these conditions would present. And so we look forward to continuing to probe those specific higher risk conditions in our postmarking safety and effectiveness studies.

Dr. Cohn: Thank you.

Dr. El Sahly: Thank you. I have a question to the FDA. They agreed to the presenter. And it has to do with, you know, the up to six months, there was a decrease in severe LRTD in the infants. Beyond six months, I was doing rapidly, you know, the math from the slides to see what happens after six months, and the numbers kind of narrow between the groups. But wouldn't it have been better to present the data as Kaplan Meier so we can account for that and at least see it visually, understanding that the primary endpoint was up to six months, but in order to have a big picture of the data?

Dr. Sen: This is Goutam Sen from CBER, FDA. I will request Dr. Hong-Nguyen to respond to that.

Dr. Gruber: If permissible, we'd be happy to go ahead and show you the Kaplan Meier that carries out to 360 days for severe medically attended LRTI. Is that all right?

Dr. Hong-Nguyen: Yes, that would be fine. I mean, the numbers were pretty small, but, yeah, I would defer to Pfizer then to share data. Thank you.

Dr. Gruber: Yeah. So, again, this is Pfizer, Bill Gruber. We'd be happy to share that. If we can bring up slide one with the permission of the Chair. So this represents the Kaplan Meier out to 360 days. I think, as we described in the table, much of that, of course, is driven by the first 180 days. And the rates, for instance, between 180 and 360 days, at least for medically attended LRTI, are fairly comparable, 35 and 39 if you do the math. But the point being that you don't see an erosion or essentially kicking the can down the road with increased infection rates in the vaccine group. So, to our eyes, this is very reassuring.

Dr. El Sahly: Thank you. Dr. Omer.

Dr. Omer: So a couple of questions: Regarding the preterm births, understandably the power was calculated for other endpoints. But could you let us know, were there any computations of expected difference at a given power for this secondary endpoint or, you know, for a given difference, what would be the expected power? Any of those calculations, were they performed or could that be shared? The second thing is, since in this country there are differences and inequities in preterm birth by race and demographics, have you done any analysis within the US of preterm birth and birth outcomes by some of those factors, understanding that there were limited numbers? But if that is available, that would be helpful.

And one comment, since it's been mentioned a few times, that the preterm birth differences, the imbalances were restricted to upper middle income countries, namely South Africa. I think that, in and of itself, is an accurate representation of what the data were presented. However, there's some context needed because low and lower middle income countries only comprised 3% of the sample, as I understand just basically, basic arithmetic calculation. Correct

me if this perception is incorrect. So it is okay to say that it was, you know, South Africa, et cetera. But perhaps we shouldn't infer from that, that that difference, one way or another, could be commented on, on other non-high income countries. So just to add that context, because the other countries were just 3% of the sample.

Dr. Gruber: Maybe I can take that last comment first, and then I'll ask Dr. Munjal to respond to the other two. So, you're right. And I tried to make the point, perhaps I wasn't clear, that in terms of talking about low middle income countries and low income countries, the numbers are small. And it's hard to make a meaningful comparison there, but at least we're not seeing, in terms of the observed cases, an adverse split. To me, the more important comparison, the more useful one, is upper middle income to high income countries where we had baseline rates of prematurity that were similar. So whatever factors were contributing to prematurity, strikes me as being more likely to be in common in that circumstance. And in looking at the high income countries where we had two and a half times as many prematures to look at, we have a 5.1% incident that's in each group. So I grant your point about the low and middle income countries, but, to my mind, the better comparison is high income where we have the most precision. And there we're not seeing a difference. I'm now going to defer to Dr. Munjal to answer the other two.

Dr. Munjal: Thank you. I'd like to start first with the question about prematurity and efficacy. So the rates of prematurity cases, in infants who were premature, were too low in the study to be analyzed. Of note, when available, a synergist was allowed to be administered in the study. We had 12 participants who were administered synergists, two in the placebo, two in the RSVpreF, and 10 in the placebo group. And none of those infants had cases due to RSV. And so, overall, the number of cases in preterm infants was very low.

I'd like to take next the question on preterm, as analyzed in the US, by race and ethnicity. And if you could show slide one, please. So this is a busy slide. If I can just walk you through it. We looked, and the numbers are small but, I think, are useful to reflect upon. So the total US population is in the right hand column. And then we have race by non-white and white US participants, and ethnicity by Hispanic and non-Hispanic. And if you look at the percentages, because the denominators do differ, we had no difference in preterm delivery between non-white and white US participants between the RSVpreF and the placebo group and between the RSVpreF and placebo group for ethnicity. And then I'll hand it back to Dr. Gruber, unless you have any additional questions.

Dr. El Sahly: Can you keep that slide for a minute?

Dr. Munjal: Yeah, absolutely. Could we please, bring back the slide on race and ethnicity in the United States, slide one, please.

Dr. El Sahly: Okay. Thank you. Dr. Ault.

Dr. Ault: I think my question may have been answered already, but I'll ask it anyway. You know, one of the things, preterm labor has a lot of different causes and a lot of different confounders, and people have already said that. But, you know, one of the confounders, because of the timing of this, is COVID infection, especially the Delta virus was especially associated with maternal morbidity and preterm delivery, and some of that's iatrogenic. If there's fetal monitoring going on, obstetricians will get involved in severely ill mothers and deliver infants as a result of maternal illness. So I was curious, and I think you kind of said this indirectly, but, you know, was there any seasonality or relationship to the Delta variant or COVID rates, especially in South Africa, since it sounds like that's what's driving the data?

Dr. Munjal: Yeah. Thank you for the question. And we acknowledge, as you do, that COVID-19 was associated with many adverse events. And so we collected this in two ways: In the trial, we collected, when a maternal participant was ill with a respiratory illness, we collected it. And we also collected anytime a maternal participant had a locally done COVID, SARS CoV-2 positive swab. So we tried to systematically collect the data as much as possible, but we did not swab the maternal participants. So the number of identified COVID positive women in the trial was exceptionally low. And so we couldn't identify that factor as a specific driver for prematurity. And when we look across the study from the time, for example, that the upper middle income countries started enrolling in South Africa through to the end of the trial, we see variations month by month in prematurity, but no specific clustering of those cases. But we do acknowledge that COVID-19 was prevalent almost during the entirety of that duration when we are enrolling in those countries,

Dr. El Sahly: Dr. Feikin, your question was answered? I thought you had one.

Dr. Feikin: Oh, well, I did. It actually was on COVID as well. I mean, it is pretty extraordinary that this, you know, that this whole study took place during the COVID pandemic, and we know so many things changed in terms of viral epidemiology and health seeking. I did notice that there was a slight imbalance in SARS CoV-2 positivity. Overall, it was 3.9% in the vaccine group and 3% in the placebo group. And you just said that you think that's an underestimate, and I'm wondering if you have data, particularly for South Africa, comparing the two groups in terms of SARS CoV-2 positivity and whether there might be a greater imbalance in South Africa related to the question that was just brought up.

You know, in that other study for the other manufacturer's vaccine, it was notable that the difference in preterm delivery really was only significant from April to December of 2021, which

coincided with the Delta wave, which is the most severe. So I'm also sort of struggling with whether there might be a potential confounding factor of COVID, particularly in South Africa.

Dr. Munjal: Yeah, thank you for the question. So among our preterm births, for example, there were 12 that were COVID positive, three in the RSVpreF and nine in the placebo group. So those numbers are really too small. So that's why I was hesitant to draw any conclusions. And, specifically, a lot of those tests were passive reporting and from high income countries. So we're hesitant to make any determination about South Africa because in the maternal participants during the time of the pandemic, we wanted to do a low impact study. And so we were not bringing them in and systematically swabbing them. So when we reflect upon the rates in our study, I think it probably profoundly underestimates the COVID-19 rates that were probably occurring in these women.

Dr. El Sahly: Dr. Bernstein.

Dr. Gruber: Oh, just –

Dr. El Sahly: Go ahead, Dr. Gruber.

Dr. Gruber: Yeah. You know, given that there wasn't complete saturation for identifying COVID-19, the hypothesis that's been raised is a possibility in terms of a confounder in South Africa. We just don't have the sensitivity to have determined that as part of this study.

Dr. El Sahly: Okay. Dr. Bernstein.

Dr. Bernstein: Thank you, Dr. El Sahly, I just have two questions: Specifically, one is, although vaccine and safety are the key elements and no serologic correlative protection is known, can you comment on how the most amount of immunogenicity data that's been presented should be factored into this discussion?

Dr. Gruber: Yeah. So let me first address the immunogenicity that we have that Dr. Munjal presented. That was really what propelled us into moving into a phase three study, that and the safety experience we had in phase two. And that was that for children immunized, whether at 24 to less than 27 weeks or older, had high amounts of antibody. On a log scale, maybe we just put up slide one just briefly. Well above that red line there, which represents the level of palivizumab that's been associated with the prevention of children coming into the intensive care unit, now this represents the amount of antibody that was present at birth in the infants. So that suggests that the level of antibody was sufficient to provide protection. And then as Dr. Munjal shared with you, because you're achieving such high levels of antibody, that persists well until six months and is still above that palivizumab line. We actually did obtain sera on participants, the infants in the study. And we will be looking at that later to potentially identify more precisely what threshold might be that could be associated with protection.

Dr. Bernstein: That would be great. Thank you. And another quick question: Are there additional data, since cutoff period was eight months ago in September, are there additional data that you can share with us?

Dr. Gruber: Yes. Yes. Yes. We can. We have shared this data with the FDA. It's not in your briefing document, of course, because the file that generated that document, basically, was a data cut in September. But I'll ask Dr. Munjal to speak to the nature of additional safety information that we have. I'll begin, though, with the bottom line and that is it does not change the overall risk benefit profile. The nature of the observations, for instance, in terms of prematurity, remain the same in terms of no statistical difference. But let me ask Dr. Munjal to speak to that.

Dr. Bernstein: Are the clinical numbers increased though?

Dr. Munjal: Yeah. So for all the infants and ongoing safety follow up, we have regular internal reviews and regular reviews with our external data monitoring committee who continues to review on blinded data and reaffirm the, the benefit risk profile. Maybe I can speak to two outcomes that might be of interest of you since the trial has concluded. As Dr. Gruber mentioned, the FDA has had access to this information, but they may not have reviewed it because it's been recently submitted. So since the time of the data analysis, almost all the births were complete and actually all births were complete in November of 2022. So I can tell you now that in addition to the data that you've seen on the 370 preterm births, we had seven additional. Those seven additional cases were four in the preF and three in the placebo group. So they didn't really change the overall analysis.

Similarly, if we look at infant deaths, most of the infants now are older in our study. In fact, all infants are now over six months of age. Since the time of the analysis, we had five additional infant deaths, three in the RSVpreF and two in the placebo group for now a total death count, in infants and young children, because they're now young children, to eight in the preF and 14 in the placebo group.

Dr. Bernstein: Thank you.

Dr. Munjal: Thank you.

Dr. El Sahly: Dr. McMorrow.

Dr. McMorrow: Thank you. Returning to the question about COVID incidents in the mothers and preterm birth, I'm wondering, you have serum from these women, because you've collected samples at the time of delivery to look at transference, and so I was wondering if that's a possibility that you might be able to look at that.

Dr. Gruber: Yeah, so that's a very good suggestion. We'll take that, obviously, under advisement and consider looking at that.

Dr. El Sahly: In terms of while we're talking about other viruses, we saw that the overall medically attended lower respiratory tract disease did not differ between vaccine and placebo, which actually is kind of, it's not the primary endpoint, but it's kind of disappointing ‘cause we were looking forward to a dent in that outcome. Was a multiplex performed to see what viruses brought these kids to the medical emergency rooms and hospitals, et cetera?

Dr. Gruber: Yeah. So I will let Dr. Munjal speak to the details of how information was captured and how that reflects on the overall LRTI.

Dr. Munjal: So we looked at both co-infection in our RSV cases, and then we looked at the other circulating viruses in the non RSV cases. So I'll talk first about our RSV cases. Of our RSV cases, about 40% were co-infected. The adjudication committee and the protocol determines that if RSV is present, it should be considered a case. We consider RSV to be the dominant pathogen as the most conservative estimate of RSV efficacy. So about 40% of those cases that you saw at the MA-LRTI were actually co-infected cases. And when you look at efficacy by RSV alone or RSV co-infection, there's concordance there. So when you're seeing the RSV MA-LRTI, it's RSV and RSV with other pathogens.

Now let's look at the cases that were RSV negative. Those are still under investigation because we are still actually analyzing all of the additional cases in the study. But the predominant circulating viruses were rhinovirus, SARS CoV-2, parainfluenza virus. But rhinovirus by far and away dominates both co-infection and other. And we think this is because this was a very unusual time during the pandemic, and a lot of the circulating respiratory viruses

by non-pharmaceutical co-induction, non-pharmaceutical interventions were actually prohibited. And so we had a very unusual time period.

