Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

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

Zoom Video Conference

February 28, 2023

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

Participants

Chair	Hana M. El Sahly, M.D.	Professor, Baylor College of Medicine	Houston, TX
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	Henry (Hank) Bernstein, D.O., MHCM, FAAP	Professor, Zucker School of Medicine	New Hyde Park, NY
	Amanda Cohn, M.D.	Chief Medical Officer, National Center for Immunizations and Respiratory Diseases, CDC	Atlanta, GA
	Holly Janes, Ph.D.	Professor, Fred Hutch Cancer Center	Seattle, WA
	David Kim, M.D., M.S., M.H.A.	Director, Division of Vaccines, HHS	Washington, DC
	Steven Pergam, M.D.	Professor, Fred Hutchinson Cancer Center	Seattle, WA
	Stanley Perlman, M.D., Ph.D.	Professor, University of Iowa	Iowa City, IA
Consumer Representative	Jay Portnoy, M.D.	Professor, University of Missouri Kansas City School of Medicine	Kansas City, MO
Alternate Industry Representative	Gregg Sylvester, M.D., M.PH.	Vice President of Medical Affairs, Seqirus Inc.	Summit, NJ
Temporary Voting Members	Daniel Feikin, M.D., M.S.P.H.	Respiratory Diseases Consultant	Coppet, Switzerland
	Marie Griffin, M.D., M.P.H	Professor, Vanderbilt University School of Medicine	Nashville, TN
	James Hildreth, Sr., Ph.D., M.D.	President, CEO, Meharry Medical College	Nashville, TN
Guest Speakers	Fiona Havers, M.D., MHS., FIDSA	RESP-NET Hospitalization Surveillance Team, NCIRD, CDC	Atlanta, GA
	H. Keipp Talbot, M.D., MPH, FIDSA	Professor, Vanderbilt University Medical Center	Nashville, TN
	Natalie J. Thornburg, Ph.D	Acting Chief, Laboratory Branch, Coronavirus and Other Respiratory Viruses Division, NCIRD, CDC	Atlanta, GA
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	Robin Strongin	National Consumers League	

	Meredith Whitmire	National Association of Nutrition and Aging Services Programs	
	Martha Nolan	Healthy Women	
	Kenneth Mendez	Asthma and Allergy Foundation of America	
	Lindsay Clarke	Alliance for Aging Research	

Contents

Opening Remarks: Call to Order and Welcome

Dr. El Sahly: Good morning, everyone. I would like to welcome the committee members, the public, and the FDA for the 179th meeting of the Vaccine and Related Biological Products Advisory Committee meeting, set for two days, February 28th and March 1st. On the first day, the meeting will be in open session to discuss and make recommendations on the safety and effectiveness of ABRYSVO vaccine, manufactured by Pfizer with a requested indication for BLA number 125769 for active immunization for the prevention of acute respiratory disease and lower respiratory tract disease caused by RSV in adults 60 years of age or older.

I would like to kick us off by introducing Dr. Sussan Paydar, the Designated Federal Officer for today's meeting. Dr. Paydar.

Dr. Paydar: Thank you, Dr. El Sahly. Good morning, everyone. This is Dr. Sussan Paydar, and it is my great honor to serve as the Designated Federal Officer for today's 179th Vaccines and Related Biological Products Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, CBER, and the Committee, I'm happy to welcome everyone for today's virtual meeting. Today the committee will meet in open session to discuss and make recommendations on the safety and effectiveness of ABRYSVO respiratory syncytial virus vaccine manufactured by Pfizer Incorporated with a requested indication in Biologics License Application number 125769, STN 125769-0, for active immunization for the prevention of acute respiratory disease and lower respiratory tract disease, LRTD, caused by respiratory syncytial virus in adults 60 years of age and older. Today's meeting and the topic were announced in the Federal Register Notice that was published on February 1st, 2023.

At this time, I would like to introduce and acknowledge outstanding leadership of my division director, Dr. Prabha Atreya, and the excellent work of my team whose contributions have been critical for preparing today's meeting, Ms. Valerie Vashio, Ms. Karen Thomas, Ms. Joanne Lipkind, and Ms. Lisa Johnson. I also would like to express our sincere appreciation to Mr. Derek Bonner in facilitating the meeting today. Also, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one like all the previous VRBPAC meetings. Please direct any press media questions for today's meeting to FDA's Office of the Media Affairs at FDAma@FDA.hhs.gov. The transcriptionists for today's meeting are Catherine Diaz and Deborah Dellacroce 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 then state your first and last name, institution, and areas of expertise. And when finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slides, in which we will begin with the chair, Dr. Hana El Sahly. Dr. El Sahly.

Introduction of Committee

Dr. El Sahly: Good morning. Hana El Sahly. Baylor College of Medicine, Adult Infectious Diseases. My research focuses on clinical vaccine development.

Dr. Paydar: Great. Thank you. Dr. Adam Berger.

Dr. Berger: Hi, Adam Berger. I'm the Director of the Division of Clinical Healthcare Research Policy at the National Institute of Health. I'm a geneticist by training. I oversee all of our clinical trial policies here for the Agency.

Dr. Paydar: Great. Thank you, Dr. Henry Bernstein.

Dr. Bernstein: Good morning. Good morning. I'm Hank Bernstein. I'm a Professor of Pediatrics at the Zucker School of Medicine at Hofstra Northwell. I'm a general pediatrician with expertise in vaccines. Thank you.

Dr. Paydar: Great. Thank you. Captain Amanda Cohn. Good morning. I'm Amanda Cohn. I'm a pediatrician and medical epidemiologist at the Centers for Disease Control and Prevention with expertise in vaccine policy.

Dr. Paydar: Great. Thank you. Dr. Holly Janes.

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

Dr. Paydar: Thank you so much. Captain David Kim. Dr. Kim? Okay. We'll move to the next person. Hopefully he'll be able to join us later. Dr. Steven Pergam.

Dr. Pergam: Hey Suzanne. I'm Steve Pergam. I'm a Professor at Fred Hutch Cancer Center, and my major focus is on infections in immunocompromised hosts, and I am an infectious disease physician by training.

Dr. Paydar: Thank you, Dr. Pergam. Dr. Stanley Perlman.

Dr. Perlman: I'm Stanley Perlman. I'm a Professor of microbiology and immunology at the University of Iowa, and my specialty is in Coronaviruses and in pediatric infectious diseases.

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

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

Dr. Paydar: Thank you, Dr. Greg Sylvester, our alternate industry representative. Okay, Dr. Sylvester is not currently available. We'll come back to them a little later. Next, we'll do a roll call for our temporary voting members. I'll begin with Dr. Marie Griffin. Dr. Griffin.

Dr. Griffin: Good morning. I'm Marie Griffin. I'm a Professor Alverta of Health Policy of Vanderbilt University School of Medicine. I'm an internist and pharmacoepidemiologist.

Dr. Paydar: Thank you. Dr. Danielle Feikin.

Dr. Feikin: Hello. I'm an internist by training. I spent 20 years at the U.S. CDC working as a medical epidemiologist. I've spent the last five years as a consultant and temporary staff member at the World Health Organization focusing on RSV and Covid vaccines. I'd like to state I'm not representing any official WHO position today. I'm just here as myself. Thank you.

Dr. Paydar: Thank you, Dr. James Hildreth. Dr. Hildreth?

Dr. Hildreth: Good morning. Thank you, Susan. I'm James Hildreth, the president and CEO of Meharry Medical College. I'm professor of internal medicine. I'm an immunologist by training, and my interest is in viral pathogenesis and how the immune system responds to viral infections. Thank you.

Dr. Paydar: Great, thank you. I'm going to go back and see if Captain David Kim is available. If not, if he's still not present, I'll call on Dr. Greg Sylvester. I wonder if he is available. Okay. So they will join us soon, I'm sure. We have a total of 13 participants, 12 voting and one non-voting member.

Conflict of Interest Statement

Dr. Paydar: I proceed with reading the FDA conflict of interest disclosure statement for the public record. The Food and Drug Administration, FDA, is convening virtually today, February

28th, 2023, the 179th meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Hana El Sahly is serving as the chair for today's meeting. Today, on February 28th, 2023, the committee will meet in open session to discuss and make recommendations on the safety and effectiveness ABRYSVO Respiratory Syncytial Virus Vaccine manufactured by Pfizer Incorporated, with a requested indication in Biologics License Application #125769 (STN 125769/0) for active immunization for the prevention of acute respiratory disease and lower respiratory tract disease, LRTD, caused by respiratory syncytial virus in adults 60 years of age and older. 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 conflict of interest laws and regulations. The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, including but not limited to 18-USC Section 208 is being provided to participants in today's meeting and to the public. Related to the discussions of this meeting, all members, RGE, and SGE consultants of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouse or minor children, and for the purposes of 18 US Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are current or under negotiation.

FDA has determined that all members of this advisory committee, both regular and temporary members, are in compliance with federal ethics and conflict of interest laws under 18-USC Section 208, Congress has authorized FDA to Grant waivers to special government employees and regular government employees who have financial conflicts of interest when it is determined that the Agency's need for special government employee services outweighs the potential for a conflict of interest created by the financial interest involved, or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Based on today's agenda and all financial interests reported by committee members and consultants, there has been one conflict of interest waiver issued under 18 US Code 208 in connection with this meeting. We have the following consultants serving as temporary voting members, Dr. Marie Griffin, Dr. Daniel Feikin, and Dr. James Hildreth. Dr. Gregg Sylvester of Seqirus Incorporated will serve as the alternate industry representative for today's meeting. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the committee. Dr. Jay Portnoy is serving as the consumer representative for this committee. Consumer representatives are appointed as 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. Fiona Havers, Team Lead, Respiratory Virus Hospitalization Surveillance Network Team, Coronavirus and Other Respiratory Viruses Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia. Dr. Helen Keipp Talbot, Associate

Professor, Vanderbilt University Medical Center, Nashville, Tennessee. Dr. Natalie J Thornburg, Acting Chief Laboratory Branch, Coronavirus and Other Respiratory Viruses Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia. 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 DFO and exclude themselves from the discussion, and their exclusion will be noted for the record. This concludes my reading of the conflicts of interest for the public record.

At this time, I would like to hand over the meeting over to our chair, Dr. Hana El Sahly. Thank you.

FDA Introductions

Dr. El Sahly: Thank you, Dr. Paydar. The FDA introduction is next on our agenda. Dr. David Kaslow, Director of the Office of Vaccine Research and Review at CBER will provide the welcome notes from the FDA. Dr. Kaslow.

Welcome — Dr. David Kaslow

Dr. Kaslow: Thank you, Dr. El Sahly, and welcome all to this 179th convening of VRBPAC for a two-day meeting in open session to discuss and make recommendations on the safety and effectiveness of actually two pioneering RSV vaccine candidates. Pioneering as they represent 21st century science and technology over the shortcomings of previous efforts of a half a century ago, structural immunology and engineering over empiric vaccinology, against a respiratory virus that causes life-threatening disease in the youngest and oldest, particularly those with comorbidities.

The convening of VRBPAC focuses on respiratory sensorial virus disease in older adults, as will be reviewed by presentations this morning. The committee will then consider two RSV candidates, one a bivalent without adjuvant, the other, a monovalent with an adjuvant. The particular product for consideration today is one submitted by the sponsor, Pfizer, in BLA125769, the other for consideration tomorrow by the sponsor GSK in BLA 125775. Let me conclude this brief welcome by thanking the committee members for their time today and tomorrow, by thanking those from the FDA who reviewed these submissions and helped organize this meeting, by thanking our presenters, and by thanking those who have joined this public open meeting virtually. We look forward to a productive meeting today and tomorrow. Back to you, Dr. El Sahly.

Dr. El Sahly: Thank you, Dr. Kaslow. Next, Dr. Goutam Sen, the review committee chair from the Division of Vaccines and Related Products Application, Office of Vaccine Research and Review. Dr. San will go over the BLA for ABRYSVO RSV vaccine in adults 60 years of age and older. Dr. Sen.

Biologics License Application for ABRYSVO in Adults 60 Years of Age and Older — Dr. Goutam Sen

Dr. Sen: Good morning, everybody. Thank you, Dr. El Sahly, for the kind introduction. My name is Goutam Sen from Office of Vaccine at CBER FDA. It's my pleasure to introduce you today's discussion topics, which is Biologics License Application for respiratory syncytial virus vaccine, ABRYSVO, by Pfizer. Next slide, please.

Here is the outline of my talk. I'll briefly discuss about the respiratory syncytial virus disease in older adults, description of ABRYSVO, the vaccine in our discussion, overview of ABRYSVO's Biologics License Application, the clinical package submitted by Pfizer, overview of today's agenda, voting question for the committee. Next slide, please.

RSV is one of the leading causes of respiratory infection in older adults. RSV has two major subgroups, A and B, which cocirculate. Both can cause severe disease. Palivizumab, a monoclonal antibody is approved by FDA for prevention of serious lower respiratory tract disease caused by RSV in children less than 2 years of age. Currently, Palivizumab is not approved by FDA for use in older adults. In the US, RSV is responsible for approximately 177,000 hospitalizations and roughly 14,000 deaths annually in adults 65 years of age and older. Currently, there is no licensed vaccine to prevent RSV disease in older adults. Treatment of RSV disease for older adults consists primarily of supportive care. Therefore, RSV disease represents a serious condition with an unmet medical need for older adults. Next slide, please.

Each 0.5 ML dose of ABRYSVO vaccine contents 60 microgram each of lyophilized recombinant Pre-Fusion F protein from RSV-A and RSV-B subgroups expressed in CHO cells, a total of 120 microgram protein. The dosing regimen is a single dose of 0.5 mL administered

intramuscularly. Applicants proposed indication: active immunization to prevent acute respiratory disease and lower respiratory tract disease caused by RSV in individuals 60 years of age and older. Next slide please.