And so in other studies that have shown a reduction in all-cause MA-LRTI, they were functioning under the assumption that RSV was the dominant pathogen, 40 to 60 and sometimes 80% of cases. In our study, RSV was 22% of the all-cause cases and so not the largest driver of bronchiolitis. We don't expect this to be the case. And so we really look forward to those post-marketing effectiveness studies to see if we're going to drive down the rate of all-cause in a more typical season where RSV would tend to be the dominant pathogen.

Dr. El Sahly: Okay. To stay on the topic of more usual season, given that the study was ongoing at the cutoff, did a good chunk of these infants catch the intense wave we witnessed in the fall?

Dr. Munjal: So in the Northern Hemisphere, a lot of the infants had enrolled, out of that six month period, by the time of the intense 2022 wave. But they did catch the wave of the summer and fall of 2021 into 2022. But we are looking at multi-seasonal data in over half of our infant participants. You saw a glimpse of that in some very early cases that the FDA showed, and they're in our briefing document. And we are looking forward to analyze that second year data as we continue to go forward. That doesn't constitute the primary analysis, obviously, but we think it'll be interesting to keep showing that data as we go forward out into that second year for the 55% of participants.

Dr. El Sahly: Okay. So 55% of them remained in the last –

Dr. Munjal: They follow for two studies, and, actually, a lot of those are in the Northern hemisphere because we started up in those sites first. Yep.

Dr. El Sahly: Okay. All right. Very good. Thank you. Dr. Berger.

Dr. Berger: Hi. Thanks. I've been sort of thinking about FDA's presentation, and specifically their slides 30 and 31, where they actually presented subgroup analysis based on gestational week administration of the vaccine. And so they broke it down by 24 to 28 weeks. 28 to 32. 32 to 36. And I've just, I noted that the negative bounds for the early administration seemed to actually weigh pretty negative, negative 26.6, negative 44.6, for instance. I'm just wondering if there's anything from the final analysis that actually breaks this down a little bit more and whether either FDA or, Pfizer is planning to include, you know, this type of a breakdown as part of the post-marketing studies. Again, mostly it's ‘cause I'm looking at the questions themselves and the question are whether it's safe and effective for 24 to 36 weeks of gestational age. It's a question of whether or not we should be thinking about whether there's a more effective administration timeframe for the vaccine. Thanks.

Dr. Sen: This is Goutam Sen. I'll request my colleague Dr. Hong-Nguyen to respond to that. Thank you.

Dr. Hong-Nguyen: So as mentioned, you know, this was not powered for these endpoints and we, out of interest because we did think it could be relevant, and we actually were hoping to hear some input or ideas from others, including the committee, on this.

Dr. El Sahly: Okay.

Dr. Berger: Maybe a redirect to Pfizer, if that's something that they might have additional data on. And, for instance, you know, is that something that they might include as part of the post-marketing study? ‘Cause that type of breakdown might be important to make sure that we're actually administering this in a way that's going to be the most effective for both mothers and their infants.

Dr. Gruber: Yes. Thanks very much for the question. With permission of the chair, I'll respond. Bill Gruber.

Dr. El Sahly: Yes, go ahead.

Dr. Gruber: Let's bring up slide three, please. So I think you asked two separate questions. One is what do we already have, what we might be acquiring the short term that would better inform the level of efficacy based on the time of the gestational age at the time of vaccination. And you saw the referenced data from the FDA. Here's a slide that we have that puts this into a visual to be able to represent the nature of the point estimates of efficacy in the confidence intervals. And, as you can see, the point estimates are, you know, relatively close, albeit lower a bit in the 24 to less than 28 weeks. But the confidence intervals are quite large and encompass, of course, the point estimates for some of the other age groups. And you can see this for both, you know, medically attended illness in the first 90 days, as well as the first 180 days. It's unlikely that we will have sufficient cases that will further inform these results from the current trial.

But certainly when we, with an indication between 24 and 36 weeks in the post-approval space, we ought to be in a position through discussions with the FDA to set up the appropriate sort of effectiveness studies to get that type of information. But I think the nature of this interval, obviously, affords an opportunity to maximize the potential for mothers to be vaccinated to protect their children. And we think that's important in the face of the data that we have.

Dr. El Sahly: Dr. Gruber, to stay on this slide, it's not for shortage of cases in the 24 to 28, if anything, they have the most cases.

Dr. Gruber: Well, but I think, you know, again, this study was never powered to look –

Dr. El Sahly: I know.

Dr. Gruber: -- specifically at all the gestational ages. Right? And so the confidence intervals for themselves speak to that. Right? So when you're looking at the 24 to less than 28 weeks, the confidence interval is large because you lack precision. And so we can hopefully gain that precision with a post-approval effectiveness study.

Dr. El Sahly: Most of the women were in that group, 24 to 28, maybe the denominator is large. Right?

Dr. Gruber: Yeah. I'll let Dr. Munjal speak to the nature of the enrollment. I think she spoke to it earlier, and I believe it's in the briefing document, but the nature of the proportion within each gestational age. Dr. Munjal.

Dr. El Sahly: Yeah. Because the cases, there's quite a few.

Dr. Munjal: Yeah. There was a good representation from all the gestational ages, the gestational ages of the latter two. If you can bring up slide three, you can see that we had a few more in the 32 to 36 week gestational age. This was primarily driven by a push in our high income countries. And some of the cases that we see distributed throughout the gestational ages did occur in low or low middle income countries. So what we had done, actually, was originally designed the study around a potential seasonal enrollment and then actually opened it up to year-round enrollment due to the COVID pandemic. So we gave an additional push for some of the latter gestational ages in the Northern Hemisphere.

Dr. El Sahly: Okay. Thank you.

Dr. Berger: If I could make one quick, last note.

Dr. El Sahly: Yes.

Dr. Berger: It's that negative bound that just really bothers me, to be honest. Because your primary criteria was 20% lower bound for the overall, which I understand you meant that, but

looking at that one time frame of early administration, it wouldn't meet the pre-specified endpoint. So, you know, I think it's really important to make sure that you are collecting that information, even if it's in the post market environment. Thanks.

Dr. El Sahly: Dr. Janes.

Dr. Janes: Thank you. I wanted to follow up on the discussion of low birth weight. And so earlier, Pfizer brought up some slides, I think, that very helpfully showed us the distribution of birth weight as a continuous measure, as opposed to the categorical summary, including the briefing documents. And I'm wondering if such a summary can be shared with the group, using the data from the phase two-B trial. The data from the phase two-B trial seemed helpful here in the sense that there are multiple dose groups. And so I'm wondering if Pfizer or perhaps FDA can dig into that a little bit and tell us if there's anything that's learned, in terms of evidence of or lack of evidence, for a dose response between the dose of the vaccine and a potential effect on the distribution of birth weight.

Dr. Gruber: So with permission of the Chair, this is Bill Gruber from Pfizer. Can we answer that?

Dr. El Sahly: Yes, please.

Dr. Gruber: So I'm going to ask Dr. Munjal to speak to the nature of what was captured in the earlier phase two study, versus what was represented for phase three, low birth weight or birth weight.

Dr. Munjal: I apologize that I don't have a visual for you today, but just in terms of the numbers, the preterm birth weights were only 25 of the over 600 participants that we had in the trial that were enrolled. And because most of them were late preterm, what we find is very similar to what you saw in the phase three study, that the average birth weight isn't really

affected. So we can certainly present that data to the FDA, but because of the very low numbers and rather near term babies that we have, we don't see a difference in the average mean birth weight in the studies, either by vaccine dose or overall.

Dr. Janes: Did we see the estimates of, I guess, proportion low birth weight by dose, or could you bring that up and share that with us again?

Dr. Munjal: Yeah. For the phase two-B study, I'm afraid that I don't have the numbers for you right now. What I can tell you is in, and this was shown by the FDA, in the 120 microgram group, there were six cases, four in the 120 microgram with aluminum, eight in the 240 and four in the 240 with aluminum, with three in the placebo group. So we had a total of 25 cases in the two-B study. And relative to the total population, that was quite small. And, as I said, they're late preterms. And so their birth weights didn't really budge the overall mean birth weight in the phase two-B study.

Dr. El Sahly: Does that answer your question, Holly? We're good?

Dr. Hong-Nguyen: Sorry to interrupt. This is Dr. Hong-Nguyen from the FDA. I just wanted to make a comment that we were having similar interest in this topic, and details on characteristics of preterm births for the study 1003 were not provided to our knowledge. So, actually, an information request has recently been sent to the sponsor. And, you know, so we are also concerned or looking into this.

Dr. El Sahly: I want to go back to a question pertaining to co-infections. So if, in fact, co-infected with RSV, they counted for the endpoint. Did you observe any difference in co-infection between groups, vaccines, and placebo? Or were they evenly distributed?

Dr. Munjal: Yeah, there's no difference in co-infection between the RSVpreF or the placebo group in terms of the distribution overall.

Dr. El Sahly: Okay. And in terms of the tests used, in your presentation, you indicated that the lab had to use the Pfizer assay, right? Or if they did not use a Pfizer assay, the education commission committee had to look further into that. Right? Were a number of cases dismissed because of not using the assay? And, if so, were they also evenly distributed between vaccine and placebo?

Dr. Munjal: Yeah. So we had 1,332 LRTIs within six months, and 98.5% of those had a swab result, either local or central. So the compliance, overall, in the study was very, very good. Seven of the 174 cases that we represented for the primary endpoint of LRTI did have local cases validated, that meant that it was a local molecular test that was FDA approved and that the lab was certified. And both of those parameters were, the adjudication committee had to actually verify those with actual certificates of proof.

Dr. El Sahly: Okay. So, in essence, if an investigator had an RSV case, it eventually made it either by virtue of using the Pfizer assay or a locally FDA approved assay, right?

Dr. Munjal: That's correct.

Dr. El Sahly: Well, no cases were thrown out because of the assay?

Dr. Munjal: So long as they had a valid assay, a valid molecular assay. And so we, for example, if you had a participant who had a local antigen and a central RSV result, both of those results would've been presented to the adjudication committee. So they don't dismiss cases, but they look at the totality of the data and they evaluate that. So the adjudication committee could have determined, for example, that a local case trumped the Pfizer assay or a Pfizer trumped the local assay. But we didn't have discordance of any particular number. And with that 98.5% compliance rate of the LRTIs, the vast majority of infants had the swabs performed systematically on the Pfizer test.

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

Dr. Bernstein: Yeah, thanks. I was wondering whether or not there was, given some of the concerns about prematurity with the administration of RSV vaccine, I wonder if people are aware of any study that perhaps giving RSV vaccine to some pregnant women comparing the infants who just received Nirsevimab. And so it would be interesting, I think, to know whether giving RSV vaccine during pregnancy plus Nirsevimab versus just Nirsevimab itself or just the RSV vaccine itself, whether any of those would be equally efficacious or not.

Dr. Hong-Nguyen: This is Dr. Hong-Nguyen from the FDA. We are not aware of any direct evidence that currently addresses this question.

Dr. Berger: Thank you.

Dr. El Sahly: It's a clinical trial designed for you, Hank.

Dr. Bernstein: We could address the premature issue if it was Nirsevimab. It's just as good.

Dr. El Sahly: Okay. Dr. Feikin.

Dr. Feikin: Pardon me if I missed this, but I was wondering about co-administration of other vaccines during pregnancy, not at the same time, but any time during pregnancy, and whether you documented that, and, if so, whether you were able to do a stratified analysis of the preterm births by whether women got another vaccine during pregnancy. And then related, just one more question related to that, I'm going back to South Africa again. I mean, one potential difference between South Africa and the US is that they were using the J&J vaccine exclusively, an adenovector COVID vaccine, I think, until like mid to late 2021 when they started using your vaccine; whereas in the US it was all mRNA vaccines. So I'm wondering, in South Africa in particular, do you have data on co-administration of the J&J vaccine? Thank you.

Dr. Gruber: Thank you. So, again, Bill Gruber from Pfizer. I'll ask Dr. Munjal to address just the general question about additional vaccine use during pregnancy and then specifically related to any information we'd have about COVID-19 vaccine J&J in South Africa.

Dr. Munjal: So regarding other COVID vaccines throughout the pregnancy and even after pregnancy, these were strongly encouraged in the study. And, actually, we had sites that were interested in maternal immunization. So compliance to other vaccines in pregnancy was common despite actual natural reductions that we saw, likely relative to the COVID-19 pandemic. Between the vaccinated RSVpreF group and the placebo, we saw no differences in rates of maternal vaccination during pregnancy or during the study. We also saw no difference in those vaccination rates in the preterms specifically.

What we're doing now is probing further through all those different vaccines and the different timings as well. Although, some of the maternal participants passively reported a vaccine by type, for example, a flu vaccine or a COVID vaccine without knowing the specific determined manufacturer. But we are continuing to probe that data.

Dr. Feikin: Thank you for that. I just wanted to clarify, so you didn't see an increase in preterm births in those who got an additional vaccine, but were you able to stratify the RSV versus placebo disparity by whether another vaccine was given?