On September 30th, 2022, FDA received the Biologic License Application from Pfizer for ABRYSVO. The clinical package includes safety, immunogenicity, and efficacy data from an ongoing pivotal Phase Three study, C3671013, conducted in the US, Canada, Finland, the Netherlands, South Africa, Argentina, and Japan, with approximately 34,000 participants. Additional safety data from approximately 1200 ABRYSVO, the final formulation, recipients across five clinical studies conducted in the US, Australia, and UK were also submitted. Next slide, please.

So here is the overview of today's agenda. After my introduction, Dr. Natalie Thornburg from CDC will discuss about RSV virology, strain variation, and surveillance measures, followed by Dr. Fiona Havers from CDC will discuss the RSV epidemiology and disease burden in older adults. Dr. Talbot from Vanderbilt University will talk about durability of naturally accurate immunity and susceptibility to repeated RSV infection. There will be short break, followed by Dr. Alessandra Gurtman from Pfizer, will present their findings from the safety and efficacy of viral and RSV Pre-Fusion F vaccine in adult 60 years of age and older. Next slide please.

My colleague, Dr. Nadine Peart, the Lead Medical Officer from Office of Vaccine will present FDA’s review of efficacy and safety of ABRYSVO respiratory syncytial virus vaccine in adults 60 years of age and older. There will be a 40-minute lunch break, followed by Open Public Hearing, additional question and answer session for CDC, sponsor, and other presenters.

There'll be a short break, then committee discussion and voting, and meeting will be adjourned. Next slide, please.

So here is the voting question number one for the committee members. Are the available data adequate to support the safety of ABRYSVO (RSV Pre-F) when administered to individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV, please vote yes or no. Next question. Next slide please.

Here is the voting question number two for the committee members. Are the available data adequate to support the effectiveness of ABRYSVO (RSV Pre-F) for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older? Please vote yes or no. Next slide, please. Thank you for your attention.

Q & A

Dr. El Sahly: Thank you, Dr. Sen for presenting the overview. I would like to invite the committee members to use the reaction button to raise the hand should they have any questions to Dr. Sen or Dr. Kaslow. I have a quick question in that the BLA is for, the efficacy indication is for the acute respiratory infection and lower respiratory tract disease, but the question is for lower respiratory tract disease. So should we focus the review and discussion on that question? Or what do you propose the committee should be doing?

Dr. Sen: Thank you. Dr. El Sahly. That's a very good question. So I do not want to steal the thunder from my colleague's presentation. Natalie's part, she'll discuss about why the question doesn't include acute respiratory disease in her presentation in details. So I'll request you to wait for that.

Dr. El Sahly: Absolutely. Thank you so much. I do not see any raised hands in the Zoom. So we thank you. Dr. Sen. Next on the agenda, I would like to welcome Dr. Natalie Thornburg, acting Chief Lab Branch, Coronaviruses and Other Respiratory Viruses Division, National Center for Immunization and Respiratory Diseases at the CDC. She will go over RSV virology, strain variation, and surveillance measures. Dr. Thornburg.

CDC Presentations

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

Dr. Thornburg: Hi. Thank you. Can I do a quick audio check? Can you hear me all right?

Dr. El Sahly: Yes, we can.

Dr. Thornburg: Great. Wonderful. So my name is Natalie Thornburg, and I'll be talking to you today about a little bit of background about respiratory syncytial virus and the virology, strain variation, and our surveillance measures. Next slide, please.

All right. So RSV, a respiratory syncytial virus is a filamentous virus that's part of the *Orthopneumovirus* family. It has an approximately 15 kilobase genome, which is about half the size of a coronavirus genome, and it has a single stranded negative sense RNA genome. And that means it has the flip flop of the actual genes that code for proteins. It has 11 viral proteins and can be generally divided into two subgroups, or serogroups, A and B viruses. And RSV A and B viruses cocirculate. Next slide, please.

All right, so this is just a cartoon of what a variant might look like. Internally, the single stranded RNA genome is coded in nucleoprotein with associated L polymerase and P phosphoproteins. There is a matrix protein that makes up the variant shell and is just inside a lipid bilayer. There's two major transmembrane proteins, G, or glycoprotein, and F, the fusion

protein. Attachment of G to the cell may happen through cellular CXCR, CX3 CR1, and fusion through the F protein, or fusion. F and G are both targets for neutralizing antibodies. However, absorption assays indicate most neutralizing activity is directed against the F protein. Next slide please.

So the attachment protein, or the G protein, defines RSV A and RSV B viruses, historically speaking. And that's because it has the most heterogeneous sequence. It has two large mucin-like domains that provide antigen masking. Next slide, please.

All right, so this is a map of the RSV genome. I pulled this from a publication, and this is a truncated image and does not include the three-prime end of the genome, which encodes a very large L polymerase. L polymerase is very conserved and not a target for neutralizing antibodies. So we're going to focus on other parts of the genome. Across the top of this inside box, the gene products are listed. So you can see NS1, NS2, N, P… Those are the gene products, and I want you to specifically focus on G and F genes. This is the number of substitutions per site, not at the gene level, but the amino acid level. So we're talking about protein substitutions here. Percent variability across the entire gene product of A and B viruses are shown in parentheses. So that's in black all the way at the top.

So if there is, at each, across the whole gene, if there's 10% variability between an RSV-A virus and an RSV-B virus, it says 10%. Just below that, there's percent variability across the entire gene, not at the amino acid level, within g B-viruses. So there's variability within lots of different B-viruses. And so you can see for example, in the G gene product, you can see between 2 and 12% amino acid variability within all of the published RSV-B sequences.

So the substitutions per site of each amino acid is shown in the graph. So the height of the bar represents the absolute number of substitutions whenever you look at all of the available

RSV sequences. Again, pay attention to the G and the F gene products as they're the targets of neutralizing antibodies. So you see a lot of variability, as I said before, in the G gene product, but most of the neutralizing antibody activity is directed against the F protein, which you can see some variability, but less variability.

And so just for context so you can understand how variable RSV published genomes are, if you look at influenza viruses, if compare, say H1 to H3 viruses, you actually see less than 40% conservation between hemagglutinins of an H1 virus for an H3 virus. So that's 60% diversity. And so that would exhibit much more diversity if you are looking at F, because those are both targets of neutralizing antibodies. So you're seeing 15 in RSV, A to B, as compared to 60% or H3HA as compared to H1HA. When you compare it to say, coronaviruses, the omicron spike to ancestral spike had about 3% of amino acid changes, which was about 38 out of 1200, 12 to 1300 in the spike protein. So they were more concentrated in the receptor binding domain, which is the target for neutralizing antibodies, which contributed to partial escape. And that was, there was 15 amino acid changes observed out of 222. So that's a 7% divergence that allowed that shift to happen. Next slide.

So the F protein may not have that much sequencing diversity, but it does have structural diversity. And this is a crystal structure published by Barney Graham of the same protein in two different structural forms. So it exists in at least potentially more structural forms that present differently to the immune system. And you can see just by looking at it that the left version of the protein looks very, very different than the right version of the protein. The left is a demi-stable Pre-Fusion F, and the, and the right is a more stable postfusion F. Projected onto the surface of those crystal structure are different colored regions, and those represent antigenic regions of the protein, where antibodies might bind. And so you can see the presence of different antigenic

regions in these two different structural forms. So it has the same protein sequence, but that rearrangements puts different amino acids together to allow antibodies to bind in one form and not bind another form.

And I told you earlier that pre-absorption of antibodies indicates the most potent neutralizing antibodies are directed against the F protein, not the G protein. Well, similarly, those pre absorption studies have determined that the most potent neutralizing antibodies tend to be directed towards site 0, which is present in the Pre-Fusion form of F and not the postfusion form of F. And that is colored in red. As you can see, it's kind of very large and at the top of Pre-Fusion F. And the least potent neutralizing antibodies are directed against site one, or colored in blue. And then it's sort of scaled in different antigen sites. So there are neutralizing antibodies that bind to several of the antigenic sites. So for example, palivizumab is not directed against site 0. Alright, next slide.

So I've gone back to this slide just to remind you of the variability in the G gene. And that is why the G gene, historically, when genotyping, was sort of first defined for RSV in the 1990s, that's why it was used to define genotypes. Because if there's differences, then you can identify those differences whenever you sequence the virus. Alright, next slide.

All right, so I already showed you that G protein is the most diverse sequence in the genome, and therefore it's been used historically, before the dawn of whole genome sequencing, to identify genotypes of the virus. And this is just a list of example genotypes, and it's not important to memorize the genotypes or anything like that. From a 2017 publication studying published RSV genomes that are just available in public databases. I think they looked at about 1100 of published genomes collected between the 1960s and 2014. And so this is just a list of examples of genotypes that were identified in public repositories. So often terminology like GA,

GA1, GA2, GA 3, or the G gene A viruses was used. GB. Although there is some that were identified in specific locations that were named slightly differently. So like for example, ON, NA1, those are A viruses. BA viruses are B viruses. Next slide please.

All right. So the two subtypes or serotypes of RSV viruses A and B have been found to cocirculate. And this is just a study of community transmission of RSV in Khalifa, Kilifi, Kenya between 20 or 2003 and 2017. And what you can observe is first, seasonality. Not all areas demonstrate seasonality, especially near the equator, it can circulate year-round. But in many places, RSV has been shown to have a seasonality. Often, A and B viruses cocirculate. So A is kind of a yellow line, and B viruses are shaded in aqua. In some seasons, one subtype is more dominant than the other. And they can be, but not always, alternating dominance. So one season you might have really dominant B circulation, and the next year, A viruses, but that is not always the case. Sometimes you have a pretty good distribution of A and B viruses. Next slide, please.

All right. And so this is just the same study where I showed you the list of genotypes. And this is just the number of samples that were identified of different genotypes in publicly available databases. So 2017 study, sequences were collected from specimens between 1961 and 2014. There were just under 1100 sequences that were studied. The inset shows you sequences that were identified from specimens collected between 1961 and 2000. It's in an inset because it has a different scale. It's only up to 25 sequences, just because there weren't that many viruses or assessments available to study. And then the scale for the remainder of the timeframe is larger. It's up to 180. And so really all I want you to see is that each year, again, A and B viruses are cocirculating. Sometimes there's a genotype dominance by year that can increase and then decrease. But there's not really, really, it's not like what we're seeing with coronaviruses. Like almost everything in the northeast currently is circulating XBB.1.5. But you also have to

remember that the number of sequences that is being studied here is much, much smaller. And the timeframes are not as tight. So in, CDC for our genomic viral surveillance for coronaviruses, we do weekly bins, currently. And this is an entire year looking at things together. Next slide.

Again, historically, genotypes are defined by the G gene because they're the most diverse in the sequence. G and F are targets for neutralizing antibodies, but F has been found to have the most potent neutralizing antibodies. So I want to just show you the amino acid variability across the genome of the F gene. And this is at the protein, well, it's at the gene level. This is from that same study examining published sequences of RSV viruses. And it shows you the linear cartoon of the gene of the F gene, kind of on the bottom with colors. And those colors are mapped to the bar graph on the top. And it shows RSV-A viruses on the left and RSV-B viruses on the right. It kind of has two scales, an above the x-axis scale and below the x-axis scale. Below the scale are synonymous mutations. So what that means are nucleotide changes that do not result in a change in the amino acid sequence. So there are silent mutations, if you remember, from basic biology courses. Or non-synonymous mutations are listed above the x-axis. And those are changes that result in the code of the amino acid, which would matter for antibody binding to the protein sequence. So those are more important for antibody binding to the F protein and probably neutralization. And it just shows proportion of total viruses. So it's on a scale of zero to one. So 1, 100%, 0.5 is 50%.

And then you can see the gray sections are the antigenic regions. So, because proteins fold, antigenic regions are not continuous, meaning the amino acids that an antibody might bind are not always right together in the gene sequence, because they fold around. They can be separated whenever you just look at an amino acid sequence across. So if you want to look at site 0, which is the target for the most potently neutralizing antibody, you can see it's just to the right

of MPE-8. And then, again, immediately to the right, the other half of the antigenic region is just to the right of the area listed as alpha two, alpha three, beta three, beta four.

And so what I want you to see is that there is not a great deal of sequence variability in s studying these 1100 sequences. There is more sequence variability in the RSV-B viruses on the right side of this graph than RSV-A viruses. When you look at that site zero there are some non-coding changes in RSV-A viruses, but no non-coding changes in RSV-B viruses. There are some changes in the site 0 in RSV-B viruses. But again, the limitations of this data are the limited number of sequences. This only looked at 1000 to 1100 sequences. Just in general, RSV has not been sequenced as heavily as coronavirus and influenza viruses. All right. Next slide please.

So how is CDC planning to do genomic surveillance of RSV viruses? We think it's very important to start doing genomic surveillance of RSV viruses to understand seasonality in different regions, understand the circulation of A and B viruses, and then understand the genotypes that are circulating, as well as potential changes in the genome that might affect neutralization after either vaccination, infection, or treatment or prophylaxis with a monoclonal antibody product.

And so one of the core parts of our plans for genomic surveillance is our NVSN network. Now, I know we're talking about adults today, but this is a pediatric network. We do have some other networks with that involve adults as well to just be sort of a check to make sure what we see circulating in children is the same as what we're seeing circulating in adults. But there have been lots of community transmission studies that indicate that school-aged children tend to drive transmission in most communities. Additionally, children, whenever they're experiencing their first or second infection, they tend to shed much higher titers of virus and therefore their

specimens. We can recover much better sequences than we can from utilizing specimens from adult infection, where they shed less virus, because of probably previous infection.

So NVSN, or the New Vaccine Surveillance Network, is a year-round acute respiratory illness surveillance. And it started with three sites between 2000 and 2009 and expanded to seven sites from 2016 to the current time. It's prospective surveillance in inpatient ED and outpatient clinics, uses PCR testing for multiple respiratory viruses, including RSV, and it has population denominators and market share used to estimate disease burden. But for our purposes, for viral sequence surveillance, we collect really good quality specimens and can do a deep dive on those specimens to look at A, B genotypes and sequences as well. Next slide please.