Dr. Munjal: Comparing –

Dr. Feikin: Do you understand what I'm asking?

Dr. Munjal: Yeah. Comparing the RSVpreF and the placebo group, there was no difference in other vaccines given. I think the J&J question is a very interesting one, and we'll continue to look at that. We have not specifically looked at the J&J vaccine as a concomitant vaccine between the

different groups. But looking at COVID-19 vaccines overall and other maternal vaccines, there was no difference between the RSVpreF and placebo group.

Dr. El Sahly: Okay. I do not see any raised hand, which would be a good time for me to ask a question that is on my mind, for sure, and, I think, on the minds of many. So to give time for my colleagues to begin formulating the questions, should they have any.

Co-administration with flu and with Tdap. We worked hard, especially our colleagues in the OB GYN community, to bring up the vaccination rate to where they are against these two pathogens. One of them causes mortality in the infant. One of them causes significant morbidity in the mother. And we came a long way. There seems to be, you know, a narrow window to vaccinate, which if the data presented by the FDA holds true, then that window is even narrower. With a vaccine that diminishes Tdap responses by more, you know, by 20% as an estimate, but as low as less than a half, given the confidence interval, and that lowers responses to flu antigens by, I would say, 15-20%, but potentially, but did not meet, you know, the third cutoff for the lower bound of the confidence interval. From an implementation standpoint, what are we going to tell our OB GYN colleagues to prioritize? And are we confident that, you know, giving these vaccines together or in proximity that is closer than or one month apart, that we would not be negatively impacting the health of the mother and the child? And that is probably a question more to the FDA.

Dr. Sen: Hello. This is Goutam Sen. I'll request our CDC colleague to respond to that.

Mr. Toerner: Hi. Good afternoon. It's Joe Toerner again. I am from FDA. It's a great question. Again, look forward to your discussion about this topic. You know, we presented the data that was under review. Data that, as part of our review, end up in product labeling typically. So we place in product labeling information that we think is important for providers to know. And so,

you know, it would be up to the provider to understand what's in labeling, to understand the data on the co-administration and come to a determination about, you know, vaccine administration. And, you know, our position is to recommend labeling. I mean, that's our deliverable to you all is labeling. So it's important information to convey in labeling, so that a provider can make a determination of use of the product.

Dr. El Sahly: Okay. So then I would open the floor for, you know, many of my colleagues to weigh in on this. But I can begin by indicating that these data are concerning. Issue of preterm labor aside, which is a very important issue, you know, given the window, given the interference with these antigens and given how critical we think these two immunization programs are for pregnant women, you know, making sure that, should this vaccine be licensed, that until we know better, it cannot be co-administered. Dr. Ault.

Dr. Ault: We talked about some of this same type of thing when we were talking about co-administering COVID and Tdap when it was, when we were pushing COVID vaccines a couple years ago during pregnancy. And, again, in the absence of data, similar to what we're talking about today, I think it boils down to you would rather people get vaccinated than not get vaccinated with both vaccines. So if simultaneous vaccination is the best option, then that's an option. Of course, a lot of this is going to have to be studied in a post-marketing environment. I'm actually at the American College of the OB GYN National Meeting in my hotel room right now. So I can run across the street and ask some of my colleagues. But, you know, there are maybe four to six visits between 24 and 36 weeks that you would have an opportunity to do the pertussis, the Tdap vaccine, and this vaccine. Of course, flu we're going to be giving seasonally, and that would come up, you know, during the fall of the year. But, you know, it's something we really need to look at post-marketing.

Dr. El Sahly: Yeah. I mean, the COVID situation was slightly different in that there was, in the absence of vaccinating the mother, there was a significant morbidity and mortality associated to the mother and the child. So, yes, at that time, yes, give what you can right, you know, whenever you catch the pregnant woman in a visit. But this is slightly different in terms of risk benefit.

Dr. Ault: I mean, there are probably other people on the call that have more expertise in pertussis than I do, but, you know, I guess my view of that data that's accumulated over the last decade is we don't have a great marker for serological protection. And, again, just getting the vaccine is the important thing to protect the newborn from pertussis.

Mr. Toerner: Yeah. Hi. This is Joe Toerner again. This is a great discussion. And, you know, our colleagues at the ACIP provide for, you know, clinicians in the United States advice on vaccine administration. So it's a topic for a discussion as well for that particular group.

Dr. El Sahly: Dr. Cohn, I think. Dr. Cohn.

Dr. Cohn: I was trying to decide if I was going to jump in here or not. I will quickly jump in. I don't remember all of the data, but we have had other times of where we did have co-administration data with pertussis vaccines where one or two of the antigens was lower, specifically when co-administered with meningococcal vaccine, I think. And, you know, in general, for most healthy people, we do feel like serological data is not terribly helpful. You may need all of those antigens to be higher in terms of maternal transfer antibodies. So I don't think you can take prior experience and apply it here, but I do think that we have managed some complicated co-administration issues in the past through the advisory committee on immunization practices.

Dr. El Sahly: Yeah. So that's the second time the TDAP/mening is brought up. But that, to my understanding, is when it's given to adolescents, right, as a booster to –

Dr. Cohn: No. So the specific recommendations were around younger children that were at increased risk for meningococcal disease, who we really needed to make sure were fully protected. That was when you would have, that's when we were more concerned, and I'm sorry. It might have been pneumococcal. I think it was. I'm sorry. It's something to do with childhood vaccines and co-administration in that 4-6 year-old age range.

Dr. El Sahly: 4-6 year-old, by then, you know, they were out of the mortal flu morbidity range. Okay.

Dr. Cohn: Yeah. Yeah.

Dr. El Sahly: So it's somewhat different. Okay. Any additional questions to Pfizer, to the FDA from the committee members? I'm going to go through my notes. One question pertaining to the woman who died of hemorrhage from bleeding at home, was that another premature delivery or not really?

Dr. Gruber: So I'll ask Dr. Munjal to speak to the specifics of the woman who died due to hemorrhage.

Dr. Munjal: Thank you. So this was a maternal participant who was vaccinated at 31 weeks, four days of gestation. And so actually the delivery occurred precipitously at home at 57 days post vaccination. The woman was 39 weeks, four days. All of our maternal participants do have an intention to deliver in the hospital, so this was an unplanned home birth. And, unfortunately, by the time she got to the hospital, in order to have an administration of blood products, she had already hemorrhaged to a significant point. Um, but that was a term birth at 39 weeks, four days gestation.

Dr. El Sahly: Okay. So it's a full term. Thank you.

Dr. Munjal: Full term.

Dr. El Sahly: The other question is, I'm assuming an AESI, Guillain barre, Bells Palsy, any neurologic complaints were AESI and none were detected in those 3000 women?

Dr. Munjal: That's correct. The background incidents in pregnancy overall is low. So even with a larger dataset, we wouldn't have expected to see those types of conditions, but we did thoroughly look for them. We also looked at surrogate AE, adverse events, that might indicate autoimmunity. And we didn't detect any noticeable differences between the RSVpreF and the placebo group. But any given numbers for conditions like thrombocytopenia, diabetes, hypothyroidism, they were pretty low in the study.

Dr. El Sahly: Okay. Thank you. Okay. So here's a question, I guess, to maybe the biostatisticians amongst us. In order to rule out that the vaccine is associated with preterm delivery, I mean, give or take, what is it 20% increase, based on, if we are to use this as prelim data to design a trial to either rule out or rule in this risk, what sample size would we be looking at?

Dr. Gruber: Or can we have one of our statisticians address that.

Dr. El Sahly: Thank you.

Dr. Gruber: I'm going to ask Dr. David Radley to speak to that question.

Dr. Radley: Hello. David Radley here, Pfizer Statistics. We did look at this and, as was noted, the difference between the groups in terms of the prematurity is rather modest in terms of an effect. It's less than a 20% increase in the relative risk reduction. So that would require a fairly large study to, if we were to design it as an endpoint, we think approximately something of the order of 10,000 subjects would be needed.

Dr. El Sahly: 10,000 exposed or 20,000 if we are one to one.

Dr. Radley: 10,000 in a one-to-one study of a vaccine versus placebo.

Dr. El Sahly: So five in each arm. Okay. Holly, did you have something to say?

Dr. Janes: No, I think that's reasonable.

Dr. El Sahly: Okay.

Dr. Gruber: We have one follow up, just a moment though, if that's okay.

Dr. Munjal: The assumption of 10,000 would be the study in a sort of post-marketing effectiveness and safety era where the rate of prematurity, like we see in US participants, is about 10 to 11%. So the reason why we couldn't detect differences of any significance in the phase three study is because the rates of prematurity were lower than what we typically see in background rates, and that is, in part, due to the fact that some of the conditions at 24 weeks were predetermined. And so some women actually experience conditions of prematurity that may be precipitating prior to the 24 weeks even.

Dr. El Sahly: So what you're saying is that, in a post-marketing environment, any woman can get this vaccine during 24 and 36 weeks, and their average risk would be much higher?

Dr. Munjal: Yeah. So in our study, we'd had singleton births, and a lot of the rates of prematurity in the United States is driven by multiple births.

Dr. El Sahly: Right.

Dr. Munjal: And so in a post-marketing safety study, we would be looking specifically to include multiple gestational ages and not just singleton births. In the study, it was important to us that we had single cord blood in order to attack, detect immunogenicity. So we did singleton births in the phase three study.

Dr. El Sahly: And what are your thoughts on the –

Dr. Gruber: Can I –

Dr. El Sahly: Yeah, go ahead.

Dr. Gruber: I'm going to follow-up and I'm going to ask Sarah Macdonald to also speak to this, but just an important point that I think individuals familiar with conducting clinical trials are aware of. There's a self-selection process, obviously, in circumstances where people are enrolling for our clinical trial. So they're already taking measures and probably have underlying health practices that reduce their risk. But in an open population, for lots of reasons, that one included, we're likely to have a higher rate of premature. But, again, let me ask Sarah Macdonald just to speak to some of the mechanics of this.

Dr. Macdonald: Hi, Sarah Macdonald. I'm an epidemiologist in Pfizer Safety Surveillance research team, and also the study lead for the plan post-marketing safety study. I just wanted to note that the post-marketing safety study will be using multiple, very large databases in commercial claims data as well as Medicaid data. And we will be evaluating the safety, including endpoints such as preterm birth, in all women individuals who are receiving the vaccine throughout the US. And so we will, we do expect to have a very large sample size, and we'll be able to monitor preterm birth further in that study.

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

Dr. Feikin: Yeah, I wanted to follow up on the post-marketing pharmacovigilance. And I wanted to ask FDA a question about their involvement in that and working with the company. And I don't know how this works, and I'm wondering how often do you get reports about the data, and what is your involvement in reviewing the data as it comes in, and how do you set thresholds for taking action? Or what's the process of, if there were a signal, how you would determine if it's, if it's crossed some threshold for you?

Dr. Sen: Thank you. This is Goutam Sen from Office of Vaccines. I'll request my colleague Dr. Meghna Alimchandani to respond to that. Thank you.

Dr. Alimchandani: Hi. This is Meghna Alimchandani. I'm going to speak really in very general terms here, not specifically for the study. We review, there are certain studies that are safety post-marketing requirements. There are certain studies that can be safety post-marketing commitments. All of these studies are tracked very closely by the FDA. We review the protocols. The final protocols are usually submitted post-approval, but we have a lot of discussion before approval with the sponsors in making sure that the study is adequately powered and the design is able to look at the question to meet the study purpose. So all of that goes into the interactions with the sponsor before approval. And then post approval, we review the final protocol. We get annual status updates from the sponsor. We also get interim reports, and then we get final study report. So there is a lot of interaction throughout the study through as the results are coming in. Does that answer the question?

Dr. Feikin: Yes, it does. How often do you get interim reports?

Dr. Alimchandani: So that is, again, determined on a case-by-case with the sponsor. We can have annual interim reports. For certain studies, we have six month reports. We can have at a greater frequency. So minimum is the annual PMR PMC status update reports. But for certain studies we've had, we've asked for more frequent interim reports. Thanks.

Dr. El Sahly: Dr. Holly Janes.

Dr. Janes: I wanted to follow up on the discussion around the fact that the participants in the phase three trial are, you know, self-selected for being the types of participants who had enrolled in such a study, as well as, you know, by virtue of eligibility criteria being not representative of, you know, all pregnancies in the US. Given that fact, and given that there are populations at higher risk for preterm birth, you know, those with multiple, you know, multiple pregnant, prior preterm birth, and those with, you know, pregnant with twins and triplets, multiple fetuses, I

guess a question both to FDA and Pfizer are, is there any thinking about this potential safety signal and what implications it might have for those who are at higher sort of baseline risk for preterm birth? If this 20% increase risk were to apply to such a subgroup, that would put them at, you know, pretty high absolute risk of preterm birth, what are the thoughts around that?

Dr. Gruber: Perhaps that was directed more to the FDA in terms of their perspective. I see a representative standing up.