All right, so this is just an example of A and B virus distribution across those different sites between the 2016-2017 season and the 2019-2020, sort of just before the pandemic season. And what you can see is difference between sites. So some sites you have RSV-B virus dominant versus RSV-A virus. These are just pie charts representing the percents of A sequences versus B sequences. Viruses A is being shown in gray, B in blue. Sometimes it's fairly equally distributed at all sites. They're cocirculating in each season. And then there's sometimes it's a little bit more homogeneous, like in 2019-2020, really all of our sites demonstrated dominance of circulation of RSV-B viruses. And there can be sort of a back and forth like we saw in the Kilifi study of one year A might be a little bit more dominant, in the next year, B. But that isn't always that always the case. Like for example, Seattle, we saw two years of A dominance, and then the next two years, it looks like B dominance. All right, next slide.

This is just an example of some of the genotypes we saw from just one year. This is actually the 2015-16 season that we saw. And basically, so each site has a different color. The genotypes are listed, A and B viruses again. We saw A and B viruses both circulating that year.

We saw very similar genotypes circulating. We saw a dominance of ON1 across the NVSN sites in this particular season. And then the for the B is the dominance of BA virus. And they were not really clustered by locations. So I know you can't read the words, but you can kind of see the different colors, and you can see that the colors intermingle with each other. And so the sequences weren't clustered by community, indicating the same viruses tended to be circulating across the whole country. So, while we saw some sort of regional difference in dominance of A versus B, we didn't see regional differences in the specific viruses that were circulating. All right. And next slide.

I believe this is my summary slide. Okay, so in summary, F and G are targets of neutralizing antibodies, with most potent antibodies directed against F. G is the most heterogeneous gene and is used to identify genotypes. There's less heterogeneity in F but more observed in B viruses in comparison to A. RSV-A and B viruses cocirculate and can show sort of a back and forth season to season, but not always. And NVSN specimens can be used for A and B surveillance. And as well as, we plan to utilize it heavily in the upcoming years as genomic and viral surveillance. All right, and that is all for me. Thank you.

Dr. El Sahly: Thank you, Dr. Thornburg for this very informative and engaging presentation. Next Dr. Fiona Havers, who is Team Lead for RESP-NET Hospitalization Surveillance Team, Coronaviruses and Other Respiratory Viruses Division at the National Center for Immunization and Respiratory Diseases at the CDC. Dr. Havers will go over RSV epidemiology and disease burden in older adults. Dr. Havers.

RSV Epidemiology and Disease Burden in Older Adults — Dr. Fiona Havers

Dr. Havers: Great. Thank you very much. I appreciate you having me here today. Next slide. So today I'm going to talk about the RSV epidemiology and burden in older adults. Going on to the next slide, RSV is a frequent cause of severe respiratory illness in older. While it's very well recognized by pediatricians, there's much slower awareness of RSV in adults among healthcare providers and the public. RSV is under-detected, as RSV testing is often not performed even among hospitalized patients. And this is understandable, because as of now, there is currently no vaccine or recommended treatment for most RSV cases. Next slide.

This pyramid here shows a range of estimates for the burden of disease in adults 65 years and older. From the bottom of this pyramid up, RSV is estimated to cause approximately 0.9 to 1.4 million medical encounters, 60 to 160,000 hospitalizations and 6 to 10,000 deaths per year. Note a very large range for these estimates. There is substantial uncertainty in the published literature about the burden of disease in this age group, and depending on the source of information, the estimates for these three metrics vary quite considerably. And there are studies that indicate that the disease burden is higher than what is indicated on this slide. But regardless of the source, however, we do know that the disease burden in older adults is substantial. Next slide.

Here's the pyramid that was just shown, as well as comparable burden estimates associated with influenza and adults 65 years and older, using estimates published by CDCDC. The burden of disease varies annually for both RSV and influenza, generally speaking. However, based on these estimates, the burden of RSV in older adults is lower than that of influenza that, in more severe seasons, may approach the number of medical encounters in hospitalizations that we can see for influenza in some seasons. There are a number of studies that show clinical outcomes among older adults with RSV are comparable to those with influenza. Note, of course,

that influenza has a widely-used vaccine, and without this vaccine, the burden of influenza would be much higher. Next slide.

This graph shows estimates for rates of laboratory-confirmed RSV-associated hospitalizations over four pre-pandemic seasons from 2016 to 2020 by adult age group. These data come from RSV-NET, a CDC population-based hospitalization surveillance system in 12 sites. These rates are shown per 100,000 population. As you can see, hospitalization rates in adults increase with increasing age, with hospitalization rates that are highest in those 80 years and older. However, please note that there is considerable uncertainty around these estimates. These are likely conservative rate estimates, and other published studies put the estimates of hospitalization rates higher. As noted in the footnote, most of these data rely on PCR testing with nasopharyngeal swabs, which is the most common clinical testing performed in hospitals. However, there is evidence from multiple studies that the use of acute and convalescent serology saliva or pharyngeal swabs and other testing modalities to identify additional cases that NC-PCR testing is not as sensitive as previously thought, and that some studies use large multipliers to account for this. But regardless of how rates are determined, it is clear that rates of hospitalizations increase with increasing age and that those in their seventies and eighties are most affected by severe RSV disease. Next slide.

If you want to point out that the age distribution of hospitalized cases also differs by racial and ethnic groups. These data also come from RSV-NET, and as you can see highlighted in the red, median age of American Indian, Alaskan Native, Black, and Hispanic patients hospitalized for RSV is younger than, than White and Asian Pacific Islander patients. On the left, you can see the proportions by race and ethnicity of hospitalized patients in different age groups. Generally speaking, in younger age groups are the higher proportion of Black and Hispanic

patients. And as you can see, the proportion of White patients, shown in gray, increases with increasing age, likely reflecting the age structure of the underlying population. Next slide.

RSV also causes a substantial burden of outpatient disease, as well. The data on this slide show rates of medically attended visits for RSV in adult 60 years and older over 10 seasons. In this study, investigators tested patients who presented to outpatient clinics with acute respiratory infection and found that 11% had RSV. Among those, 19% had a serious outcome, which the investigators defined as hospitalization, emergency department visit, or pneumonia. Note that there are two lines on this chart, with a higher dash line showing rates in those with underlying cardiopulmonary disease. Rates were nearly two times higher among patients with chronic cardiopulmonary disease compared with those without these underlying diseases. Next slide.

I did want touch briefly on the impact of the COVID-19 pandemic on RSV in adults. These are case counts of hospitalizations from RSV-NET from 2015 through the current season, with pre-pandemic seasons, which generally go from October through April, are shown in blue. and the 2020-2021 season shown in red, and the 21-22 season shown in orange, and the current ongoing 2022-2023 season shown in green. As you can see, pre-pandemic RSV hospitalizations in adults consistently peaked in early January. However, there was very abnormal circulation during the pandemic, with almost no RSV-associated hospitalizations the first year, and an atypical surge in the summer and fall of 2021. Then, as I think many of us are aware, there was a very severe early RSV season in the fall of 2022, with a large number of hospitalizations in adults. And these peaked earlier than usual, in early December 2022, and that's shown in green on the slide. Next slide.

All right. I'm now going to move to talking a little bit more about clinical outcomes and comorbid conditions. RSV is a frequent cause of pneumonia in hospitalized adults. This was

shown in one large study, The Etiology of Pneumonia in the Community, which was a multi-center study of patients hospitalized with community-acquired pneumonia. For all patients that met study criteria, extensive testing for multiple pathogens was undertaken. RSV was detected in 3% of adults hospitalized with pneumonia. Although in this study, 62% of patients had no pathogen detected. Other studies have shown that the proportion of those with pneumonia that have RSV to be higher. Regardless, RSV was the fifth most commonly detected pathogen in adults with community-acquired pneumonia. I'd also point out that RSV is a very frequent cause of COPD exacerbations and other respiratory illnesses that would not meet the criteria for this particular study but that are very frequent causes of hospitalizations in older adults. Next slide.

Underlying conditions play a big role in RSV hospitalizations in older adults. We found that in RSV-NET, among adults hospitalized who had laboratory confirmed RSV, almost all, 94%, had a recorded underlying condition, with nearly half having three or more conditions. Cardiovascular disease, chronic lung disease, and diabetes were the three most frequent underlying medical conditions. These are among patients who have clinician-driven testing, and patients with underlying medical conditions may be more likely to be tested for RSV than those who do not have underlying conditions. But the proportion of patients hospitalized for RSV who have comorbid conditions is very high. Next slide.

Comorbid conditions greatly increase the risk of hospitalization. One condition that is clearly associated with increased risk is congestive heart failure. This slide with RSV-NET data shows population-based rates of RSV-associated hospitalizations among patients with congestive heart failure in blue and those without in orange. Overall, 28% of hospitalized adult RSV cases had CHF, and hospitalization rates were eight times higher in patients with CHF compared to those without. The difference between the groups was larger in those who were 50 to 64, at 14

times higher, compared with those who were 65 years and older. But even among the older age groups, those who had CHF were 3.5 times more likely to be hospitalized for RSV than those who did not. I also wanted to point out that hospitalization rates are not only higher in those with cardiovascular disease and underlying cardiopulmonary disease, but I wanted to point out that RSV has been associated also with acute myocardial infarctions and stroke, as well as, as I mentioned, a frequent cause of COPD exacerbation. Next slide.

Immunocompromised adults, including immunocompromised older adults, are also at increased risk of severe disease from RSV, including lower respiratory tract infections, ICU admissions, and death. The greatest risk is among lung transplant and hematopoietic cell transplant patients, as well as other immunocompromised populations, such as those receiving chemotherapy for leukemia or lymphoma. Incidence of symptomatic illness is high in some of these groups. For example, in two prospective studies of lung transplant patients, the incidence of symptomatic RSV illness was 12% over a two-year period and 16% over a single season, respectively. Severe outcomes are frequently seen in immunocompromised patients with RSV infection. Progression to lower respiratory tract illness is very common, and mortality can be high. For example, in one study of hematopoietic cell transplant patients, mortality is 26% in those with lower respiratory tract infection due to RSV. Next slide.

Overall, among all adults hospitalized with RSV, a large proportion are severely ill, as measured by the proportion admitted to the ICU and the proportion who died. In these RSV-NET data from over three seasons, we see that about 19% of hospitalized patients of hospitalized adults of all ages are admitted to the ICU, and 4% died. Mortality was highest in those 65 years and older, at 5%. However, note that the proportion admitted to the ICU was higher even among younger patients 18 to 49, reflecting that younger patients hospitalized with RSV are likely to

have underlying medical conditions that made them more vulnerable to severe outcomes. Again, RSV net data only reflects those hospitalized with lab-confirmed RSV, and more severely ill patients may be more likely to be tested for RSV, so these data may slightly overestimate the proportion of severe illness. But this, the numbers consistent with, these data has been shown in other studies as well. Regardless, it's clear that RSV can and does cause severe illness in hospitalized adults. Next slide.

In addition, long-term care facility residents are vulnerable to RSV infection. It's a frequent cause of respiratory illnesses in this population and is well-documented as a cause of severe outbreaks in long-term care facilities. For example, one study showed that 13.5% of all residents of a single facility has symptomatic PCR-confirmed illness in a single month during an outbreak. RSV in long-term care facilities also contributes to substantial disease burden and costs in the healthcare system. In an industry sponsored study using Medicare data to estimate RSV attributable hospitalizations among long-term care facility residents, they estimated that across six seasons, these costs more than 50 million, with an average length of length of stay of 5.3 days, and accumulative hospital stay days of more than 32,000 days over that study period. Next slide.

RSV-associated hospitalization in older adults can also result in a loss of functional status and independence. Branch et. al at Rochester did a study in 302 adults aged 60 years and older in two sites in New York state. They collected data on two measures of functional status longitudinally, shown in the

two panels in the figure. Pre-hospital measures are shown in blue, and up to six months post-hospitalization are shown in yellow. They also looked at the pre-hospitalization living situation and divided the cohort into those living independently on the left, those living with assistance in

the center, and those living in a facility on the right. As you can see, there was a significant change in the activities of daily living, even at six months post-discharge, for patients who required assistance or who lived in a facility at baseline. They also found that 14% of patients required a higher level of care at discharge and that one third of patients had decreased activities of daily living, or ADL, scores at six months post-discharge. This loss of independence and functional status is often not considered when assessing the burden of disease in older adults, but it is a very important outcome to consider when looking at the epidemiology and the impact of RSV disease in this population. Next slide.

In conclusion, RSV is a frequent, often unrecognized cause of severe respiratory illnesses in older adults. There's a high burden of severe disease with some variability across seasons. Hospitalization rates increase with increasing age. Adults with comorbidities, including immunocompromised adults and also long-term care facility residents are at risk for severe illness. A high proportion of those hospitalized with RSV have severe outcomes, including ICU admission and death, and RSV illnesses can result in long-term health consequences, including a decrease in functional status and independence. I want to thank everyone. Next slide. I want to thank VRBPAC for inviting me to speak today as well as to acknowledge people on the slide and thank many others. And I think Dr. Thornburg and I are now potentially available for questions.

Q & A

Dr. El Sahly: Thank you, Dr. Havers. Dr. Thornburg, please turn on your camera, and my colleagues on the committee, please use the reaction button to raise hands so I can invite you to ask your questions. I will begin by question to Dr. Thornburg. What's the hypothesis behind the

remarkably higher variability in the G protein or G gene compared to the F one. F is the one that is driving much of the neutralization. I know it's more hypothetical realm, but is there a hypothesis behind that? I would've thought the opposite would be true.

Dr. Thornburg: So sorry. So you're, you're asking why? Oh, why… My guess is it doesn't have as much of a function. So it's got these big mucin-like domains kind of on the side of it. So that's where huge sugars are able to bind and block parts of the protein. And so I think it's probably a more limited part of the protein that is required for the function of the virus. And anytime a virus really requires a protein for its replication cycle, it tends to be more conserved than other parts of the virus. So my guess is, is just the hyper variable regions in G don't really do anything in the binding of the virus to the cell or the entry of the virus to the cell.

Dr. El Sahly: Okay. All right. Although we didn't see it in the other proteins, but that's again a hypothetical consideration. Dr. Perlman, please unmute and turn on video.

Dr. Perlman: Yes. Hi. I have a question for Dr. Thornburg. So we know from the COVID-19 evolution of the virus SARS-CoV-2 evolution, we watched it evolve both for binding better to the receptor and in response to the immune response. And we also then went back and looked at cold, common cold coronaviruses, which were not thought to change like 229E, and found that they had changed as well over many years. So is there any sense, do you have enough information yet to know whether RSV is changing? Or is that still, we can see all these different genotypes, but is there any directed evolution that's of interest?

Dr. Thornburg: I don't know. I don't really think our sequencing data is deep enough to say with certainty. Certainly we have very, very limited sequencing data from specimens collected before 2000. So we do see genotypes sort of emerge and then decrease in prevalence. But again, the scale of that particular graph, first of all it's just absolute number of sequences, but it was like

185. And so when you look at that as comparison to the depth of our current coronavirus sequencing, it's 10,000 sequences a week just in the United States alone. And not collected in any sort of systematic way through the last 20 years, the RSV sequences. So I think it's going to be several years. You know, we can, we're working on going back to 15-16 season to really start generating that data from systematically collected viruses. But we just don't have that data yet.

Dr. Perlman: Thank you.

Dr. El Sahly: Dr. Bernstein, please unmute and turn on your camera.

Dr. Bernstein: Thank you. Great presentations, Dr. Thornburg and Dr. Havers. I have one question for each of you. Dr. Thornburg, you mentioned how RSV subtypes A and B cocirculate, and you showed a slide that the epidemiology had variability around the country by different seasons. So I wonder, how does the severity of lower respiratory tract disease vary by subtype in older adults?

Dr. Thornburg: So I don't know specifically in older adults. When subtype-specific severity has been looked at just in all populations, the data's been conflicting. Some studies have indicated B viruses might cause more severe disease. Some say A. Others are really inconclusive. So I would say there's no strong data yet to determine that.

Dr. Bernstein: Thank you. And Dr. Havers, a lot of the epidemiology that you shared was for those older adults that are 65 and up. Today's discussion, both companies today and tomorrow are studying for 60 and above. Is there, does the data apply for 60- to 64-year-olds?

Dr. Havers: Yeah, no, that's a great question. I don't know if it's possible to show slide six for my presentation. We actually broke down the different age groups that show that the hospitalization rates between 60 and 64 are, as expected, somewhat intermediate between those 50 to 59 and those 65 to 69. I would say that we sort of see a bigger inflection point around 70,

75. Certainly, adults 60 to 64 are hospitalized for RSV, and they generally tend to be people that have underlying medical conditions. But the hospitalization rates in that age group compared to older adults, like older or older adults, is lower. But I mean, it does go up with increasing age. The hospitalization rates really kind of take a bigger jump when you get into the seventies and the eighties. So it is definitely a significant cause of hospitalization in the 60 to 64 age range, but the hospitalization rates are slightly lower than in those 65 or 75 or 85. Does that answer your question?

Dr. Bernstein: Yeah. Thank you very much.

Dr. El Sahly: Dr. Portnoy, please unmute and turn on camera.

Dr. Portnoy: Great. Thank you so much. I'm still trying to digest all of the information that's been presented. There's so much of it, and it's very interesting. I guess my question involves persistence of immunity to RSV. As a pediatrician, we also saw a spike in RSV in our children, but we sort of assumed that was young children who hadn't previously been exposed to it because they were protected by the measures used during coronavirus. So it wasn't surprising that we would have an increased amount earlier in children. To see it in adults also suggests that maybe the immunity's not lasting as long and that they're acting like people who hadn't been previously exposed. Do we have any information about how persistent immunity is, and does it depend on which strain of RSV has caused the infection?

Dr. El Sahly: If I may interject here, Dr. Portnoy, that is precisely what Dr. Talbot will be presenting in a few minutes, durability of immunity after natural infection. Would you be okay waiting on that question?

Dr. Portnoy: I'll wait. Thank you.

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

Dr. Hildreth: Thank you. I have a question for both Dr. Havers and Dr. Thornburg. Dr. Havers, the higher rates of RSV infection in younger minorities was very striking. Can you unpack that a bit for me and help me understand why that would be the case?

Dr. Havers: Yeah, no, that's a great question. It's something that we're looking at very closely at CDC. We have seen that there are higher rates among American Indian, Alaska Native, Black, and Hispanic adults compared with White and Asian American and Pacific Islander adults. And as you can see, the median age for those groups was younger than for the White and Asian Pacific Islander adults. I think that is probably related to higher prevalence of underlying comorbidities in those populations compared to White and Asian Pacific Islander adults, as well as socioeconomic status, access to healthcare, and other contributing factors that lead to healthcare disparities. And I think I think that's probably what is causing the sort of disparity in both the median age and the proportion of hospitalizations at younger age groups, as well as population-based rates, which we're looking at very closely now.

I would say that the gaps between the three groups that I mentioned, the American Indian, Alaskan Native, Hispanic and Black compared to Asian Pacific Islander and White populations is, the disparities are bigger in the younger age groups compared to the older adults. And I think that's probably because there's sort of maybe more of an equalizing of the number of underlying comorbidities among older adults. But I think that all of the things that contribute to health disparities in this country are also contributing to health disparities for RSV hospitalized patients.

Dr. Hildreth: Thank you. Dr. Thornburg, I was interested to know whether or not there's data to show that neutralizing antibodies to the F protein and G protein can be synergistic.

Dr. Thornburg: I don't think we have a lot of great data. A lot of the G protein neutralizing antibody data has been generated, just like in different cell types, so in vitro. Correlates of immunity have been really difficult with RSV in general, and I think Dr. Talbot will be talking about that. But there has been heavy use of human challenge models to try to identify correlates of immunity for sterilizing protection versus symptomatic infection. And the best is mucosal IgA directed towards the F protein. But I don't think they looked at anti-G antibodies in those human challenge models.

Dr. Hildreth: Okay. Thank you. Thank you.

Dr. El Sahly: Dr. Feikin, please unmute yourself.

Dr. Feikin: Hi, my question is for Dr. Havers. You showed us that almost all of hospitalized elderly adults have some underlying illness, who test positive for RSV. My question is, do you have any information about whether the reason for that hospitalization is due to an exacerbation of that underlying illness versus an RSV-specific lower respiratory tract infection?

Dr. Havers: I think that it varies. I think it can be both. I think that many of these admissions, and this has been shown in multiple studies where they had enrollment criteria of patients who came in with CHF exacerbation, COPD exacerbation, or acute respiratory illnesses.

The one slide that I showed was for people with radiologically-confirmed pneumonia. So there is clearly an impact on like straight up pneumonia. But I do know that, I mean, it is a frequent cause of, it causes c CHF exacerbations, and it also can cause COPD exacerbations. So I think that it can be hard to tease out.

I mean, people often come in with respiratory symptoms, but then that then leads to a CHF or COPD exacerbation or exacerbation of their underlying condition. So I think it is there's a direct causal link between the RSV infection and the reason for them being hospitalized. I think

that it just speaks to the fact that RSV can cause a range of severe illness both by exacerbating their underlying medical conditions and also causing pneumonia or other sort of lower respiratory tracts infections directly. Did I answer the question?

Dr. Feikin: Yes. Thank you.

Dr. El Sahly: You know, teasing out these data requires two clinicians adjudicating every case.

Dr. Havers: Yes.

Dr. El Sahly: It's a major undertaking for this and other viruses. Dr. Pergam.

Dr. Pergam: Thanks. This is a question for Dr. Havers. I'm curious a lot of the data that you presented is sort of pre-Covid pandemic, and I'm curious if you can discuss rates of RSV in adults just in relevance to when these studies were conducted, rates of RSV in adults during the period of sort of like 2020 through 2022 in comparison to prior years. If that data's available. I know that time is a little bit challenging to get that in in real time, but I'm just curious if there's data from CDC that discusses that specific timeframe.

Dr. Havers: Yeah, we do have that data, and it's actually in slide nine. You could see that on what I presented. We also have a dashboard that actually shows multiple seasons, publicly available data that shows unadjusted rates for multiple seasons that you can compare, that you can look at. And we do have, it's clearly hospitalizations were down during the pandemic. The rates of laboratory confirmed RSV, even despite the fact that there was probably increased testing for RSV, because there was the quad test where people were testing for covid, flu A and B and RSV. So I think there was probably increased testing for RSV in the pandemic compared to pre-pandemic years.

But we did see that there was virtually no RSV in the 2020-2021 season, that sort of standard winter season. It started to go up in the fall of 2021. And we did, a year ago, see

somewhat of an aseasonal, like atypical seasonal, increase in hospitalizations. And then we did see it in the fall, a big increase in RSV compared to the two previous seasons. And we saw increased hospitalization rates compared to before the pandemic. So there was definitely decreased circulation during the 2021 through 2022 period. And then we actually saw more hospitalizations in adults in the fall of 2022 than we had in pre-pandemic years.

So some of it's a little bit difficult to test out, since there were changes in testing practices, but I would say that probably there were more patients being hospitalized with RSV than last, this last, during the sort of current season in the fall of 2022 than pre-pandemic. So I think and we definitely saw that in children as well. So there is data available on that. And I think during the pandemic there was less hospitalizations. And now it's back.

Dr. El Sahly: Dr. Holly Janes.

Dr. Janes: Thank you. I think a question for Dr. Havers. I understandably given the surveillance, the vast majority of the data you presented was on hospitalizations and deaths and severe outcomes. But what do we know about the burden of infection and how it varies a across subpopulations? Or what do the symptomatic data tell us about the burden of infection in the population? Thank you.

Dr. Havers: No, that's a great question. I do think that there is a lot of, I didn't present data on symptomatic infections. We do know that sort of, there's, on that pyramid I showed we have to ask at the top and hospitalizations the medically attended disease. And there's another layer at the bottom where there's probably millions of infections in adults that are symptomatic that don't necessarily require medical care. There's varying estimates in terms of exactly what that is, but that is definitely a contributing factor to the overall disease burden. And I didn't focus on that, but it should be noted that there's a lot of people, including older adults, who get RSV. They

don't necessarily seek medical care, but it does impact their life for at least a number of days, and could potentially have sort of longer-term sequela for them if they have underlying lung disease or other conditions. So you know, there is a substantial burden of disease among people who are feeling sick, but don't seek any medical care in older adults.

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

Dr. Kim: Oh, good morning. First, I'd like to check in as a committee member. This is David Kim. I represent the Office of the Infectious Disease and HIV/AIDS Policy in the Office of the Assistant Secretary for Health at HHS. And I have a question for Dr. Havers regarding RSV infections generally. Do we have any information, any data, on the burden of disease as they relate to asymptomatic infections and those who are asymptomatically infected to be able to transmit and propagate the disease? And do the current surveillance mechanisms allow us to collect data on asymptomatic transmission?

Dr. Havers: There have been studies that have done prospective cohort studies where they've swabbed people weekly and detected that there definitely can be asymptomatic infection. I actually would pass that question to Dr. Thornburg, if Dr. Thornburg wants to comment on that as well.

Dr. Thornburg: Yeah. So when I mentioned earlier those human challenge models where it's young, healthy adults, not older adults. So clearly, it's a little bit different. So in young, healthy adults in the human challenge model, they've found that if you enroll a group of participants and give them RSV, about half of them become infected as, assayed by RT-PCR diagnostics. And of the half that become infected with productive detectable virus in the nose, half of those patients have cold symptoms and half don't have cold symptoms. And they're all

almost always mild, but you know, just because of this population, they enroll very healthy people.

Dr. Kim: If I may, has there been any speculation on what the 'are not' factor might be for RSV compared to other infections causes?

Dr. Thornburg: I don't know that. Fiona, do you know that?

Dr. Havers: I don't have a good number off the top of my head that I could quote on that. I think it's hard to measure. But I think it's probably somewhat similar to, I'm not going to say that, or not as similar to SARS-CoV-2, but the sort of epidemiology of there being a fair amount of like asymptomatic transmission and infection is probably similar. And then the tip of the iceberg is people getting symptomatic and severe disease. But it is a very frequent cause of respiratory illness every year in the population. And so I think that's hard. But I don't have a reliable source that I can quote off the top of my head for the 'are not'.

Dr. Thornburg: Yeah. And just as far as like repeat infections go, I know this isn't what you asked, but you know, people periodically get reinfected throughout their lifetimes. And I think I've seen numbers ranging from its typical for a person to get an RSV infection every like 5 to 10 years.

Dr. El Sahly: Well, Thank you. Dr. Thornburg, Dr. Havers for these two presentations and answering these questions. I would like to now invite Dr. Talbot, Dr. Keipp Talbot, Associate Professor at Vanderbilt University Medical Center in Nashville. Dr. Talbot will inform us on the durability of naturally acquired immunity and susceptibility to repeated RSV infections. Dr. Talbot.

Clinical Considerations of RSV in Older Adults

Durability of Naturally Acquired Immunity and Susceptibility to Repeated RSV Infections — Dr. H. Keipp Talbot

Dr. Talbot: Good morning. Thank you for inviting me. I'm glad to see a lot of questions popped up early in the other talks about the durability and reinfection, and so hopefully I can answer some of those. But as Dr. Thornburg pointed out, most of the challenge studies I've been done in young healthies, probably because the ethics of challenging an older adult.

All right. So to begin with, we'll talk about an overview of immune response to infection. We'll talk about preexisting immunity. Please remember that almost everyone was exposed to RSV as a child. So all the infections that we'll be discussing an adult will be reinfections, and I'll mention that multiple times. We'll talk about infection in an adults, so what we see are risk factors and what antibodies look like. We'll also talk about this in frail older adults. We'll talk about the durability of immune response, and we'll also talk about the proximity of reinfection. Next slide.