Mr. Toerner: Yeah. Good afternoon. It's Joe Toerner, FDA. That's a great question. I guess it's a concern with any clinical trial and any clinical development that we see in review at FDA is it's a self-selected population, and they're generally healthier and, with exclusion criteria applied, it's, you know, it's a different population. And we always worry about that. When we approve a drug or license a vaccine, we always worry, in the post-market setting, once it's applied to a general population. So your question's a good one, and, you know, it's just something that we pay close attention to. You know, during our review, we recognize it's a healthier population, but also something that we want to pay close attention to post-marketing, when a drug is approved or a vaccine is licensed.

Dr. El Sahly: Insofar at this clinical trial is representative of the average pregnant person, how did this inclusion/exclusion criteria align? Because this is a phase three, and it should have been representative of an average pregnant woman.

Mr. Toerner: This is Joe Toerner. I'll just give one example. It's my understanding that only singleton pregnancies were included. Yes. And I'm going to ask my colleague to provide a bit more information about the inclusion criteria.

Dr. Hong-Nguyen: This is Dr. Hong-Nguyen. For a multiple gestation, it was an exclusion criteria having multiple or twin pregnancies. But, interestingly, one case, I believe, in South

Africa was actually a twin gestation that ended up into the safety population. And perhaps Pfizer can elaborate a little bit more.

Dr. Munjal: Iona Munjal from Pfizer. So we had a single case of twins in the study. The misread normal ultrasound was reanalyzed by the obstetrician after vaccination and noticed a twin pregnancy. Those participants are included not only in the safety population, but the efficacy population. So from South Africa, we represent two infants in the RSVpreF group, which actually constitute a single vaccination.

Dr. El Sahly: Dr. Cohn.

Dr. Cohn: Thank you. I'm just going to keep going back to this, but this is potentially the first vaccine I can think of in the US where we are recommending a vaccine for our pregnant woman that is not recommended for the adult population in this age range. So it's not recommended for persons who are not pregnant in this population. And our post licensure monitoring plan sounds very familiar and similar and not really very, not very confident that we're really going to be able to detect or sort through some of these many complicated questions that have been raised today.

For example, you know, will we have more infant pertussis cases? Will we, you know, maternal outcomes, which, I think, you know, we do care about the health of the mom who is getting this vaccine, not just the infant outcome. And so I really, I guess I want to hear from Pfizer, has there been any discussion about more of an active type of approach or using medical records that are much more helpful than, for example, claims databases, which is not only is it hard to link mother to baby, it's also hard to link mother to vaccination status. Moms get vaccinated very often outside the healthcare system. And so I'm just, you know, co-administration, all of those different factors I think are going to be very, very hard to identify and

then understand signals that come out of this type of large database Medicaid study that you guys do for frankly, every single vaccine. And this doesn't feel like a normal vaccine. So I'd like your perspective, I guess.

Dr. Gruber: Yeah. So, Dr. Cohn, again, this is Bill Gruber from Pfizer. I'm going to ask Sarah Macdonald to speak to the nature of the robustness of the approach. Of course, I'll say at the outset, we're open to discussions with the FDA about the best approach to gain information that would be useful, and we think the approach we're proposing makes sense as far as doing that. But, Dr. Macdonald.

Dr. Macdonald: Hi. Sarah Macdonald here. Thank you for the question. A couple of points I want to make. The details for the analysis plan and the study endpoints are still in discussions and under development, and we will be working closely with the FDA to finalize those plans and the exact analysis. As I mentioned, we are using very, very large healthcare claims data sources, which allows us to evaluate very rare outcomes and, in large populations, including populations of patients that were excluded from the trial due to comorbidities and other reasons. So we will have a very robust and large population size, which is a key advantage.

We also can conduct medical chart reviews for outcomes and so can further confirm the findings, in that way, for the final analysis. So we feel confident that our approach is a robust approach. It will evaluate a number of key safety endpoints, and we will be discussing the details of the specifics regarding the analysis and the outcomes with the FDA, and ensure that we are evaluating the safety for these key endpoints in a robust manner. We also have our pharmacovigilance system as well, which will be conducting near real-time monitoring for safety endpoints. And, as I mentioned, we can, if a signal is identified through our pharmacovigilance system, we can then modify the safety study to further characterize the risks for those outcomes.

So we feel confident that we do have a robust system in place to both identify signals and confirm and characterize those results in the safety study.

Mr. Toerner: This is Joe Toerner from FDA. Thank you for that. We would, we would affirm as well, we would expect a robust post-marketing surveillance program should this vaccine be licensed. Thank you.

Dr. El Sahly: Thank you. Dr. Omer.

Dr. Omer: A couple of things regarding the post-marketing surveillance or pharmacovigilance plan. As I understand, it primarily relies on claims data in the US. And I want to bring up a couple of things related to that. Of course, you know, this committee is focusing because of its mandate on US licensure. However, the data we are looking at comes from more than one part of the world. So from an ethical perspective, I'm wondering if there are any plans to follow up that signal in countries like South Africa, because we, in the US, are benefiting from data from other parts of the world. And the signal almost exclusively seems to be restricted to South Africa.

But more equally importantly, from a scientific perspective, so if I look at it, you know, what I would expect the post-marketing surveillance to show, if, you know, everything in the trial is duplicated, of course, it's more likely than not, it will show that in the US, if these data are reported in the US, and if the post-marketing surveillance is exclusively US claims-based data, we expect to see similar or, it would be less surprising if, if the same findings are there as the trial data. But even from a scientific perspective, if a signal is, is coming from outside the US and the fact that even in post-marketing surveillance, the early adapters are different from those, you know, who get vaccinated in subsequent years, I see value in post-marketing surveillance that is not just the US. So any thoughts about looking at pharmacovigilance data outside the US

or if, you know, a line searcher is not granted readily outside the US or change of indication, you know, whatever framework may be, what are the plans to follow up geographically in a comprehensive manner?

Dr. Gruber: Yeah, so I'll give you the short answer and then ask Dr. Wilkins to give you the broader answer. And that is that pharmacovigilance activities will not be restricted solely to the United States. But, Dr. Wilkins.

Dr. Wilkins: Thank you. Jamie Wilkins with Worldwide Safety. I think it's important to reiterate that our pharmacovigilance system for Pfizer is global. And so wherever we do end up syncing licensure for the vaccine, we'll have the relevant conversations with those regulators and, of course, immediately implement pharmacovigilance and surveillance activities in those regions. I do want to emphasize also that we will have very diverse data with our US pharmacovigilance activities, including Medicaid, which should give us insight into, you know, very diverse racial and socioeconomic insight. But to reiterate, once we go into low and middle income countries, we will undertake the same activities and any studies that are required for safe use of the vaccine in consultancy with those regulators. I would also like to emphasize that we regularly undertake activities such as with the Bill and Melinda Gates Foundation to also start to shore up infrastructure for pharmacovigilance activities worldwide and in lower middle income countries.

Dr. El Sahly: Dr. Pergam.

Dr. Pergam: Thanks. This is a little bit of a random question, but I think it's important. You know, Pfizer laid out a little bit in terms of what they were planning for immunosuppressed studies, and I'm sort of riffing off what Amanda Cohn talked about. You know, a lot of times for vaccines, we think about the immunosuppressed populations and studies and looking at vaccine

responses. In this, we're actually talking about a younger population. So we're really not going to be prepared to answer questions for women who are pregnant who are immunosuppressed about their potential responses to this vaccine. And I'm curious whether in the discussion around studies in immunosuppressed populations, whether Pfizer has thought about targeting younger women as a question to at least make comparisons to the women who are in these studies to look at potential outcomes in that group in terms of antibody responses.

Dr. Gruber: Yeah. So, again, Bill Gruber from Pfizer. I'm going to ask Dr. Munjal to speak to this. Obviously in conjunction with our older adult indication, we are exploring other avenues to look at immunocompromised populations, as well as ultimately, potentially younger age groups. But, Dr. Munjal.

Dr. Munjal: So there's a number of different avenues in which we seek to answer this question. One is through the post-marketing study that you heard from Sarah, which it will specifically target immunocompromised individuals. And the other is through a study that we had just initiated, targeting high risk individuals, 18 to 60, and immunocompromised individuals. So that study will be looking at non-pregnant individuals. Although, actually, pregnancy is not an exclusion criteria. But the study specifically is not targeted towards a pregnant population, but we're not excluding participants if they're pregnant and choose to elect to enroll in that study.

Dr. El Sahly: Okay. Thank you. So that would be the third meeting, I think, back-to-back where signals in the data or data that are not available yet or uncertainties are sort of answered or we rely on answering in the post-marketing framework. However, I want to, you know, remind us of the COVID-19 experience in order to answer some of the uncertainties, and we did that very well, we had to, the CDC had to have the V-Safe and other proactive interventions in order to supplant some of the uncertainties in the pre-marketing, pre-authorization phase. I don't think

there is a plan for that here, or in the, you know, couple of meetings we had pertaining to RSV vaccines. And the claims database and the passive data collection and the fragmentation, quite frankly, of the healthcare system just makes this task, you know, quite large and decreases sort of the confidence that we'd be able to inform the public quickly and fully around all these uncertainties. So I'd like to hear Pfizer's and FDA's viewpoint because this pertains also to the other Pfizer product that we discussed or the same product and another population.

Dr. Gruber: Yeah. So maybe I can start and then the FDA. I'll speak briefly and the FDA can speak to this. You've characterized something that occurs basically with every vaccine, that there's a limited amount of information that one can get in terms of the overall safety that has to be balanced with what you learn about the potential benefit. And that's really what the committee is being asked to address today, right? The nature of the benefit of potentially protecting, you know, broadly, with a broadly applied vaccine, against 16,000 hospitalizations, over 300,000 visits compared to an uncertainty. Certainly, to our eyes, there is no definitive evidence to suggest that there, in fact, is an increased risk of prematurity.

And so the question is, do you hold hostage the potential benefits of the vaccine for something for which you have no statistical significance at this point, and for which you would need a sizably larger population under pharmacovigilance to identify. And, of course, it's our position that the benefits here justify moving forward and capturing that information as part of a pharmacovigilance plan. But I'd like, of course, for the FDA to speak to that as well.

Dr. El Sahly: I think my question is, let's say we're, you know, going down the pharmacovigilance route, but, you know, passive collection from claims databases and the fact that the healthcare system is, you know, multi-layered and complicated in the US. It's not like in

some other countries where maybe things are a bit more streamlined. I don't know. That's the question here.

Dr. Hong-Nguyen: This is Dr. Hong-Nguyen from the FDA. The FDA has presented the data from these findings on efficacy and safety. And, in general, we ask the committee to opine on pre-licensure data. I mean, we have all considerations for post-marketing, but we're really presenting the data that we have here today and ask for your input and considerations.

Dr. El Sahly: Dr. Feikin.

Dr. Feikin: Yeah. While we're on this topic, maybe somebody like Dr. Cohn could address this, but CDC does have a system called the Vaccine Safety Data Link that includes different large health organizations across [indiscernible -- garbled audio] with health records. And my understanding from what I read about is that they have evaluated multiple [indiscernible -- garbled audio] before. And they do something called rapid cycle analysis where [indiscernible -- garbled audio] on access rates and potential adverse events. So to me it seems like a much more nimble system to obtain results than what's been described by the company and the FDA. I don't know if somebody else, maybe from CDC, can comment on the Vaccine Safety Data link.

Dr. Cohn: Yeah. Yeah. So, Dr. Feikin, thank you. Do you mind if I respond? So I think you're exactly right. The Vaccine Safety data link has over a hundred thousand births a year, so probably about 10,000 pregnant women a month, and frankly is a much more robust, and there's a lot more that you can do given that they are medical record data that is very different than claims data. It's certainly not perfect, but I don't think that it takes away. I know that we're asked to just, so the vaccine data link will certainly look at some of these questions. And I think that, for example, the prematurity signal or imbalance is, the incidents will be high enough that you could look at that particular question pretty quickly. You may not be able to look at a question

like whether or not we're seeing increases in infant pertussis or anything like that quite as quickly, just given the incidents in the population.

I don't think the Vaccine Safety Data Link should be a reason. It feels like this committee is frequently asked to review the data at hand without having any transparency about what these pharmacovigilance products that the companies produce. They just do a lot of analysis, and we never see the results of those. Like, I don't recall having those results brought back to this committee, or do I recall having the companies really share their methodology because it, we have been using this data. Claims data is incredibly powerful to detect signals. And we've been using it a lot to try to get answers more quickly. But in the setting of linking vaccine immunization records, linking mother/baby data, the more you try to get out of these large claims databases, I'm going to not be quite as convinced, I guess, is what I'm trying to say.

So I think you can ask very straightforward, a baby got vaccinated. Did they have these outcomes? That's easy. This is pregnant women and infant outcomes, and pregnant outcomes, I think, are much more complicated. And I frankly think, and this is me speaking, that we should have more transparency on these pharmacovigilance plans, and that they should have strong plans prior to this meeting. There's been a long time for these plans to be developed.