So this is a very, very busy slide, but it's really just to highlight that RSV enters through the respiratory tract. And because there's some preexisting immunity due to prior infection, there's quite the breadth of immune responses from innate to antibody related. There's definitely a neutrophilic, a dendritic, a lymphocyte response, but then this is also complimented by RSV IgG, the serum, and pulmonary or nasal IgA. I want to point out here briefly that interferon gamma has a strongly protective response, and that'll be important later as we talk about immune responses in the elderly and the reason that RSV is so successful at reinfection. Next slide.

So this is a cohort that was done that looked at preexisting immunity in younger adults compared to older adults. There were 30 in each age group. The median age for those that were young was 26 years of age, and those that were older were 74 years of age. Specimens were drawn from these adults between May and June, so after and before an RSV season. And this was to grasp what is the preexisting immunity prior to an RSV infection. All participants were medically stable, which means no hospitalization within the last two months. So these are not the extremely frail or the ones with uncontrolled or unstable medical problems. Next slide.

This slide summarizes the antibody responses, both serum or plasma IgG and nasal IgA. What you see in Part A is that the young and elderly have similar levels of neutralizing antibody titers. You'll also see that the young and old, remember these are healthy older adults, have similar F-specific plasma IgG. And if you look at Part D, you'll see that when it comes to RSV F and total IGA, the young and elderly have similar amounts found in total nasal wash. Next slide.

However, for what we see in antibody responses, there's a significant difference when it comes to interferon gamma. These slides show the interferon gamma responses to different proteins in A and B and then the CD4 responses based on interferon gamma. What you will see will be a marked difference in the young and in the elderly, with the elderly having much less of an immune response. And remember, these are much less of an interferon gamma response, and these are fairly healthy, older adults. Next slide.

So what level of preexisting immunity is consistent with risk of infection? So this is one of those challenge studies that Dr. Thornburg mentioned. This one included 61 healthy adults, 18 to 55 years of age. There were all challenged with live RSV, and sera and mucosal antibodies were measured pre- and post-infection. So this was looking at what levels of antibodies would predict protection. 36 of those, so over half, became infected. So remember, they've all seen RSV

before, yet still 36 became infected. And of those, 28 were symptomatic, or 68% were symptomatic. Next slide.

So this slide shows the preexisting humoral immunity and the risk of infection. Those that are uninfected are in the white circles, and those that are infected are in the dark black circles. The top two graphs show anti-RSV IgA and anti-F protein IgA. So these will be nasal antibodies, and what you see is that there's a lower level of IgA in the infected compared to the uninfected. The bottom slide is the serum neutralizing antibody. You'll see the RSV naive infants on the far left with little to no serum neutralizing antibody, uninfected and white, and infected and black again. And what you see is that there's very little difference between the serum neutralizing antibodies between those infected and uninfected. So the main difference is in the nasal IgA. Next slide.

So this is a peak into duration. We'll talk a little bit more about duration. But in that same cohort, they looked at antibody responses pre- and post-RSV infection, 0 days before inoculation, 28 days post inoculation, and 180 days or six months after inoculation. And what they see is preexisting antibodies for almost everyone, with a rapid rise after infection, but unfortunately a decline back to pre-infection levels at six months. So just to point out, that means prior to the next RSV season, antibody levels were at the level that they were prior to the infection seen here. Next slide.

So infection and frail older adults. What do we know? So Anne Falsey's group looked at a cohort of frail elderly adults. So these are actually frail, and they were followed over a 26-month period. And during that 26 month period between 1992 and April 1994, there were 28 RSV infections that were diagnosed. Because they followed this group prospectively. They had

antibody levels pre-infection, and what they saw, the mean neutralizing antibody levels were lower in those that were infected compared to those that were uninfected. Next slide.

So we'll talk about the durability of the immune response. So we saw previously that antibody levels felt within six months to pre levels. So this was another study that was done in young and older adults, and this is a representative sample. So this occurs in both older and younger adults. What you'll see in the dark black line is the microneutralization assays and the gray, or enzyme immunoassay, to the F protein. The dark arrows are time of infection. So you will see at time of infection that there is a rise in antibody levels in both the microneutralization and the enzyme immunoassay. But then those levels once again fall rapidly.

So next slide is the proximity of infection. So this comes from a nice review paper from Dr. Graham and it talks about reinfection. And there's one key component of the RSV virus that helps it reinfect. And one of them is it suppresses the interferon mediated antiviral responses. We did see earlier that older adults have a less effective and less responsive interferon gamma response. And so this also predisposes them to more infection. There's also something that we don't quite understand, is the failure to protect against reinfection. Dr. Thornburg nicely outlined the genetic diversity of the F protein. It does somewhat change, but nothing like HIV, Covid, or influenza, other RNA viruses, that would explain the reason for failure to protect against reinfection. Next slide. Thank you.

So this is one of those hallmark studies in RSV. It was done and published in 1991. Carolyn Hall was the lead author, and she has led any of the early RSV work along with Ed Walsh and Anne Falsey at Rochester. So they took 15 adults that have been naturally infected with RSV, and they challenged them on a regular schedule with RSV to see if they became reinfected and if they became symptomatic. So they actually took them two months after natural

infection and exposed them and challenged them with RSV. They did it at 4 months, 8 months, 14 months, 20 months, and 26 months. You'll see in this slide, at 2 months, 47% of them were infected. This was the highest rate of reinfection. After that, rates were lower. And you almost wonder if it wasn't because there was natural infection, and then two months later, RSV, that they may have developed a higher immune response, resting or preexisting. Of those that were infected at 2 months, 85% of them were symptomatic. And please remember, these were not necessarily elderly adults. Next slide.

So how often can a person be infected? Turns out quite often. Of those that were in the study, 10% were reinfected at least once in the 26-month period. 47% of them were infected at least two more times after a natural infection. And as we mentioned, the highest reinfection time point was at the first challenge at two months. Next slide.

So the main takeaways that are incredibly important for this are that natural RSV infection does not provide durable or complete protection from reinfection. Anti-RSV antibodies return to pre-infection levels within six months after infection, and reinfection can incur as early as two months after the last infection. Older adults have weaker interferon gamma responses to RSV than younger adults, likely making older adults more susceptible to infection and to severe infection. Each of the authors summarized their papers in the discussion talking about likely the need for annual immunization. They all responded that vaccines would provide some protection, but like natural infection, would not be durable or complete, and that likely annual vaccination would be necessary. Next slide.

Q & A

Dr. El Sahly: Well, thank you so much, Dr. Talbot. That was very informative, and I hope it began to answer some of the questions posed by the committee members a little earlier. I would now invite the committee members to use the raise hand function for questions to Dr. Talbot. And I will begin by asking a question regarding cellular immunity. You have shown us data that a major difference between young adults and older adults is the cellular antigen specific responses. However, in the subsequent challenge models and natural infection models, that was not looked at. And so any idea on the role of the cellular immunity as we progress in age, and susceptibility to infection?

Dr. Talbot: Yeah, that's a great question. I think one of the reasons there have not been good cellular data is that these studies were done in the 90s. And there have been some done more recently. But one of the problems with cellular immunities is the standardization of it across laboratories and how do you use that. As we age, immune senescence actually changes multiple arms of the immune system. Some are upregulated and some are downregulated. And so it is likely that multiple arms of the immune system working would be beneficial to prevent infection. There is little data, however, on that, and I think it would be a great area of study.

Dr. El Sahly: Okay. All right. Thank you. Dr. Pergam.

Dr. Pergam: Dr. Talbot, that was a great review.

I appreciate the data. I was just curious, can you remind us if there is any cross protection for, say, an adult who gets an A strain of RSV versus a B, and whether that has a relevance in terms of how we're thinking about the vaccine studies that we're evaluating today?

Dr. Talbot: Yeah. There's not a lot of really great descriptive work in adults, especially older adults about cross immunity. There are some assumptions that there would be, but there hasn't been a great description of it.

Dr. El Sahly: And are you familiar with any cohorts in hospitalized elders, looking at their cellular responses to the virus?

Dr. Talbot: No, unfortunately not. I know some that are underway, but not that are already done.

Dr. El Sahly: Okay. All right. Maybe on your next presentation, we'll hear about those. Any additional questions to Dr. Talbot? I see Dr. Bernstein, but I don't see his hand. Do you have a question? Okay, Dr. Bernstein.

Dr. Bernstein: Great talk. Thank you very much. I just, how is immunosenescence measured by the different age groups, as, like Fiona mentioned, about 60 to 69, and then 70 to 79, and then 80 plus, and then you fold in chronic medical conditions. How do they measure Immunosenescence?

Dr. Talbot: Welcome to the world of adult medicine, Hank. It's very complicated. So yes, unfortunately immune senescence is not necessarily due to just age. And so you can have a healthy, fit 80-year-old who does not appear to have a lot of immune senescence, and then have a 60 year old who appears to be very immunosenesced. There have been attempts to measure that looking at CMV levels, looking at frailty, looking at other endpoints in immunity. And there hasn't necessarily been a consistent way that's been accepted by everybody, which makes the study of vaccines even more difficult in this age group. There is increasing immune senescence with age, but age does not necessarily tell you how immune senesced a particular person is, which makes it more complicated. And I forgot the second half of your question, Hank.

Dr. Bernstein: No, I knew it was going to be a little gray. How does one fold in frail patients, then, when thinking about ages and everything and underlying medical conditions. What’s the definition of a frail individual?

Dr. Talbot: Yeah. A frail individual is one that is lacking residual, so any minor insult can cause great illness and also loss of independence and loss of daily activities. The way to study frail older adults is to enroll them in randomized clinical controlled trials. Unfortunately, if you're a frail older adult, you may not be driving, you may not be leaving the house. You may not be doing extra visits out of the house. So participating in clinical trials can be very difficult. And there are a few places in the US that do it well. It's great if you can take a bus to them and do the study in their setting. So there's actually not a lot of good data in those frail older adults because they do not necessarily participate in studies. We see a lot of very healthy seniors who participate in Senior Olympics and read to the blind and do all kinds of fabulous things because they're out and about. So that's a huge area that needs investigation.

Dr. Bernstein: What percentage of residents in long-term care facilities are considered frail?

Dr. Talbot: I do not know the exact number, but very high.

Dr. Bernstein: Thank you.

Dr. Talbot: Thank you.

Dr. El Sahly: Thanks. Dr. Perlman.

Dr. Perlman: Yeah. So I just have a question about one of the pieces of data that you presented. So when you talked about reinfection at two months after the previous infection. So is there any information in those trials from any immune correlates or virus loads? Is it really just zero protection at two months? Or do you think that something else is going on? Could this be immunopathological? Could it be lower virus loads and more immune responses?

Dr. Talbot: Yeah. So obviously the study did not, I shouldn't say obviously. In the early 1990s, late 80s, there wasn't a lot of PCR used for viral detection. And so these studies actually

use viral culture in serologic responses to determine infection. So we're lacking a lot of that data. Why these particular people were susceptible at two months is unclear.

Dr. Perlman: And are those studies going to be repeated, or are they being repeated now that we're doing more human challenge studies?

Dr. Talbot: I don't know. And so there's kind of two questions to that. One is, can we repeat it in young adults with some of the newer techniques, cellular immunity as doc — and immune responses such as antibodies and PCR in addition to culture would be phenomenal. The second question is how do we obtain that data in the older adults, the ones that are most likely to be hospitalized from RSV.

Dr. Bernstein: Thank you.

Dr. El Sahly: Dr. Griffin.

Dr. Griffin: Hey, yeah, Marie Griffin. Hey Keipp. Nice talk. Yeah, it sounds like they're from your talk, there's no real correlative protection. Do we know anything else about how you would measure protection, or is there any other data on correlative protection?

Dr. Talbot: Yeah, not that I saw. And it's really hard because in the vaccine world we tend to use serum IgGs or correlate. And as you notice, it wasn't the best predictor of who would be infected compared to the nasal IgA. So I think that's going to be a work in progress.

Dr. El Sahly: Yeah. More, more importantly than I guess a virus that's capable of infecting young, healthy adult every two months if you expose them fully, is understanding the correlates of protection from severe disease, which doesn't seem to be just antibodies for sure.

Dr. Talbot: And I think one of the things, too, is if you can prevent the cold, or the RSV upper respiratory tract infection, you will likely also prevent the severe disease. But knowing where that cutoff is will be incredibly important.

Dr. El Sahly: Yeah. Okay. Well Thank you. Dr. Talbot. Great ideas for a lot of research projects for you. Next on the agenda is a 10-minute break. It's 10:17 now. So let's reconvene at 10:27.

Sponsor Presentation

Dr. El Sahly: Good morning, everyone. Welcome back to the first day of our RSV vaccine meeting, 179th meeting of the VRBPAC. Our next session is the sponsor presentation. Dr. Alejandra Gurtman, who is the Vice President of Vaccine Clinical Research and Development at Pfizer will go over the safety and efficacy of Bivalent RSV Pre-Fusion F vaccine in adults 60 years of age or older. Dr. Gurtman.

Safety and Efficacy of Bivalent RSV Pre-Fusion F Vaccine in Adults ≥60 Years of Age — Dr. Alejandra Gurtman

Dr. Gurtman: Thank you, Dr. El Sahly. Good morning, members of the committee, FDA, and ladies and gentlemen in the audience. It is a real pressure to be here today. I am Dr. Alejandra Gurtman. I'm an adult infectious disease specialist and Vice President in the Vaccine Research and Development Group at Pfizer. I would like to thank the FDA for organizing this VRBPAC and the VRBPAC chair and members for their time. It is my privilege today to present to you Pfizer's RSV Pre-Fusion F Candidate Clinical Development Plan in the context of our request for licensure of the vaccine.

We are seeking the following indication, prevention of acute respiratory disease and lower respiratory tract disease caused by respiratory syncytial virus in individuals 60 years of age and older by active immunization. The vaccine presentation is 120 micrograms without an adjuvant. Each dose contains 60 micrograms of each Pre-Fusion protein antigen in a 0.5 mL

injection. The presentation is a vial with an adaptor for injection in a Pre-Filled syringe. The vaccine is to be stored at 2 to 8 Centigrade and used within four hours after reconstitution.

My presentation today will follow this agenda. After I provide a brief introduction on the unmet medical need, I will review the RSV Pre-Fusion F vaccine Pre-Fusion F Candidate Development program for our vaccine, including clinical safety and clinical efficacy data. After this, I will review our pharmacovigilance plan and the benefit risk and will provide conclusions for my presentation.

RSV Infection is common, with nearly all children infected before the age of two. Repeat infections can occur through life. Although RSV typically causes cold-like symptoms, some persons are at higher risk for serious illness from RSV, including infants, children, and younger adults with certain conditions like chronic lung or heart disease. Older adults are also at high risk for serious illness to RSV, which is either caused by the virus itself, bacterial superinfection, or deterioration of already existing chronic medical conditions. In fact, in the US, the burden of the disease is substantial among adults 65 years and older, with RSV estimated to cause between 60,000 and 160,000 hospitalizations and between 6,000 and 30,000 deaths. Yet, despite the burden of disease treatment remains as supportive care, and there are not approved target preventions options to date.

After more than 50 years of RSV research and vaccine development efforts, groundbreaking structural work by the National Institute of Health elucidated that RSV F on the virus exists as an unstable Pre-Fusion form. As shown on the left of the cartoon, RSV F is anchored on the surface of the virus where it fuses the viral and host cell membrane during cell entry. This fusion process is a result of a dynamic and irreversible change of F from its metastable Pre-Fusion confirmation to a stable Pre-Fusion confirmation. Only the Pre-Fusion

form of the virus can bind to human airway cells, presiding in the virus entering the cells where it can replicate, causing illness. Antibodies specific to the Pre-Fusion form are most effective at blocking virus infection. The Pfizer stabilized Pre-Fusion vaccine candidate is substantially more immunogenic compared to F antigens not stabilized in the Pre-Fusion form. Shown here, from early studies in non-human primates, we can see a 54 higher neutralizing titers with a stabilized Pre-Fusion F vaccine candidate and a postfusion F candidate.

So what was our rationale for a bivalent RSV Pre-Fusion F vaccine? Historically, RSV vaccines targeting F have been monovalent with sequence base 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 levels of F-based cross neutralization between the A and B subgroups. However, the sequence variability between RSV-A and B F protein, highlighted in blue on the structure on the slide, localized to the Pre-Fusion-specific site 0. A bivalent RSV vaccine containing one Pre-Fusion F construct, each from the RSV A and B subgroups could elicit more balance immunity to the two subgroups, which we have shown in both preclinical and clinical studies, compared to other monovalent Pre-Fusion and vaccine candidates. The recent analysis of global RSV epidemiology supports the Ontario RSV-A and Buenos Aires RSV-B remain dominant genotypes and are the basis of Pfizer RSV Pre-Fusion bivalent vaccine. We also known 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 RSV Pre-F.

Our older adult clinical development program is comprehensive and includes adults 18 years of age and older in six different studies. We conducted two Phase 1/2 studies that included older adults with those regions, absent and presence of aluminum, and the second study included

CPG aluminum as an adjuvant. The early phase studies also included arms with and without influenza vaccine. We demonstrated that the addition of aluminum increased local reactions and did not have any immunological benefit, and the addition of CPG aluminum did not show any benefit either.

Displayed here are RSV neutralizing geometric mean titers and geometric mean fold rises for RSV subgroups A and B in participants 65 to 85 years of age. Neutralizing antibody titers and GMFRs are shown for the final RSV Pre-F selected dose of 120 micrograms without aluminum from our Phase ½ study at 1, 6, and 12 months after vaccination compared to pre-vaccination titers. GMFRs of 9.84 for A and 8.54 B were seen one month after vaccination. Neutralizing antibodies declined through the first 12 months but remained 3.8-fold higher at 12 months after vaccination compared to before vaccination, indicating good antibody persistence.

In the study where we evaluated CPG aluminum, all RSV Pre-F vaccine candidates elicited robust serum neutralizing responses when administered with influenza vaccine. As you can see on the left graph of the slide, there was no notable difference in neutralizing response between the formulations, including those containing CPG aluminum. No difference in T-cell response between those levels or with and without CPG aluminum was observed one month after vaccination. This study was important because our preclinical data with CPG was promising, but as I just showed you, in humans, the inclusion of CPG aluminum showed no substantial benefit in enhancing the immune response compared to RSV Pre-F formulations with aluminum at any dose level or compared to RSV Pre-F alone.

Based on these two studies, as I shared, we demonstrated that RSV Pre-F was highly immunogenic in a non-adjuvanted formulation, and adding aluminum or CPG confer no immunological benefit, and the formulation without aluminum had fewer local reactions. The

final dose selected was 120 micrograms containing 60 micrograms of A and 60 micrograms of B strains without an adjuvant. And before initiating the large Phase Three study, we decided to evaluate the safety and efficacy of the final dose and formulation selected in a human challenge study. An RSV Pre-F immunization was highly effective against symptomatic and asymptomatic RSV infection and shedding of the infectious virus in healthy adults.

Before we get into the resource listed here, let me just begin by delivering background information. There were 70 participants, 18 to 50 years of age, randomized one to one to receive RSV Pre-F or placebo. And approximately 20 days after injection, participants were inoculated intranasally with an RSV-A virus and observed for 12 days. Vaccine efficacy of 86.7 was observed for symptomatic RSV infection, confirmed by any detectable viral RNA for at least two consecutive days. Vaccine efficacy of 100% was observed for symptomatic RSV infection, confirmed by any quantifiable viral RNA on at least two consecutive days. And efficacy against RSV infection, regardless of the presence, absence, or severity of symptoms, was 75% for any quantifiable RT-PCR results on two consecutive days. In addition, RSV Pre-F elicited large increases in neutralizing titers and a substantial increase in the RSV F-specific CD4 T-cell TH1 response at one month after immunization. Again in the study, the vaccine was safe and well tolerated.

After we completed the human challenge study, we moved to three Phase 3 studies, including a clinical lot consistency study, a concomitant flu administration study with a high dose adjuvanted flu vaccine, and the Phase Three pivotal study, which will take most of the remaining of my presentation. In summary, and before starting our Phase Three pivotal study, we were able to show that RSV Pre-F induced high levels of neutralizing titers, and the addition of aluminum or CPG did not provide any immunological benefit. The vaccine was highly

efficacious in protecting against symptomatic respiratory disease in a human challenge study, and this resource allowed us to obtain FDA breakthrough designation. And a single dose, bivalent, and adjuvanted RSV Pre-F subunit vaccine at a good tolerability and safety profile.

So with this data, we initiated the Renoir study, which is our vaccine safety and efficacy study in older adults. This is a global Phase Three study designed to evaluate efficacy, safety, and immunogenicity of the Pfizer by bivalent Pre-Fusion F subunit vaccine for two seasons. The renewal study is being conducted at 240 sites in seven countries, including the US. The study was targeted to enroll up to 45,000 participants 60 years of age and older. Participants will randomize one to one to receive either RSV Pre-F or placebo. The placebo is an exact match without the protein and with the same excipients. Randomization was stratified by age. Participants were eligible if they were healthy or have stable chronic conditions, including stable cardiopulmonary disease, diabetes, asthma, or COPD. Those with an immunocompromised condition were excluded, and the study was designed to cover two RSV seasons.

As you know, in the US and in many countries, RSV has been a seasonal disease, and the study was conducted during the Covid pandemic when the RSV season became unpredictable. We started the enrollment in August of 2021 when RSV was circulating. In each of the countries where the study is being conducted, we have different methods to follow the RSV season from the beginning of the season to the end.

Regarding safety monitoring, a subset of participants completed a daily e-diary to monitor local reactions and systemic events for seven days after vaccination. When we look at all participants, unsolicited adverse events were captured through one month after vaccination in all participants, and serious adverse events and newly diagnosed chronic medical conditions are captured through the end of the study, which as I mentioned, covers two seasons. All participants

undergo active surveillance for acute respiratory illness by completing a weekly e-diary, which I will describe to you in a few minutes.

Finally, a subset of participants had blood draws at three pre-specified time points to assess immunogenicity. Now, I would like to turn your attention to the objectives of the study for safety. The objective was to describe the safety profile of the RSV Pre-F vaccine. The primary efficacy objective was to demonstrate the efficacy of RSV Pre-F in preventing RSV-associated lower respiratory tract illness with at least two or at least three signs and symptoms in the first RSV season following vaccination. There are several secondary efficacy objectives, including efficacy against first episode of RSV-associated acute respiratory illness during the first season, and efficacy against severe RSV-associated LRTI in the first season. Additional objectives include efficacy of the vaccine in the second season and across two seasons.

The focus of today's presentation is safety and efficacy against lower respiratory tract illness and acute respiratory illness in the first RSV season after vaccination. Before I go to how the cases have been captured, I will cover some important statistical considerations. As with many vaccine efficacy studies, Renoir was assigned as a fixed event trial. The analysis and presenting today was a per protocol, pre-planned interim analysis, and for the endpoints I'm presenting today, this is considered the final analysis. We have agreement with regulatory agencies on the licensure criteria, including vaccine efficacy with a lower bound of at least 20%, as well as agreement on the case definitions for RSV-associated lower respiratory, RSV-associated acute respiratory and RSV-associated severe illness. We have adjusted the type one error for this interim analysis.

Participants complete a weekly active surveillance diary from day 15 until the end of the season one. If a participant experienced an acute respiratory illness such as nasal discharge, nasal

congestion, sore throat, cough, sputum production, wheezing, or shortness of breath for more than one day, he or she is prompted to collect a mid-turbinate nasal swab, optimally on day two or day three after the onset of symptoms, but within seven days from the day of onset. The electronic diary communicates with investigational site to potentially initiate a respiratory illness visit, which could be performed as telephone, telehealth, clinic, or home visit. In-person visits are conducted if the investigator deemed it is necessary for the participant to be seen in person, and if this is the case, an additional nasal swab is collected. Finally, the swabs are shipped to the Pfizer Central Lab for PCR testing.

To understand how cases are captured in the study, I will describe the key study definitions, one as a participant completes an acute respiratory illness assessment for the symptoms I just mentioned to you. Lower respiratory tract illness is the finest and acute respiratory illness with at least two or at least three signs or symptoms of new or worsening cough, sputum production, wheezing, shortness of breath, or tachypnea. And severe LRTI is defined as a low respiratory tract illness present with at least one of the following objective criteria, hospitalization due to RSV, new or increased oxygen supplementation, and new or increased mechanical ventilation including CPAP. I will not be presenting to the analysis on severe illness as we did not accumulate enough severe cases at the time of this analysis.

A case definition of RSV-associated ARI or RSV-associated LRTI is made when a participant has at least two or at least three signs and symptoms or severe illness and a positive validated RSV PCR test. I will now present the interim analysis results of the study, starting with enrollment and demography. We enroll more than 35,000 subjects, and 34,284 were included in the safety database. The RSV Pre-F and placebo groups were balanced when looking at sex, race, ethnicity, and age. Please note that approximately 38% of participants are over the age of 70.

And the age range is 60 to 97 years old. Of note, one participant was 59 years old. In terms of pre-specified high-risk conditions, these data includes all participants, and approximately 50% of all participants had at least one pre-specified high risk condition. 15% in each group had at least one chronic cardiopulmonary condition, and about 19% in each group had diabetes.

I am now excited to share with you the safety results. Let's start with local reactions by maximum severity within seven days of vaccination, which were more frequently reported in the vaccine group than in the placebo group, at 12.2 versus 6.6% respectively. The most frequently reported local reaction was pain at the injection site, followed by redness and swelling. Both reactions were reported in a low percentage of participants. Most local reactions were mild, lasted one to two days, and resolve. Systemic events are shown on this slide by maximum severity within seven days after vaccination. As you can see on the left, the proportion of participants who reported the systemic event within seven days were similar in the vaccine and placebo at 27.5 and 25.7%, respectively. The most frequent reported systemic events were fatigue, headaches, and muscle pain, and were similar across the groups. Fever rates were very low at 1.4% in each group. There was only one grade four event of a fever of 40.1 centigrade on the day of vaccination in a participant who is in the placebo group. Most systemic events were mild or moderate and short duration. Not seeing much difference in safety when compared to placebo should potentially encourage uptake of the vaccine in the future.

And for unsolicited adverse events from vaccinations through the one-month follow-up visit, about 9% of participants in each group reported any adverse event. The frequency of related, immediate, severe, and life-threatening adverse events were similar in the vaccine and in the placebo groups. At the bottom part of the table, you can see that newly diagnosed chronic medical conditions were also similar in both groups. There were three SAEs deemed by the

investigator to be related to the vaccine, and I will present them to you in the next few slides. Adverse events leading to withdrawal from the study or leading to death were also similar in the vaccine and placebo groups. Adverse events leading to death were reported in 52 RSV Pre-F recipients and 49 placebo recipients. The primary cause of death most frequently reported were in the system organ class of cardiac disorders. None of the death were assessed as related.

As I just mentioned, three RSV Pre-F recipients reported serious adverse events assessed as related by the investigator. The first was an allergic reaction seven hours after vaccination, which resolved on day five. It was deemed to be a delayed allergic reaction and not anaphylaxis. I will describe the cases of Miller Fisher syndrome and Guillain-Barre syndrome on the next slide. A participant from Japan experienced initial symptoms of fatigue and ataxia on day nine after vaccination, followed by bilateral ophthalmoparesis. A lumbar puncture or electrophysiological studies were not performed. She was seen by a neurologist several weeks later when the neurological event was resolved, and a retrospective diagnosis of Miller Fisher syndrome was made. Please note that she had a sore throat infection treated with antibiotics that preceded the event. This case meets level four of the right on collaboration, which means that there is insufficient evidence to meet this diagnosis.