Dr. El Sahly: Okay. I do not see any more raised hands, and we used up all the time and then some. So –

Dr. Alimchandani: Hi, Dr. El Sahly. This is Meghna Alimchandani again from FDA.

Dr. El Sahly: Yes.

Dr. Alimchandani: If you have a few minutes, we have some backup slides that we wanted to go over for post-marketing safety studies, just some general information. Slide, I think, it's 19 through 21. Good. So while the slides are being brought up, to Dr. Cohn's point, I mean, when

we do have findings, if we do have any safety signals from any source, any sponsor studies, or studies that FDA has done or any other source of data, then the process would be to add that information to the label to make a safety related label update. So that's how, you know, that would be communicating those results from those studies.

For the next few slides, I just wanted to take a moment to talk about, in general terms, post-approval safety studies and the different types of post-approval safety studies. So, as someone, you know, brought up, we have the sponsor studies, we have two big categories. We have sponsor studies, and then other studies. In the other category, we have studies that may be conducted by the US Government, such as, the CBER Biologics Effectiveness and Safety BEST initiative or, as was mentioned, CDC's Vaccine Safety Data Link, or any other academia, any other studies. And then going back to the sponsor studies, we have post-marketing requirement studies, commitment studies, or voluntary sponsor studies. Next slide, please.

Okay. So in terms of the types of sponsor conducted studies, I wanted to take a few more minutes to talk about when we do, when FDA makes a determination in our decision making process, our internal process for PMRs versus PMCs. So the FDA Amendments Act, FDAAA, gives us a lot of authority to require certain studies from the sponsor. And these are targeted safety studies to assess a specific serious risk. They have to be powered to assess that specific serious risk. We have a lot of interaction with the sponsor before the final protocol is found acceptable or not. And we really, we track the milestones very closely. So that's that first category of PMR acquired safety studies as a condition of approval.

And then the second category is PMCs or post-marketing commitment studies. These are agreed upon studies within FTM applicant. We don't have a lot of regulatory teeth on these studies, but we do track them. We do review the protocols for these studies. And usually the

PMCs are general safety surveillance studies, not so much a targeted safety study for a specific serious risk. And then the third category are voluntary studies that the sponsor may undertake that are neither PMRs or PMCs. And, if you go to the next slide, please. I think we have one more slide.

So this just, again, goes over our regulatory authorities for post-marketing requirement studies. These are the purposes, the study purposes that are laid out in the regulations to assess a known serious risk, assess signals of a serious risk, or to identify an unexpected serious risk. And what our internal process consists of is we will go back, have routine discussions, take the input from the VRBPAC in our decision-making process, make a determination about the pregnancy study, the pharmacovigilance plan for this product, we will take that to central leadership, have further discussions, and then make a determination about the final pharmacovigilance plan.

Okay. So that's all I had. I hope that helps. Thanks, Dr. El Sahly.

Dr. El Sahly: Thank you. I see, is it Dr. Omer? Did I miss a question from you?

Dr. Omer: I raised my hand towards the end, so you didn't quite miss my question, but if I may ask my question?

Dr. El Sahly: Yes. And that would be the last. And then we would break and then come back.

Dr. Omer: Yeah. So in the post-marketing surveillance plan, I would strongly urge both the sponsor and the FDA to ensure that there is sufficient power for analysis by race, ethnicity, as well as risk status within the US because that is important for ensuring ongoing safety of this vaccine.

Dr. El Sahly: All right. Thank you, Dr. Omer. And I want to thank everyone for their very informative discussions and viewpoints. We will be taking a break. We have here on the agenda

15 minutes, but maybe we can make it 10 minutes. And now it's 3:27. Let's reconvene at 3:37. Thank you all.

Committee Discussion

Dr. El Sahly: Well, thank you all for rejoining for hopefully the last portion of our meeting today. In this last portion of our meeting, we will be deliberating the data together. I would like to invite everyone, either by raising their hands, or maybe I should also go around the room as they appear in the Zoom so that each committee member has an opportunity to weigh in on what they think are the highlights, lowlights, uncertainties of this data in terms of answering the two questions posed by the FDA.

But, however, as you are letting us know what your thoughts are, please refrain from stating how you will be voting. This is not a request to ask how you will vote. You will vote, you know, whichever way you want once the prompts are on, and then you can, there will be another opportunity for you to explain what weighed the most on your vote. So let's begin. Maybe I'll go around the names as they appear, which means Dr. Amanda Cohn is always, no. Should be Berger. Why is her name? Okay. Dr. Cohn.

Dr. Cohn: I think it's technically Berger and Bernstein alphabetically, but.

Dr. El Sahly: I know. Your name on my screen is before that. I think mine is not arranged alphabetically. Makes it more interesting, and everyone should be awake.

Dr. Cohn: Are you asking us a question about efficacy right now, to only address that question right now? Can we see, are you asking us to talk, like, do we have the questions?

Dr. El Sahly: Well, on the agenda now, everyone, if you want, if you have additional thoughts on the data or questions or uncertainty, of course, you can say no, no additional comments, and

we'll move on. And then we will put the questions, we will vote, and then people will explain their vote.

Dr. Cohn: Okay. Great. Thank you. Sorry. So I've said a lot already, so I don't need to say much more. I do want to say, I think the study data are incredibly impressive. I think this is, you know, having done this vaccine trial in pregnant women, you know, in and of itself is a huge accomplishment. And I think the company and FDA did an amazing job of presenting the data at hand.

I do feel like we should be raising the bar higher than we have. And this is set out before we have an opportunity to review, so it's not really related to the data that were shared today, but, you know, we have multiple other vaccines that have enrolled, including COVID, many more thousands of people to look at for safety. And we should have been doing that, when it comes to pregnant women, especially given that there is not a risk of RSV in the pregnant women. That doesn't mean that I don't think this vaccine has incredible value. And I actually think, to me, enrolling more people in these clinical trials and having really strong post licensure evaluations, because you still won't detect rare outcomes, will be what we need to reassure the public and to give pregnant women the data that they need to make the decision to get vaccinated. And so I think I'll end there.

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

Dr. Berger: I wanted to say I'm going to celebrate the fact that I somehow didn't have to go first because my name usually puts me right up there at the top. So, you know, I appreciate the opportunity to give a couple of words here. I think, you know, to address specifically what you asked in terms of uncertainty, I think there is some, you know, uncertainty in terms of when we actually should be administering this vaccine right now. You know, I think that, especially that 24

to 28 question, I think, is up there, you know, in terms of efficacy rate, when it is going to be important to make sure that we understand when's the best time to be actually providing this vaccine if it gets approved.

But, you know, there's also the safety signal piece that Dr. Cohn just mentioned as well. You know, again, we're going to need to have more information on whether the preterm birth and delivery is a, you know, if there's anything real there, we want to make sure we are aware of this. But this really does address a real strong need. You know, there isn't another option here for prevention, and, you know, it really could save a lot of lives. So I do think a lot of this is going to lie on the post-marketing requirements. And I'll say, you know, to use the FDA parlance, the requirements, not the commitments here, I think we want to make sure that these are actually carried out because the information is important for us to make sure that we're, you know, informing pregnant persons on how to actually, you know, move forward with treatment in this case. So that's all I have to say.

Dr. El Sahly: Thank you. Dr. Monto. Dr. Arnold Monto. I don't know if you are having audio or issue.

Dr. Monto: I'm trying.

Dr. El Sahly: Oh, we can hear you fine. Let's go.

Dr. Monto: Whenever you want to click and have it work, it doesn't want to follow. I'm not sure about the idea of larger clinical trials as being necessary at this point. I think it has been a challenge to do anything during the past pandemic, and I think the sponsor should be complimented by moving ahead and doing this, in spite of lack of seasonality and other things which you would ordinarily be paying attention to in a study of this type. I'm troubled, as everybody is, by the prematurity issue. And I'm not sure that running it through another maybe

season is going to give us an answer. And I think we've heard that observational studies, as we go forward, will fairly quickly give us an answer if there is a problem there.

We learned how to bite the bullet and get things out during the SARS CoV-2 vaccine approvals. I think things will straighten out as we learn more about return seasonality, because I can't see that this vaccine is necessarily going to be given year-round, if influenza vaccine is being given during a certain period, also, if this vaccine is going to be given to an older population as well. But we can't wait for all that to take place because of something which I'm surprised we haven't heard more of, and that is the enormous impact of RSV in infants in the low income countries. And they won't start using a vaccine until it's approved for use in the United States. That's the way things tend to go. So I think, for a number of reasons, I think I'm convinced that we have evidence and evidence that should give us some degree of comfort that we can bite the bullet and move ahead with robust observational studies to help us over.

Dr. El Sahly: Thank you. What are your thoughts, Arnold, on the lack of, you know, collecting the data in the setting of unusual seasons? And, of course, we wouldn't know if it's even underestimating the efficacy over, I tried to think of it, and I can't come up with an answer, but all I know is that it may not be representative.

Dr. Monto: Well, I think the problem, one of the problems, and you touched on it, was they missed the big peak that we just had, and that would've helped a great deal in terms of efficacy. But I don't think efficacy is the problem here. I think the problem is this nagging question of safety, in terms of prematurity, and we probably would not have gotten the answer. I think the other thing that we need to figure out is the duration, whether we're going to continue to need monoclonal antibodies for high-risk individuals. And that, I think, can be worked out while the

vaccine is being rolled out. It's not going to be instantaneous. It never is. And there are a lot of open questions, but we've learned how to address them.

Dr. El Sahly: Okay. Thank you. I see a raised hand from Pfizer, but my understanding is that this portion is specifically for the committee members. Dr. Feikin.

Dr. Feikin: Thank you. You know, in terms of this vaccine, I think the efficacy is high, but even for me, even more so, is the vaccine preventable burden. This is a very common disease, and a lot of severe cases will be prevented. So even with efficacy of 57% against hospitalization, I think we'd like to see higher, but that's going to prevent a lot of hospitalizations in the US because this is the leading cause of hospitalization in infants. And if you calculate the number needed to vaccinate, which I did, I hope I did it right, you'd have to only vaccinate 81 women to prevent one severe RSV LRTI case and 140 to prevent one RSV hospitalization. And I think those are favorable numbers compared to other vaccines.

I'm glad others have brought up the global burden. I know that this committee is concerned with approval in the US, clearly the global burden of severe RSV and RSV deaths is heavily in lower and middle income countries. And I think there are ripple effects from decisions that are made here. So I do think that somehow comes in, at least to my mind, in evaluating this.

You know, for safety, I'm with everybody else. It's of concern and it's confusing. I really would hope that the FDA can work with the company to come up, I'm a little bit worried that they're trying to sort of bundle one post-marketing surveillance system for the elderly, where you're looking for a very rare signal of Guillain Barre, and pregnant women where you're looking for a common outcome. 10% of women have a preterm birth. I'm not sure one system is going to be able to do both. And I think they need to make sure that they have a fit for purpose system to be able to evaluate this signal.

And I agree, it was, I'm glad that we learned the difference between a post-marketing requirement and a post-marketing commitment. This, to me, would clearly seem like there needs to be a post-marketing requirement to be able to have a system that can really, in a timely manner, pick up any imbalance. So I hope the FDA and the company really gets something together that is going to be able to evaluate this. Thank you.

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

Dr. Kim: Well, thank you. Clearly the burden of RSV disease is high, and there's a definite need for preventive care. And all things considered, this candidate RSV vaccine is a terrific crisis start for us to prevent disease and prevent severe disease. So I'm in agreement with others in continuing to look carefully at safety concerns because the vaccine effectiveness is on par with many other vaccines that are routinely recommended. So we need to continue to look at safety issues, as we would for any other vaccine.

That said, both Dr. Hong-Nguyen and Dr. Munjal noted the potential vaccine to vaccine interference between the RSV vaccine and the pertussis component of Tdap based on decreased immunogenicity, albeit it was among non-pregnant people, as Pfizer quickly pointed out. But I should also mention that the clinical significance is not known. And that was addressed by Peterson (phonetic) in the Journal of Infectious Diseases where the inflammation was displayed. And that will need to be addressed down the line. And I'm encouraged by Pfizer and the FDA and their plans to address this concern in the future.

And I don't know if I capture this information correctly, but for infants with low gestational age, Dr. Hong-Nguyen, in her presentation, noted that the vaccine effectiveness is lower when the mom is given the vaccine in early third trimester, specifically for the 24 to 27 week subgroup. The vaccine effectiveness for the 24 to 27 week cohort is less than that for the

cohort of 28 weeks or longer. So if supported by additional data, perhaps the timing of RSV vaccine administration can be adjusted to be later in third trimester, that is in series with Tdap in early third trimester and RSV vaccine later in third trimester.

I know that this is not a BLA concern, but rather a policy issue. But I just wanted to point out that there will be many future discussions on how the vaccine will be used, and I appreciate this opportunity to review the data and consider the safety and effectiveness of the RSV vaccine for the benefit of infants.

Dr. El Sahly: Okay. Dr. Sylvester. Dr. Gregg Sylvester.

Dr. Cohn: I don't think he's supposed to speak.

Dr. Sylvester: Well, okay.

Dr. El Sahly: Oh, I think he's not supposed to vote. Oh, he's not supposed to speak?

Dr. Sylvester: I know I don't vote. And I was going to say, I'm a non-voting member.

Dr. El Sahly: Yes.

Dr. Sylvester: I agree with what Dr. Monto said. And I think that Dr. Gruber has answered the question from the industry and his team.

Dr. El Sahly: Okay. Dr. Bernstein.

Dr. Bernstein: Thanks, Hana. So, for me, although it wasn't statistically significant, I'm concerned that that might be clinically significant signal. And I really don't want another experience that happened, sort of, and I may not have the facts right, but I don't want another rotavirus vaccine where intussusception was not statistically significant until it was more widely used. I do see that there are problems with co-administration, although I was comforted by Dr. Ault when he said, he reminded us about the number of visits to the OB that a pregnant woman has. But more to the point, I think that there doesn't appear to be a lot of morbidity and

mortality from RSV for pregnant women themselves, the way it was when we're thinking about those 60 and above.

And I do, on my end, although it's investigational or still being studied, I do think that all infants, healthy infants, not just those like that are recommended for palivizumab, but Nirsevimab at birth for all healthy infants, I think, really will potentially be a game changer against RSV for infants. And we wouldn't have to worry about the concern for this signal. I do emphasize what. Dr. Cohn said too, and others, that this was an incredible effort by Pfizer to conduct such a study in a large population of pregnant women, especially during the pandemic and, which only confuse seasonality, but I still have some reservations.

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

Dr. Janes: Thank you. I second pretty much all the comments that have been made, you know, really a stellar effort here and compelling. I find the data on efficacy quite compelling. In particular, the high efficacy against severe RSV disease in infants. The signals, you know, pose some challenges in terms of optimal administration and implementation of the vaccine to optimize the immune responses in infants. I'm still wrestling with the totality of evidence around both safety and efficacy. And, as others have said, you know, trying to draw conclusions about whether or not the point estimates of incidents of low birth weight in placebo recipients and vaccine recipients are, you know, represent, you know, real differences in incidents of low birth weight or our, you know, statistical artifacts and, you know, no real difference, would've been apparent had the studies been larger.

And then, as well, trying to wrestle with if there were an increased risk of incidents of low birth weight associated with this vaccine, what would be the benefit risk profile of this vaccine? Would, say, a 20% increase in risk of low birth weight be acceptable in the context of

an 82% reduction in risk of severe disease in the infant? I sort of wish that we could have some more discussion and more data on how to put these benefits and potential risks together. And, as others have indicated, I'm highly concerned about the ability to tease this out with post-marketing surveillance data, given, as Dr. Cohn has pointed out, the multiple different databases that need to be linked, both for the mother and for the infant. I think I'll leave it at there for now.

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

Dr. Portnoy: Great. Thank you. I've been struggling with this. This is a very complicated question because the person that we're vaccinating is not the person who's receiving the benefit. And so it's a very complex issue. I'm also very grateful for the possibility that RSV can finally be attenuated or, at least, reduced because I've seen the epidemics of it for my entire career. The concern that I have about the possibility of premature birth or earlier delivery, I think all vaccines have a potential to have adverse effects. In this case, we're not worried about the mother having the adverse effects. We're worried about the child being born a little bit earlier.

The problem is that if the child is born earlier, that also reduces the efficacy of the treatment because earlier birth means less antibody is transferred. So this is a very complex thing because the harm actually makes the benefit less. So there's an interaction between the two. And I'm just wondering if there would be a way to possibly take infants after they're born, before a certain gestational age, and maybe measure their antibody level, see if they have high enough titers, and, if not, put them on a protocol of synergist and boost them up perhaps. But there's always going to be some harmful effects.

The question that we have to ask is does the harm justify the benefit, or does the benefit justify the harm? And when the harm actually causes the benefit to decrease, we have to come up

with ways of dealing with that. And I'm suggesting that we might consider measuring the antibodies and giving the synergist as way of boosting it. Just a thought.

Dr. El Sahly: Thank you. Dr. Ault.

Dr. Ault: I'm not sure I have a lot more to add compared to what I've already said or what other people have said recently. I mean, I think the problem that I was struggling with, just reviewing the data, is that, you know, preterm delivery has been a thorn in the side of obstetricians my entire career. And I'm not sure we have a, you know, I'm looking for a biologically plausible mechanism for this, and I'm not sure I have a biologically plausible mechanism for preterm birth anyway, let alone throwing a vaccine into the mix. So lots of confounders and a very challenging clinical entity that we've been wrestling with for decades in the United States. But I don't want to take up too much time repeating what I've already said. Thank you.

Dr. El Sahly: Thank you, Dr. Ault. Dr. McMorrow.

Dr. McMorrow: Thank you. I'll echo the sentiments of many of my colleagues today. RSV is a very important disease in young infants. And it's one that I, as a pediatrician have looked forward to having additional preventive products for, for some time. I have concerns, as others have raised, about the duration of protective effect and also about the preterm birth signal. However, I will say that I am somewhat reassured by the divergence in some of the data on that, and by the fact that a majority of the preterm deliveries were later preterm deliveries, which –

Dr. El Sahly: You froze, Dr. McMorrow.

Dr. McMorrow: -- while certainly have important biological consequences are perhaps less. I would echo Dr. Cohn’s call for raising the bar in terms of the safety and efficacy procedures

before we get to this point in review, and perhaps consideration of larger sample size and stratification of those results when there's an indication that's for a longer duration for protection.

Dr. El Sahly: Thank you, Dr. McMorrow. Dr. Offit.

Dr. Offit: Yes. Thank you. So I think, regarding efficacy, I mean, we have 40 years of data that passively transferred antibodies, actively transferred antibodies are going to be protective and the data are convincing. And it's a polyclonal response, which is a value. So there, I have no problem with that. I think the safety, if I was only looking at Pfizer's data only, and I saw sort of their phase two data where you had sort of 240 adjuvanted, unadjuvanted, 120 adjuvanted, unadjuvanted versus placebo, that was worrisome. And then you still have like a trend, you know, 5.7% versus 4.7%. That alone would've made me uncomfortable, but not so uncomfortable that I wouldn't feel, you know, that we could move forward and then try and get post-marketing surveillance in good enough shape to see whether or not this plays out with larger numbers.

It's the GSK experience though. And I was not reassured by either the FDA and/or the company that another product, which is also 120 micrograms of preF protein, given to 24 to 36 week pregnant women, pregnant people, is, that company abandoned that program because of that. And those decisions are never made lightly. And I haven't, I've only seen what they presented in one meeting from a couple weeks ago. But that wasn't reassuring.

And I think what's at stake is what Amanda Cohn alluded to, you know, the pregnancy platform is an important platform. And, you know, I just, you don't want to mess with it. And I worry that if preterm births are in any way a consequence of this vaccine, that would be tragic in many ways. And we aren't, as Dr. Bernstein alluded to, we're not jumping without a net. I mean, in addition to palivizumab, we do have another long-acting monoclonal, which is probably going

to be available by the end of the year. So, again, we're not jumping to that net. So I guess that's the way I see this. Thanks.

Dr. El Sahly: Thank you, Dr. Offit. Dr. Omer.

Dr. Omer: Thank you. So since you've asked us to consider certainties and uncertainties, I'll frame my sort of comments in that context. There are at least three certainties. I'll start with that. First of all, RSV remains an important cause of childhood and infant especially morbidity and mortality in this country and beyond. And so we should keep in mind. And, therefore, the efficacy data is another level certainty in this trial that came out that for relevant endpoints, you know, obviously not all endpoints can be measured in a trial, which is reasonable and feasible to conduct in a timely manner, and so, therefore, the endpoint chosen for this trial were reasonable and they reflect the consensus of the overall vaccinology community that these endpoints should be chosen for efficacy. And so that has been demonstrated. So that's another certainty.

The third interesting operational certainty, if you will, that was developed, that vaccine trials for non-pandemic infections can be done in the middle of a pandemic. So I commend, not just the sponsor, obviously the sponsor, it took a lot of sponsor effort, but also investigators and subjects, et cetera., who were involved with this trial. Because it, you know, as someone who's done trials in different parts of the world, it's not easy to do, especially in a pandemic. And so that's commendable. That also sets precedent that, you know, in the future, we should not wait for a pandemic to pass for conducting trials for pathogens of importance.

In terms of uncertainty and, broadly, on the somewhat negative side of the ledger, is the fact that the co-administration data does raise some concern. And so hopefully that will be reflected in the labeling information. And our colleagues and friends at ACIP would keep those data in mind as they develop clinical and public health recommendations around this vaccine. In

terms of another contextualizing factor for this co-administration data, is that, look, you know, pertussis as an important pathogen flu is an important pathogen, especially pertussis data are a little bit more salient in this context.

But in terms of the mortality and morbidity caused by RSV, it's, you know, somewhat different order of magnitude. So just to keep that in mind as we apply the normative standards of ethics in terms of decision making of risk versus benefit. I hope the clinical consideration will take in mind these kinds of sort of things where co-administration data and all of that stuff.

The other thing about preterm, that's the elephant of the room. I think as the post-marketing surveillance plan, a global in nature post-marketing surveillance plan, that or subsequent studies that go ahead, irrespective of whether or not a foreign country authorizes it, will be important for informing the overall evidence base. But what is reassuring, what is contextualizing for that outcome, is the fact that the US data looks reassuring. That's our more immediate concern.

Although, as I think Dr. Monto pointed out, or someone else pointed out, that we shouldn't be still naive as to think that, you know, these deliberations don't impact global policy. You know, having been involved with global policy, yes, absolutely it does. But in the narrow context of the remit of this committee, the US data look reassuring. Now, the other thing that looks reassuring that even South Africa data, the near term sort of premature infants, account for a pretty substantial chunk of the preterm birth numbers in this trial. And, therefore, the second order consequences associated with near term or late preterm versus early preterm are different.

And the last thing I will say, and that's a comment to the FDA is that, look, you know, having measured and having, you know, wearing another hat within the vaccine work, ask women around the world, especially in the context of vaccines like RSV, whose wellbeing,

safety, and efficacy and sort of protection they would prioritize, an overwhelming majority of women around the world say it's their infant. So, yes, it's reasonable to have the paradigm under which we are evaluating this vaccine, but I wish we had an explicit vote on maternal safety or the mention of maternal safety in our second vote. And so as VRBPAC and FDA, you know, and I'm sure folks are cognizant that there are other vaccines in the pipeline, I think our default paradigm should include an explicit consideration by advisory committees, such as ours, of not just an implicit accounting for it, you know, in our deliberation, but explicit consideration for maternal vaccine safety, even if the efficacy indication is primarily for infant.

Dr. El Sahly: I didn't understand the question goes to not mean women, or you want them broken down? Is that what you're saying?

Dr. Omer: No. I'm saying that it says, as I recall, the framing is infant. I may be misremembering, but I'm pretty sure that the safety question is both efficacy and safety questions are for infant. What I'm submitting is that we should have, it's reasonable for a vaccine like this, which the primary indication will be for infant, to have voting on efficacy only for infant, but safety for both mother and infant that thing explicated. Because women are not just vessels.

Dr. El Sahly: I know

Dr. Omer: For her –

Dr. El Sahly: Yes.

Dr. Omer: So from that.

Dr. El Sahly: I think, yeah. That's why I didn't bring, it's safety of immunization, so it's left kind of as together, but yeah. Okay. Thank you, Dr. Omer. Dr. Pergam.

Dr. Pergam: I think I might be last before you Dr. El Sahly, so it's kind of hard to add much to what others have said. I feel the same in terms of the efficacy data. I think it's robust. I think we

all realize RSV as a major pathogen. Having had RSV at my household this year, I understand it personally, and I think it is becoming more, the awareness is really increased in the community. And I think that there is interest in having this as a solution. I'm as concerned as others about the preterm birth. I don't really have an explanation for it, which is hard. And I think we do, as Dr. Offit said, have the AZ data in our heads. And it does sort of affect how we think about this as well.

I do want to bring up something that you brought up earlier is this issue of the pharmacovigilance data. You know, we've looked at a bunch of these vaccines. We've seen sort of early signals, and I would just encourage the FDA or others, CDC, to bring this back to us at some point in time so we can actually see. I thought back to the early days of some of the COVID vaccines and the question around Bell's Palsy. And I sort of just spent some time looking at this recently and found some data that, you know, the risk of Bell's Palsy is, of course, higher in COVID, which I think would surprise many of us, not surprise many of us at this point, but I think it is important that some of this data does come back to us so we can actually evaluate it because this is becoming increasingly something that we're having to make decisions about for more and more of the vaccines that we've been seeing. And I'd love to actually understand and see that process in some of those post-marketing data as committee members, even if it's an addition to one of our meetings. I think it would be very highly valuable in helping us to understand and really be confident that the decisions we're making are being followed up.