A participant in the US developed Guillain-Barre syndrome on day eight after vaccination and one day after presenting with a non-ST myocardial infarction requiring angioplasty. His CSF and electrophysiological studies were consistent with Guillain-Barre syndrome, and therefore this case does meet Brighton Collaboration level one, which means there is a high diagnostic certainty of this diagnosis. The Miller Fisher Syndrome and the Guillain-Barre syndrome cases both had potentially confounding factors and occur in an age group that has a higher incidence of the disease. All these cases were evaluated by our external

DMC, who did not identify any safety signal. Please note that after the data cutoff, two cases of Guillain-Barre syndrome were reported from the study. The first one received RSV Pre-F eight months before and was assessed by the investigator as not related. The second event occurred 14 months after vaccination, and this participant is in the placebo group. This case was also assessed by the investigator as not related. As I mentioned before, all serious adverse events from vaccination through the data cutoff for the interim analysis were reported equally in both groups with no significant differences. The most common system organ class for the reported serious adverse events was cardiac disorders followed by infections and infestations, neoplasms, or nervous system disorders.

In conclusion, the interim analysis for the Renoir Phase Three pivotal trial demonstrated that RSV Pre-F was safe and well tolerated. Local and systemic events were mostly mild to moderate and short-lived. There were no differences in systemic events between those who receive RSV Pre-F and those who received placebo. The adverse events profile did not suggest any safety concerns for the RSV Pre-F vaccination in adults 60 years of age and older. Considering that the vaccine was well tolerated and there are no differences in adverse events between RSV Pre-F vaccine and placebo groups, this data should potentially encourage uptake once the vaccine is approved and recommended.

I would like now to turn your attention to the efficacy results. At this time, at this pre-planned analysis, when looking at RSV-associated LRTI defined by at least two symptoms, there were 11 cases in the vaccine group and 33 in the placebo, with an observed efficacy of 66.7%, with a lower confidence interval of 28.8%. For those who had at least three symptoms, there were two cases in the vaccine group and 14 in the placebo group, resulting in vaccine efficacy of

85.7%, with a lower confidence interval of 32%, indicated an even higher efficacy against those who have worse symptoms. Both primary endpoints met licensure criteria.

This slide shows the cumulative case accrual curve from day of vaccination for RSV-associated LRTI with at least two or more symptoms. The blue line is the vaccine group, and the gray line represents the placebo group. Vaccine efficacy is shown after day 15 and persists for at least six months, sufficient to cover a typical RSV season. And similarly, this is the cumulative figure for RSV-associated LRTI with at least three or more symptoms. Vaccine efficacy also persists for at least six months.

To further characterize the clinical presentation, those who have at least two or more symptoms presented mainly with cough and sputum production, as you can see on the left side of the table, versus those who had at least three or more symptoms, who had a clinical presentation with more wheezing, soreness of breath and tachypnea, which is shown on the right. And in this group, of those who have at least three or more symptoms, where vaccine efficacy was higher, there were four participants who had a diagnosis of pneumonia or bronchopneumonia, resulting in two hospitalizations and four cases diagnosed as bronchitis, all requiring corticosteroid treatment. All pneumonia cases, including the two hospitalizations, were in the placebo group.

I will now share vaccine efficacy analysis in those with at least two or more symptoms at the top, or at least three or more symptoms at the bottom of the slide. You can see that efficacy was consistent across the different subgroups, including age, and those with pre-specified high-risk conditions. When looking at those with three symptoms at the bottom, you can also see consistency in vaccine efficacy. For subject 70 and 80 years of age and older, vaccine efficacy was high, although for each subgroup, the numbers are small, and the confidence intervals are wide. When looking at RSV-associated acute respiratory illness, those presenting with at least

one symptom lasting more than a day, RSV Pre-F was also efficacious with a case period of 22 cases in the vaccine group and 58 in the placebo group, for an observed vaccine efficacy of 62.1%, with a lower confidence interval of 37%, indicating that RSV Pre-F also protects against less severe illness, primarily upper respiratory disease.

On the right side, you see the cumulative curve for acute respiratory illness where the turquoise is the vaccine group and the grace the placebo group. Please note that at the time of this analysis, not all swabs were tested for acute respiratory illness, and therefore, some of the results can change in the future. Again, we can see vaccine efficacy after day 15 persisting for at least six months, sufficient to cover a typical RSV season. It is important to look at vaccine efficacy by subgroup A and B across those with at least two symptoms or more on the top, at least three symptoms or more in the middle, or at least one symptom or those with RSV-associated acute respiratory illness at the bottom. And vaccine efficacy was consistent for both groups A and B. As you can see again here, some of the numbers are low, and the confidence intervals are wide.

I would like now to share our analysis of those participants who sought medical care because of their illness and not because of the study, representing true healthcare utilization. Several types of visits could be reported by a participant, including any outpatient or inpatient visit, such as emergency room, urgent care, home healthcare services, primary care physician office visit, a pulmonologist or a specialist office visit, telehealth, or hospitalization. Taking those medically attended visits prompted by the participant and looking at vaccine efficacy based on the first episode of RSV-associated lower respiratory tract illness with at least two or more symptoms, at least three or more symptoms, or RSV-associated acute respiratory illness that

were medically attended. You can see the vaccine efficacy ranges from 65 to 80%, with confidence intervals above zero.

And why is this data important? The data is important because RSV Pre-F has the potential to prevent up to 100,000 emergency room visits, 34 to 136,000 hospitalizations, and 250,000 to 845,000 RSV-associated acute respiratory illness outpatient visits. This is based on the burden of disease and healthcare utilization in those 65 years of age and older, and assuming that RSV Pre-F was approved and recommended, and also provided that the uptake was high, since the vaccine is well tolerated.

In conclusion, RSV Pre-F was highly efficacious in reducing RSV-associated lower respiratory tract illness in adults 60 years and older, and also in reducing RSV-associated acute respiratory illness in this age group. The study is ongoing, and we anticipate having additional data in the future.

I will now turn your attention to the pharmacovigilance plan. Pharmacovigilance activities are a critical component of activities to detect unexpected safety events rapidly. Pfizer will conduct robust pharmacovigilance activities and collaborate with regulators and international groups. Our pharmacoepidemiologic studies will include older adults in order to evaluate the safety of the vaccine and possibly rare adverse events. In our plan, we're including a post-marketing study to further assess Gil Syndrome and immune-mediated demyelinating conditions, which has been requested by the FDA.

And finally, let's look to our encouraging assessment of benefit risk. More than 17,215 adult participants 60 years of age and older receive RSV Pre-F 120 micrograms in the pivotal Phase Three study. No important identified safety risks were detected. Local reactions and systemic events were generally mild to moderate in severity. Adverse events, including related

adverse events, newly diagnosed chronic medical conditions, and serious adverse events were similar between the RSV Pre-F and the placebo groups. None of the deaths were considered vaccine-related, and overall, RSV Pre-F was well tolerated in adults 60 years of age and older. And from a benefit perspective, RSV Pre-F was 66.7% efficacious in preventing RSV-associated lower respiratory tract illness with at least two symptoms or more, 85.7% efficacious in preventing RSV-associated lower respiratory tract illness with at least three symptoms or more in the first RSV season after vaccination. In addition, efficacy was 62.1% against first episode of RSV-associated acute respiratory illness in the first RSV season after vaccination.

In conclusion, the pivotal Phase Three study provides robust evidence that RSV Pre-F is well tolerated and a safe vaccine with a favorable safety profile. The vaccine is highly efficacious in reducing RSV-associated lower respiratory tract illness and efficacious in reducing RSV-associated acute respiratory illness. The benefit to risk ratio is highly favorable and supports the proposed indication, which is prevention of acute respiratory disease and lower respiratory tract disease caused by respiratory syncytial virus in individuals 60 years of age and older by active immunization.

We at Pfizer wish to thank our clinical trial participants, without whom we wouldn't be here today, all of our sites, investigators, and their dedicated staff. We're also grateful for the guidance provided by the FDA and other regulatory bodies. We want to thank our colleagues at Pfizer and other companies for their tireless work and dedication to develop our RSV Pre-F vaccine candidate. This concludes my presentation. Thank you for your attention. I am happy to answer any questions.

Q & A

Dr. El Sahly: Thank you, Dr. Gurtman, for going over the data. I would like to invite the committee members to raise hand in Zoom should they have questions, understanding that there will be also another opportunity to deliberate further. I will kick us off by kind of two related questions, one pertaining to co-administration with influenza.

The sponsor indicated in their briefing document that in the phase one study there was interference in their co-administration phase one study. There was interference in responses to influenza vaccines when the product was co-administered with inactivated flu vaccine. And the sponsor has since designed and implemented a study looking in at, at the co-administration question. And the study is fully recruited. And there was also an expansion in one of the earlier studies, where co-administration with influenza was an endpoint. Can you help us understand further the interference with influenza vaccine responses, and why weren't these data from the additional studies presented? And that would be sort of a safety question there.

Dr. Gurtman: So thank you for the question. You are correct. In our phase one/two studies, we did look at potential interference with flu vaccine, but the studies were not powered, actually a still inferiority studies. So it's just, it was a trend. And this is one of the reasons why we are now conducting a study in this age group with the high dose and adjuvanted flu vaccine, which as you mentioned, it has been fully enrolled. And the results are going to be available very soon. And we will be submitting this data to the FDA to hopefully be able to include co-administration in the label.

Dr. El Sahly: And the related question is that the study, the pivotal study, is a two-season study, and the second season is almost over now. Is there, again, a rationale for not presenting the study data in its totality so that sort of the deliberations and the decisions are more informed?

Dr. Gurtman: Yeah. So thank you for the question. I have additional data that I would like to share with you. This data actually just became available, and it was submitted to the IND, but it has not been yet reviewed by the FDA. So at the end of season one, and I'm going to come to season two in a second. If I can please have the slide with the new efficacy. Yeah. If we can bring slide number two.

I would like to orient you, because this is now the totality of the data for end of season one. And on the slide on the left, you can see end of season one. And I want to walk in, on the right is the interim analysis. So everything that is on the right is the information that I just presented to you. Now that we have completed end of season one and all the PCR testing, you can see that vaccine efficacy actually has been maintained. And in fact, when you look side to side, for example, for those who have three symptoms, you see that what I mentioned was vaccine efficacy of 85.7 with a lower confidence of 32. Now, vaccine efficacy, now that we have 20 cases, with a split of two in the vaccine and 18 in the placebo, vaccine efficacy is 88.9% with much tighter confidence intervals, right? And the lower confidence interval at 53.6. And I use that as an example because that's where the vaccine is very highly efficacious.

But even if you look at those with ARIs and compare side to side, you see that the confidence intervals actually are much tighter. And on the first line, what is the acute respiratory illness? Which excludes, right? So it excludes those who have two and three symptoms. It's only looking at those who have at least one symptom. Vaccine efficacy now is 60% with the lower confidence interval of 33%. So I'm happy to show this. I also have completed my of course if the committee would like to see. So that's the totality of data for season one.

With respect to your second question, because of what happened with the Covid pandemic and RSV circulation, we are about to complete season two, and that data will be

coming soon once we're able to do all the PCR testing. I hope I answered that question right, but our colleagues at CDC presented the data of how the season now is, the second season is ending, and —

Dr. El Sahly: I understand the, I mean, your study is appropriately multi-season study, and seeing the data at the completion of the study would have been, at least in my opinion, more informative. Regardless we will take questions from our committee colleagues. Dr. Berger.

Dr. Berger: Thank you, Dr. Gurtman. I just have a pretty simple question. I was struck by the persistence of neutralizing titers through 12 months that you showed compared to what we saw in the earlier data related to natural immune response. I realize that the numbers of infected individuals that you have in your study are pretty low, but I'm curious if you were able to see any rates of reinfection or if that was assessed at all in this study.

Dr. Gurtman: Yeah, so in this particular study, the one, if I can bring, please, slide number one, which is a slide that I presented earlier with this study is actually obtain immunogenicity after vaccination at different time points. But we have not collected in the study. This comes from the phase 1/2 actually cases. And so I am not able to answer that question with respect to this study. But in the new, in the study that I'm presenting today, we also have immunogenicity and immune responses, and we see a very robust immune response. And there is no reason to think that immune response will persist for at least 12 months, offering potentially protection for the season and even longer.

Dr. Berger: Thank you.

Dr. Gurtman: Did I answer your question?

Dr. Berger: Yeah, no, that does. Thank you.

Dr. El Sahly: Dr. Portnoy.

Dr. Portnoy: Great. Thank you so much for that presentation. One of the concerns that I have, and one of the reasons why previous RSV vaccines apparently have not been available until now, is the risk of enhanced disease. Patients who get immunized, and then when they get the disease, it's actually worse. In fact, there was an FDA advisory panel that discussed that very issue a number of years ago. Did you observe any cases of enhanced disease? And if not, did you take any specific actions to try to avoid that?

Dr. Gurtman: Yeah. Thank you, Dr. Portnoy, for the question. We recognize that the nature of enhanced disease is really focused on circumstances, where one is immunizing naive populations, right? We have seen that in a pediatric population. But in the study individuals who are in the sixties, seventies, and eighties had a lifetime of experience with RSV. So the chance of having enhanced disease is actually pretty remote. And in fact, what we see in the study is the opposite. It's that we are able to protect the population even in those who are 80 years of age and older.

So we have not seen any enhanced disease and were not expecting with this formulation and the Pre-F confirmation in this particular population who has been already very experienced with RSV, to see any enhanced disease.

Dr. Portnoy: Okay. Thank you. I'll look forward to hearing what you find with younger populations. Thank you.

Dr. El Sahly: Dr. Kim.

Dr. Kim: Oh, thank you. Thanks very much for that presentation. In your presentation, you mentioned a number of severe and life-threatening adverse events on post-vaccination active follow up. We're talking these reported events numbering in dozens, several dozen. And you also discussed three relevant cases that you identified as being of interest.

One case of Guillain-Barré syndrome, another case of Miller Fisher and another case of anaphylaxis. Of remaining severe and life threaten adverse events, were there other conditions that you and your colleagues felt needed additional discussions and proceeded to adjudicate the adverse event that was reported to the chairman, it's relevancy for reporting for today's presentation? And I have another question, but I'll go back to the end of the line for the second question.