Dr. El Sahly: Thank you, Dr. Pergam. And so it's my turn, I guess. The clinical trial, as everyone has mentioned, was a major undertaking, importantly because it took place in the setting of a pandemic. However, in terms of big pictures, a couple of things come to mind. The first is the phase two-B. We do clinical trials phase one, phase two, so that we can identify

signals and adjust the phase three accordingly. I would argue that the signal for preterm births occurred in phase two-B study, which was pre-pandemic, at least the biggest chunk of that study was pre-pandemic, and it was only in three or four countries, as opposed to the 18 country study that followed. What that means, in terms of the design of the phase three, it may have meant, I mean, they aimed for 10,000, but for, I guess, maybe certain constraints, only 7,500 were enrolled or thereof. So that should have taken place, that should have been taken into consideration in terms of the design of the phase three, in terms of the power to answer that question, and certainly from a sample size, but also maybe mechanistically, but that's a second issue.

The other concern I'm bringing it up here, you know, in terms of big picture, but we also brought it up in terms of the other two RSV products we saw. These infants and women are still in follow up, and critical data continue to be gathered. This is not a pandemic vaccine. So in the spirit of weighing in on the totality of the data, it would've been better if we, you know, we have all the data, which would, you know, cover some of the peak that was seen later, looking more at what happens when antibody wanes, antibody levels wane, et cetera. So this would be sort of the big picture comments.

In terms of the efficacy data, they were, the primary endpoint is a relevant one. Actually, both of them are relevant, but certainly the severe disease. And in terms of the design and in terms of the reporting, these were very well performed and not easy to do, if I may say. However, you know, we, for the greatest portion of this meeting, we indicated that a lot of the premature birth took place in South Africa, but also probably a good chunk of the efficacy data came from international sites as well. So these two things are linked together, and I don't know that we can

disentangle at this phase, the two. So we are taking their efficacy data, and we will take their safety data into consideration.

The signal is significant, in the phase two, in the phase three, and in a very similar product that was given, you know, on another study. So having said that, is it reason enough to pause? Probably so. I mean, increasing the risk of or having pregnant women have 20% increased risk of premature delivery is not trivial, even if it is late preterm delivery. The fact that we're putting them into preterm delivery while we're sitting here debating the matter intellectually is not trivial.

And the issue of the co-administration, that is a policy question. However, it's also, again, it cannot be disentangled. There are four to six visits in that last, in those last few weeks. But those visits, there are many things that have to take place. And we are all assuming that these visits do take place, and we know that they often do not for a good chunk of our population. So reality here has to be considered in addition to just the statistics and how we can potentially orchestrate everything else that has to take place in those last four weeks, four to six weeks, and all the vaccinations that are needed to protect the child, the mother, and, you know, including RSV. So this is sort of my viewpoint pertaining to the elements of safety and efficacy.

Prabha, are we ready for the questions or maybe a word from the FDA before we go into the questions?

Dr. Atreya: Yes. If you think the committee has concluded the discussion, and if you think you are ready, we can go for question voting on question number one.

Dr. El Sahly: I see Dr. Marks with a raised hand, since –

Dr. Atreya: Oh, okay.

Dr. El Sahly: Dr. Marks, did you want to address the committee?

Dr. Marks: Thanks. Thanks very much. No, I very much appreciate the discussion here. It's a pretty controversial topic, and it's clear that we've had a very good discussion and look forward to the voting. I do believe that sponsor may want to make some comments based on listening to some of this discussion. And, if you don't mind, it might be nice to allow them to do so before the voting takes place.

Dr. El Sahly: If you say so, Dr. Marks. Pfizer.

Dr. Marks: Thank you. Does Pfizer want to make any comments at this point?

Dr. Gruber: Yes, we do. Can you hear us?

Dr. Marks: Yes.

Dr. El Sahly: We can.

Dr. Gruber: Okay. Great. Thank you very much. Thanks to the Chair and thanks, Dr. Marks, for the invitation to speak here at the end before the vote. We also want to express our thanks to the committee for the thoughtful consideration of the safety and efficacy of the RSVpreF vaccine. We do want to provide the following perspective prior to the vote that I think capsulizes the discussion. There is certainty that the vaccine works and would keep infants out of the hospital in the United States as soon as this winter if broadly applied. We ask the committee to balance this certainty versus no evidence of increased prematurity in a high income population, including the United States, and statistically non-significant difference overall. We are confident that post-approval will quickly resolve post-approval. Pharmacovigilance will quickly resolve the latter. We will continue to work closely with the FDA and CDC post-approval to assure that the vaccine is safe and effective. Thank you.

Dr. Marks: Okay. Thanks very much. And thank you, Dr. El Sahly, for accommodating that. Again, thank you to the committee for the discussion. I'll come back out at the end.

VOTING INSTRUCTIONS

Dr. El Sahly: Thank you both. Prabha, are we ready for posting the questions on the board?

Dr. Atreya: Yes.

Dr. El Sahly: On the screen? I'm sorry.

Dr. Atreya: Yes, I can ask, Joseph, would you be able to start the voting questions? I'm going to just give you a little bit of general guidance. Only our 10 regular members and four temporary voting members, a total of 14, will be voting in today's meeting. With regards to the process, the Chair will read the final voting question for the record, and then afterwards, all regular voting members and temporary voting members will cast their vote by selecting one of the three options, which include yes, no, or abstain. And also for the voting process, our AV staff, Joseph, will move all non-voting members and the meeting participants out of the main room. For those who are voting members, non-voting members, please do not log out of Zoom. We will be with you in a few minutes. But for the voting members, you will remain in the main room.

You will have one minute to cast your vote after the question is read. Please note that you may change your vote within one minute timeframe. However, once you submit your votes and the poll is closed, all votes will be considered final. Once all the votes have been submitted, we will take a few minutes to compute the totals and create a spreadsheet with individual votes. So then we will broadcast the results and read the individual votes aloud for the public record.

Does anyone have any questions related to this process before we begin? Not hearing anything from anyone. So what we will do is just read out the voting question here, question number one on effectiveness. And then once it is read, we will, at that point in time, the voting members will remain in the main room, whereas all non-voting members and the meeting participants will be moved out of the main room. This is a little bit tricky because of the technical

limitations of the platform, but also we appreciate your patience for moving in and out of the main room.

So once we go into the main room, we will read the question again, and then there will be a voting part that will show up on your screen where there will be radio buttons for you to cast your vote. So before the non-voting members go out of the room, can you read the question number one on effectiveness, Dr. El Sahly.

Dr. El Sahly: Yes. Are the available data adequate to support the effectiveness of immunization with ABRYSVO during the second or third trimester of pregnancy (24 to 36 weeks gestational age) to prevent RSV lower respiratory tract disease (LRTD) and severe RSV LRTD in infants, from birth through six months of age? Please vote yes, no, or abstain.

Dr. Atreya: Okay. Thank you. And at this point, Joseph will move all non-voting members out of the main room. And for those voting members, please stay in the room, remain in the room, and we will get a verbal cue from Joseph to state that all voting members are present. And then we will read the voting question again and go with the voting process.

Voting Question One

Dr. Atreya: We are ready to display results. Okay. Thank you. Go ahead. We can show the total results as well as the individual votes, right?

AV Support Joseph: Yes.

Dr. Atreya: Okay. Can you all see them?

Dr. El Sahly: Yes, we can.

Results

Dr. Atreya: Okay. Great. So we have a total of 14 voting members today, and we have 14 out of 14 voted yes, and zero voted no, and zero voted abstain. So we have a unanimous yes for this

question. 14 out of 14, 100% voted yes. Thank you. And now I'm going to read the, Joseph, I can't see the spreadsheet.

AV Support Joseph: Yes. Displaying now. Is the spreadsheet displaying okay?

Dr. Atreya: No. I can't see.

Dr. El Sahly: I can see it.

Dr. Atreya: Well, I can see it. Oh, okay. Let's see. It's too small for me to read. Full screen. Okay. Yes. Now I can see. Thank you. Although we know it's a hundred percent everybody voted yes, for the public record, I need to spell out, read out the names. Dr. Holly Janes, voted yes. Dr. Meredith McMorrow voted yes. The Chair, Dr. El Sahly, voted yes. Dr. Paul Offit voted yes. Dr. Jay Portnoy voted yes. Dr. Adam Berger voted yes. Dr. Henry Bernstein voted yes. Dr. Amanda Cohn voted yes. And Dr. Arnold Monto voted yes. Dr. Feikin voted yes. Dr. Kim voted yes. Dr. Kevin Ault voted yes. Dr. Steven Pergam voted yes. And Dr. Saad Omer voted yes. 14 voted yes.

Thank you so much. This question passed unanimously. This concludes the voting on question number one. Now you can remove the display of the results, Joseph. And now we can, Dr. El Sahly can go around the committee asking for their vote explanation on this question.

Dr. El Sahly: So we're going to break it by question, or do both and then ask everyone at the end?

Dr. Atreya: No, we're going to do each question one at a time.

Vote Explanations

Dr. El Sahly: Oh, okay. All right. So we're going to go around the room. I think, this one, I heard everyone's viewpoint about it. If you don't have any additional comments, feel free to say

no additional comments, but I'll go with the names as they appear. I'll begin by explaining my vote.

While it would've been better to see the full data set, up to six months the data are very convincing. Dr. Cohn is first again.

Dr. Cohn: Maybe we should go backwards next time, but totally great. Nothing to add. Very exciting. And a really important tool for prevention. Very excited.

Dr. El Sahly: Dr. Berger.

Dr. Berger: I'm with Dr. Cohn about maybe going backwards, but, yes, I have nothing else to add. I think it's, I think the efficacy data spoke for itself at this point. Thanks.

Dr. El Sahly: Dr. Monto.

Dr. Monto: I spent more time clicking than I will say that I like the results. And nothing more to add.

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

Dr. Kim: Well, if adopted, this is great news for kids and moms everywhere in the US. So I have nothing else to add other than to say that this is important progress.

Dr. El Sahly: Dr. Feikin.

Dr. Feikin: I have nothing to add to what I said before.

Dr. El Sahly: Dr. Bernstein

Dr. Bernstein: This has the potential to make a huge difference in the lives of many infants in their first six months of life.

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

Dr. Janes: Really exciting efficacy data. To me what's super compelling is the very high estimated efficacy against severe events, those most clinically important. Thank you.

Dr. El Sahly: Thanks. Dr. Portnoy.

Dr. Portnoy: Great. Thank you. If the vaccine actually lives up to the data that we've seen today, I can guarantee that many infants and their parents will breathe easier in the coming years. Thank you.

Dr. El Sahly: Thanks. Dr. Ault.

Dr. Ault: I don't think I have anything to add, so I'm excited as well.

Dr. El Sahly: Dr. McMorrow.

Dr. McMorrow: Nothing to add. Thank you.

Dr. El Sahly: Dr. Offit.

Dr. Offit: Nothing to add. Thank you.

Dr. El Sahly: Dr. Omer.

Dr. Omer: No additional comments. Thank you.

Dr. El Sahly: Dr. Pergam.

Dr. Pergam: Just one quick comment. I think one thing we haven't taken a moment to do is to remind people in the public why this happened in the first place. You know, Barney Graham's lab at the NIH found this perfusion protein, and I think it's really important to remind people how important basic science is to get us to this question and how important research is and investing in it to be able to develop new vaccines like this. So I think it's really a testament to the work he committed to RSV for years to see this come to fruition. So I think it's exciting.

Voting Question Two

Dr. El Sahly: Thank you all. That concludes this portion. We're going to display question two now.

Dr. Atreya: Yes, Joseph, please go ahead.

AV Support Joseph: Yes, I'm putting people back in breakout rooms again.

Dr. Atreya: No. I think that this, yes. Yes, please do.

AV Support Joseph: Ready to display results and people are back.

Results

Dr. Atreya: Thank you so much. Okay. On voting question two, we had 14 out of 14, sorry. Total 14 voting members, and 10 out of 14 voted yes, 4 out of 14 voted no, and zero voted abstain. So we have 71% voted yes and 29% voted no and zero abstained. So if you can show me the spreadsheet, I can read them out.

AV Support Joseph: Spreadsheet displayed.

Dr. Atreya: Okay. Great. Give me a second. Thank you. Dr. Jay Portnoy voted yes. Dr. Holly Janes voted no. Dr. Paul Offit voted no. Dr. Adam Berger voted yes. Dr. Henry Bernstein voted no. Dr. Arnold Monto voted yes. Dr. Saad Omer voted yes. Our chair, Hana El Sahly, voted no. Dr. Amanda Cohn voted yes. Dr. Kevin Ault voted yes. Dr. David Kim voted yes. Dr. Meredith McMorrow voted yes. Dr. Steven Pergam voted yes. And Dr. David Feikin, Daniel Feikin voted yes.

That concludes the reading of my voting results. Thank you. And, Dr. El Sahly, now you can have the vote explanation from the committee. Thank you.

Vote Explanations

Dr. El Sahly: Okay. So now we will go over individual explanations, and, again, if you have additional comments, please state so. If not, no additional comments is okay. I will begin.

In my opinion, the patterns don't lie. Individual data may have issues. And there is a pattern here that occurred, and in phase two-B, certainly should have triggered action in terms of adjusting the phase three design in order to answer whether the signal observed in the phase two

was real or not. So that was a big missed opportunity, and I feel it's unfair that we kick the can down the road to the larger public.

The issue of co-administration is very real. In an atmosphere or in an environment where congenital, we can't get so much as an RPR on a good fraction of our pregnant women. Asking to orchestrate all these nuances is a big ask and might interfere with some successes we've achieved so far. So, you know, I look forward to seeing data on, you know, from the post-marketing here, but importantly encourage continued research into vaccines that don't interfere with other antigens and, potentially, should this signal be true, safer vaccines.

And now we're going to go in reverse order, as a request by popular demand. Dr. Pergam, you're it.

Dr. Pergam: All right. I guess I'll go first. Yeah. So I don't know that I have much else to add from my prior comments. You know, the post-marketing surveillance is just going to be super crucial, and I think that's the one piece that we can all clarify. Again, I echo my comments prior that I want to see that data.

Dr. El Sahly: Thank you. Dr. Omer.

Dr. Omer: So, a couple of things. Thinking about the counterfactuals, in terms of co-administration, it certainly is something that should be followed up. But is the reasonable alternative not to have this vaccine available or to administer it separately? To my mind, even if that signal turns out to be clinically meaningful, there is a solution, which is suboptimal from a programmatic perspective but it's still better than not having this vaccine available, strictly speaking from that perspective.

You know, on the preterm birth side, what influenced my vote was the fact, and I don't take this lightly, having looked at the birth outcomes data for various vaccines, I think the fact

the US data do not show a difference, the fact that, overall, the difference is not statistically significant. Although I take this with caveat because the study wasn't powered to look at preterm birth. And I want to second Dr. El Sahly's comment about the fact that the phase two-B trial should have influenced the trial design to have more certainty around preterm birth. So even while endorsing that, I think on balance, you know, no difference in the US and the fact that these are near term births, on balance, I felt comfortable voting a yes on this. But that doesn't absolve everyone involved from doing aggressive proactive post-marketing surveillance and post-marketing surveillance that uses methods that provide early answers, rather than sort of waiting for a few years for those answers. Those methods have been developed. Systems have been developed through FDA and other federal investments. CDC has come up with methods within VSD to evaluate things quickly. I would say it would, it's an ethical imperative to deploy those methods in service of this endpoint.

Dr. El Sahly: Thank you, Dr. Omer. Dr. Offit.

Dr. Offit: Right. Well, Dr. El Sahly really summarized my feeling about this. I think that where I get hung up on that question is the word adequate. I mean, was this adequate in terms of reassuring one, that what was seen with GSK's vaccine is not going to be seen here when there were certain trends and patterns that were, if anything, not reassuring. And I do think a lot's at stake when you're asking, as Dr. Portnoy pointed out, you're asking one to protect another. And if you're, in any sense, risking premature births with this vaccine, I think there'll be a big price to pay. And so I guess I just don't feel we have enough data to be reassuring. So that's why I voted no. Thanks.

Dr. El Sahly: Thank you. Dr. McMorrow.

Dr. McMorrow: Yes. I've worked in influenza vaccines for years in pregnant women, and, despite that vaccine being available for quite many years, we still have unanswered questions –

Dr. El Sahly: You froze, Dr. McMorrow.

Dr. McMorrow: -- about it in pregnant women. And to answer. But given the facts about this particular vaccine and my knowledge of the trial design and the specific signal being late preterm birth and not being statistically significant here in the United States, I think I'm comfortable with the safety data available to date but, like others, look forward to seeing additional post-marketing surveillance.

Dr. El Sahly: Thank you. Dr. Ault.

Dr. Ault: Well, I think you raised some good points when you mentioned RPR, especially since we're having a record increase in syphilis. We're going to talk about that this week at our annual obstetricians meeting. You know, but that applies to all maternal immunizations. You know, we've done a very poor job in vaccinating pregnant women through the last two pandemics with COVID vaccine and flu vaccine under emergencies.

And, you know, I have some qualms that we might not be able to do this vaccine ‘cause of health inequities and the same from monoclonal antibodies after birth. So I know that's not the purview of the committee, but, since you brought it up, I wanted to at least get that thought into the record, you know, that there are health inequities that need to be addressed here. And like everybody else, I'm looking forward to participating in and seeing the post-marketing data.

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

Dr. Portnoy: Great. Great. I voted yes. Basically there's two adverse effects that have been discussed during this meeting. The co-administration issue, I don't consider that to be an adverse effect. That just informs the CDC and the FDA on when to give the vaccines. But it's actually not

an adverse effect, in and of itself, ‘cause that can be managed by just timing and when to give vaccines.

The other one, premature birth or earlier delivery, I know that that can be harmful to a very small percent of infants. Nobody says it's very high. It's a very small number of infants. And over 90% of these children are going to get RSV, and I've seen the harm that that does. So if I compare the very small risk of earlier birth with the almost certain risk of getting RSV and a very high risk of ending up in the hospital, I have to, on balance, say that the risk is much greater if we don't give the vaccine than if we do. So that's why I voted. Yes. Thank you.

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

Dr. Janes: Thank you. I voted no. Similar to the statements made by Dr. Offit, I interpreted literally the question around are these data adequate to support. And I felt that, on balance, I felt that there was too much uncertainty based on the data that were presented and discussed today. I'm concerned about the fact that, you know, as one envisions rolling out this vaccine to a broader and much more diverse population, which has a higher incidence of low birth weight to begin with, and I looked up in, you know, in the US there's apparently an 8.5% rate of low birth weight or preterm birth amongst infants born in the US. I'm concerned about a potential increased risk and in a more diverse population. I wasn't reassured about the fact that this apparent signal isn't seen in the US, whereas it seems to be driven by data from low and middle income countries. If anything, that makes it a bit more puzzling in my mind.

And I agree with Dr. El Sahly that I think there was plenty of potential for the phase three trial to reflect, in its design, a potential safety signal that was observed in the phase, phase two-B data, as well as in, you know, data from other manufacturers. I also second some statements that were made by others that I feel like it's not really possible for us to interpret data as if we live in

a vacuum. And I think these presentations don't ask us to, for the most part. You know, we're presented with population-based data from a host of studies, understanding the epidemiology and the burden of disease, you know, in order to motivate consideration of a given intervention. And I think that suggests that we ought to interpret the safety and efficacy data in a broader sense as well.

And I'm uncomfortable with the notion of kicking the can down the road, as others have said, towards post-marketing surveillance studies. I think it's a bit different to rely on surveillance studies to sort of confirm what appears to be a safe product, whereas here, I think that the signals are such that the post-marketing surveillance data would be asked to refute what is sort of a potential hypothesis here. And I think that's a higher bar that I'm uncomfortable, as they say, kicking down the road for surveillance. Thank you.

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

Dr. Bernstein: Thank you. I agree with Drs. El Sahly and Offit and Janes, which is why I voted no. I am concerned that this might be a clinically significant signal, even though it's a small number in a study of several thousand. Remember that there are close to 4 million births a year. So it's a small percentage of a large number is a large number. The co-administration issue is a concern. The fact that morbidity and mortality directly in pregnant women is not to the same degree in any way, shape, or form as it is in 60 year olds and older or young infants. And I think that the possibility of an alternative for all newborns at birth in the not too distant future makes me want to have more information before voting affirmative for the safety of this particular product. Thank you.

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

Dr. Kim: I have nothing else to add. Thank you.

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

Dr. Feikin: Thank you. I voted yes. Am I concerned about the preterm birth imbalance? Yes. Am I convinced that it's real? No, I'm not. And I guess when I put all the evidence together, I'm not convinced that there's a clear causal relationship between this vaccine and preterm birth. I don't think we can rule out chance. I don't think we can rule out confounding by time or place. I'm really, I'm still struck by the fact that this study was done in the setting of a pandemic, as was the GSK study, when so many things were different.

And this signal was not seen in high income countries. It was really only in certain countries that I don't think we quite understand what, my interpretation of not understanding is that we, that there's something there that we don't, that is not clear and not convincing. And I, to me, the key will be doing really good post-marketing surveillance. We have to get that right with this vaccine ‘cause there are other vaccines in the future for pregnant women. So I think this is our chance to really step it up and do the right thing and develop systems that we can get a quick answer. Thank you.

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

Dr. Berger: So I voted yes. And I'll just say largely I agree with pretty much what everyone is saying here. I just looked at the benefit risk profile of making sure that there's access, and the benefit that that would provide to infants, as being able to overcome the potential risk here from the safety signal that's coming up enough so to be comfortable relying on the requirements for post-market surveillance. So that's all.

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

Dr. Cohn: Thanks. I voted yes. I think Dr. Feikin really spoke to a lot of where my head was at in terms of me being comfortable with that level of uncertainty, given the benefits of

protecting against RSV, even in preterm, you know, 34 to 37 week babies, I think will benefit from getting this vaccine. And the potential risks in the US of preterm infants, I felt like I was comfortable with this uncertainty from that perspective. I still wish and think that, through post licensure data, that we can have providers be able to tell their patients that they are absolutely confident that this is a safe vaccine and will protect their infant, which I think that was clear. I do think that we could be doing better. I also think that the data that Pfizer presented, in particular, around the race and ethnicity and the breakdowns that we saw in the US, I just didn't feel like there was enough data to support that this signal is going to be real. So thank you.

Dr. El Sahly: Last, but not least, Dr. Monto.

Dr. Monto: There is never complete certainty when we're asked to review these topics. About the combination problems, there's always problems when you start combining vaccines, especially with pertussis. That's something we can overcome. The signal on the preterm is a little concerning, but we always have things that sometimes play out and sometimes don't play out in the clinical trials, which usually are the verge of statistical significance. And we just wish there were more in the trials.

I think we have to go on what is put in front of us. Another product being withdrawn by the company is of concern. That doesn't happen lightly, as Dr. Offit mentioned. But we need to look at what's in front of us and what we have data on. And we are only advisory, and I'm sure that those who have more access to some of the data will also be concerned about a similar product having different outcomes. So that really summarizes my vote. And there is always risk benefit, and this is a disease we've been trying to prevent for half a century, and this is the first time we've had a chance to do it with a vaccine.

Closing Remarks

Dr. El Sahly: Thank you, Dr. Monto. That concludes this portion and actually concludes our meeting. I turn it over to the FDA for concluding remarks from Dr. Marks or Dr. Kaslow or both.

Dr. Marks: Thank you very much. I 'll turn it over to Dr. Kaslow in a moment if he wants to, but I just wanted to say thank you very much to the advisors. I really want to thank you for a very robust discussion today. Thank you to our presenters, both from Pfizer, as well as the tremendous amount of work that went into this from our office of vaccines and also from our advisory committee group that puts together the meeting. So thank you so much to everyone involved today. I wish you a good evening.

Dr. El Sahly: Thanks. So Prabha, you'll adjourn the meeting, right?

Dr. Atreya: Yes. Is Dr. Kaslow going to say anything?

Dr. Kaslow: Yeah. Maybe I'll just take a minute.

Dr. Atreya: Okay.

Dr. Kaslow: A minute to echo Dr. Marks' comments. I really do like to thank the advisory committee for the really critical and probing questions and the subsequent voting discussion today, and it's really quite helpful to hear this discourse, particularly on the safety topics, including the premature delivery and premature, preterm birth observations, both the evidence that was in the BLA 125768, but also the totality of evidence, including other clinical studies, and hearing the importance of the design and the robustness of the post-marketing studies and surveillance, particularly at this important point in the BLA review cycle.

And it really is input from experts qualified by scientific training and experience in evaluating the evidence on effectiveness and safety of a product. That's a critical part of the regulatory review process. And the advisory committee has, again, served that important role

today. So let me conclude by thanking the FDA BLA review team, the Division of Scientific Advisors and Consultants, and the technical staff here at FDA that really ran another flawless virtual meeting today. Let me also thank today's speakers. And, finally, thank again the advisory committee members, including our temporary voting members, for another productive day. So with that, all be well.

Adjournment

Dr. Atreya: Okay. I would like to also continue thanking everybody. And then I want to thank our Chair, Dr. El Sahly, for going through the whole meeting since morning and since last night, I guess, actually, and to preparing for this meeting, and then all the members and then wonderful discussions that we have and then very helpful discussions for us to take notes and take it back to think about them. So greatly, greatly appreciate it. And then now I formally adjourn the meeting. Have a great evening. Meeting adjourned at 5:10 PM Eastern Time. Thank you so much.