Dr. Gurtman: Thank you. If I can please bring slide one to the screen. So when you look at any of the adverse events and you look at in blue, is the vaccine and in gray is the placebo. We have no differences in adverse events reported between the two groups. To the other part of your question, we did not see any immune mediated conditions that could have been related to the vaccine. And we have not seen any other events actually of concern except for the ones that I mentioned to you. And that's one of the reasons why we have an assessment that the vaccine is actually very well tolerated and safe. With respect to — let me maybe pause here and ask if I answer your question.

Dr. Kim: I'm asking for details for some of these most serious accuracy events that have been reported and the process that you went through to eliminate them from being associated with the vaccine. I mean, I understand that you adjudicate the matter, but were there others that gave you a pause? In terms of, because these are severe, and as you said, these are life-threatening conditions.

Dr. Gurtman: Yeah. So if I can please bring slide number two, where you have serious adverse events from vaccination. And now is through the data cut off, right? So initially presented the one month, this is now through the time that we completed the package to submit to the FDA. And as you can see, the most common SAEs were cardiac disorders, infections and infestations,

neoplasms, and nervous system disorders. And there are almost no differences between the two groups. And we have every event that is reported to us is properly assessed and is queried when there are questions that we may need to answer. And each of the SAEs have been properly assessed by my colleagues at Pfizer. And we have not seen any event that will make a pause, to use the words that you were asking, of any concern.

Dr. El Sahly: Dr. Bernstein.

Dr. Bernstein: Yes, thank you. I appreciate the informative presentation. And I also appreciate I had similar questions that Dr. El Sahly asked about co-administration with flu and/or Covid vaccine, and also presentation of efficacy over the two seasons, because it seemed the data that we reviewed was only the one. So I appreciate your responses. I was wondering whether, in fact, the GBS or inflammatory neuropathy might be a safety signal, and whether, in fact, it exceeded what would be the background or expected rate?

Dr. Gurtman: Yeah. So thank you for the question. I am going to ask one of my colleagues, Scott Kelly from our safety group, to come and answer the question in terms of observed versus expected.

Dr. Kelly: Hello, Scott Kelly, Global Medical Epidemiology. Thank you for your question. Pfizer, we did conduct a review of the literature for the background rate. To note, there is a lot of variability and heterogeneity for incidents of incidence rates of GBS, which they vary by age group, gender, preexisting conditions, region, and temporality, along with the case definition. In general, the background rates range from about 1.8 to 7.8 events per 100,000 person years. I'll stop there for the background rates, if there's any questions there. I'll move on to the observed versus expected results.

Okay, I'll proceed. So whether using any of the various background rates in the range I provided again, the ranges from the lower end using a case definition where it's neurologist confirmed. Studies in a systematic review by Shavar in 2011 that included, I think, roughly 16 studies were on the lower end of that range. Whereas additional newer data that included administrative claims data as well as electronic health records, which again, the case definition varies whether you're using a more specific incidence rate, where the criteria requires that the primary position in the record signifies GBS, as well as in inpatient setting. Those are more on the higher end of that range I suggested. No matter which incidence rate is used from the studies, the observed versus expected is above one. However, there's a lot of uncertainty in those estimates, which is exhibited by very wide conference intervals. While the trial was very large, proper assessment of any potential signal and refinement is best conducted in post-marketing studies with large databases with millions of patients or more to properly assess any potential signal for RSV in the vaccination. Thanks.

Dr. Bernstein: Thank you.

Dr. El Sahly: Dr. Griffin.

Dr. Griffin: Yes. Thank you. My question was also about the Guillain-Barre. I mean, it seems to me that no matter what the background rates are, you have to think in terms of the rate within a few weeks rather than within a year. So if it's one to seven per 100,000 person years, it's much lower for within three to four weeks. So it seems to me that one case is a red flag. Two cases is very concerning, and it's concerning to me that Pfizer doesn't think that there are any safety concerns.

Dr. Gurtman: Yeah. So thank you for the comment. I fully agree that when used, for example, Brighton Collaboration to assess potential relatedness of a vaccine is the 42 days. That has been

widely accepted. In these two particular cases, there were confounding factors. The Miller Fisher syndrome had an infectious presentation a few days prior to the presentation. And the Guillain-Barre Syndrome had a myocardial infarction the day before he started, with back pain. So, and they're both in an age group, right, where Guillain-Barre is already has a higher incidence. So we are going to be conducting a post-marketing study to assess actually Guillain-Barre and other potential delineating conditions. And that study is being currently discussed with the FDA.

Dr. El Sahly: Dr. Feikin. I hope I'm saying your name right.

Dr. Feikin: Yeah, it's pretty close. I have a two-part question. Related. The first is, I wasn't exactly clear how vaccination was related to the RSV season in this study. Was vaccination timed to occur close before onset of a typical RSV season? And what's the spread of time from vaccination to RSV season onset? And then the second part of the question is, I saw in the immunogenicity plots that you get the highest titers of neutralization about a month after vaccination, followed by some slow decline in neutralization. And I was wondering if, you showed a cumulative incidence curve out to a year, but it seemed like really no cases were occurring after six months. So within that first six months, were you able to stratify your efficacy based on time since vaccination?

Dr. Gurtman: Yeah. So thank you, Dr. Feikin, for the question. To answer the first question, as you know, Covid pandemic really disrupted the RSV season. And last year we had this inter-seasonal RSV that was on the summer. The season in the United States was, as I mentioned, the study was initiated in at the end of August of 2021 during the season. And we started in September of 2021 and the season went to July 2022 in the Northern Hemisphere. And in the Southern Hemisphere was from June to October. I do have a slide with the curves, but I think

that answers the question in terms of seasonality. We conducted the study when RSV was circulating in both the Northern and the Southern Hemisphere.

With respect to your second question, I would like to show you the new Kaplan Meyer curves, which I can bring, please. I do have the slide with the new Kaplan Meyer for the two 13 symptoms, if my colleagues can bring that up. So now that we have finished the season, as I mentioned before, and we have the data that was not available at the time that the briefing document was written. If I can please bring slide one to the screen. You have now a complete season, and you can see vaccine efficacy against LRTI with two symptoms on the left and three symptoms on the right. And on the bottom you have the RSV vaccine and the dotted line is the placebo and you can see persistence, well immune response, but actually protection, through a longer period of time. So the immunogenicity that I show you, which shows some decay to through 12 months, seems to still be protective through a longer period of time. Did I answer your question?

Dr. Feikin: I think so. So, the curves continue to separate through 270 days?

Dr. Gurtman: Yes, correct.

Dr. Feikin: Thank you.

Dr. El Sahly: Dr. Janes.

Dr. Janes: Thank you. My question is somewhat related to the prior question. You know, you mentioned that the immunogenicity data has been generated for this Phase Three study. What work has been done or is planned in terms of evaluating those immunological measures as correlates of protection? And here I'm thinking both of measures at or near the time of infection, as well as measures after vaccination. And I'm thinking also in particular of the both the humoral

and ideally the cellular immune responses that were discussed in prior talks as potential correlates of risk in terms of natural infection.

Dr. Gurtman: Thank you. Yeah. So thank you for the question. We know as it was presented today that natural history studies in older adults show clear relationship between the neutralizing antibodies and protection. But we don't have yet the correlate of protection. If I can please bring slide number one. So this is data, again, that just became available very recently and has been submitted to the IND, but has not yet been reviewed by the FDA.

But this state are the titles actually from the current Renoir study. Such as to orient you on the slide, we have immune responses. So we have GMTs and GMFRs. On the very left is by type, A and B. In the middle is by age, decade of age of 60 to 69, 7 to 79, and more than 60. And on the right, you have those with and without chronic cardiopulmonary conditions. And as you can see, the GMFRs for any of these groups actually is 12, 11.6, 12 and above. And it's pretty important to see that, in the decades, going from decade to decade of life, we still see very high levels of neutralizing titers. And so therefore, with knowing that not neutralizing antibodies are the ones that probably confer protection, and now seeing that the vaccine is almost 89% efficacious against those who have more severe disease, we have full confidence that when we see this implemented and instituted as recommended and the uptake is good that we will be able to see the same EF efficacy that we saw in post licensure effectiveness studies.

If you have a more specific question about cellular immunity, I'm not sure if I answered your question or you have more questions about cellular immunity.

Dr. Janes: Well, I guess a basic question. Has cellular immunity been characterized in this study? Dr. Gurtman: Thank you.

Dr. El Sahly: Dr. Jane's question was, did the investigators measure CMI during the study in the immunogenicity subset? Cell-mediated.

Dr. Gurtman: No. In the Phase Three, we did not do cellular immunity studies. We only have them in prior studies.

Dr. El Sahly: Okay. Thank you. Dr. Kim, you know, the sponsor CDC and FDA are going to give us an hour of their time after lunch break. Do you want to ask now or save for later, because I'm sure a lot of us have a lot of questions remaining. Just to stay on track.

Dr. Kim: Yeah. Let me maybe ask this question to the Pfizer sponsor. I was looking at your projected annual community benefit model with some interest. And it's a powerful and impactful slide. And it contained something of a sensitivity analysis for batching update to aging from 25% to 100%. And given that you also presented a slide that demonstrated high, but also declining, levels of neutralizing antibodies over time, does the model, or is there another model that also counts for the declining duration of protection, particularly over your two-year observation period, that might give us a more realistic sense of what the impact might be?

Dr. Gurtman: I'm not sure if I heard the last part of the question. I apologize. The audio wasn't good. So if you don't mind repeating that. I got the first part, but not the question itself.

Dr. Kim: Okay. So it’s simply a question of whether this model of the community benefit that you presented, whether it includes the declining duration of protection as a variable for analysis to demonstrate the projected annual community benefit, particularly over a two-year observation period.

Dr. Gurtman: Yeah. So now I understand the question. Thank you. I'm going to call my colleague Brad Gessner from the Medical and Scientific Affair Group to come and answer the question. Thank you.

Dr. Gessner: Hi, Brad Gessner from Medical and Scientific Affairs. Yeah, just to comment, there's a variety of models. Some of them are more simple, and some of them are more robust. So if you look at the NMBs, for example, the duration of protection is just taken as two years. So when you're calculating that, it's just dividing by two. And if you want an NNB that doesn't have that, then you can multiply that by two. Right? So the cost effectiveness model, though, takes a seven month. It's seven months. It goes from the efficacy that it has and takes a straight linear decay down to 24 months. So, hopefully, I answered your question. I'm not sure that there's a slide, but you can maybe go to slide one. That is the slide that goes through the data that you were referring to, that looks at the projected cases averted by the percent vaccinated. But the formal cost effectiveness model, which incorporates all of those data, and I'm sure you know that there's lots of different variables that go in there, and that there's a wide range that has been reported, as the colleague from CDC mentioned. So depending on those values, those will change as well. So it's not just the duration, but your specific question on whether we modeled declining efficacy, yes. And it was modeled over a two-year decline as a linear decay.

Dr. Kim: Thank you.

FDA Presentation

Dr. El Sahly: Thank you. I think these are all the questions to the sponsors for now. There will be opportunity to ask additional questions after the break. Next, we have Dr. Nadine Peart Akindele, Medical Officer at the Division of Vaccines and Related Products Application at CBER. Dr. Peart Akindele will be going over the FDA review of efficacy and safety of ABRYSVO RSV vaccine in adults 60 years of age and older. Dr. Peart.

FDA Review of Efficacy and Safety of ABRYSVO in Adults 60 Years of Age and Older — Dr. Nadine Akindele

Dr. Peart: Good morning. My name is Nadine Peart and I'm a Medical Officer from the Office of Vaccines Research and Review, Division of Vaccines and Related Product Applications. Today I'll be presenting the FDA review of the efficacy and safety data submitted to support the Biologics Licensing Application of ABRYSVO, the candidate RSV vaccine. Next slide please.

This is the outline for today's presentation. I'll start by providing an introduction, then we'll discuss the clinical studies submitted to the BLA, as well as the efficacy and safety data supporting the application. I'll finish by summarizing the pharmacovigilance plan, and finally summarize the data and present the questions for the advisory committee voting and discussion. Next slide. Starting with the introduction. Next slide.

ABRYSVO, or RSV Pre-F, is a candidate RSV recombinant stabilized Pre-Fusion sub-unit vaccine composed of equal parts of RSV Pre-F from subgroups A and RSV-B. It is administered intramuscularly as a single 0.5 mL dose containing 120 micrograms of antigen. The applicant's proposed indication for RSV Pre-F is prevention of acute respiratory disease and lower respiratory tract disease caused by RSV in individuals 60 years of age and older by active immunization. Next slide.

Now I will discuss the clinical studies submitted for FDA review. Next slide. The data from six clinical studies with RSV Pre-F were submitted to support the Biologics License Application. The primary data to support the safety and efficacy of RSV Pre-F in individuals 60 years of age and older is from an ongoing, multinational, Phase Three, randomized, double-blind,

and placebo-controlled trial studies C361013. Please note that I will be referring to the study as study 1013 throughout this presentation. In this study, 34,284 participants, 60 years of age and older, were randomized to receive a single dose of RSV Pre-F or placebo to evaluate the efficacy and safety of RSV Pre-F. The study is being conducted in 240 sites in the US, Canada, Finland, Japan, the Netherlands, South Africa, and Argentina.

Although the remaining studies will not be discussed in detail in today's presentation, I will briefly summarize the five other studies submitted. Study C361014 was a Phase Three lot to lot immunogenicity study conducted in the US intended to support manufacturing consistency. This study met the predefined study success criteria for demonstration of similar immune responses across three lots of RSV Pre-F. The safety database included 745 healthy adults, 18 through 49 years of age, who received one dose of RSV Pre-F. There were no serious adverse events, no deaths reported in the study, and no concerning safety events were observed after FDA review. The remaining Phase One and Phase Two studies submitted were conducted in the US, UK, and Australia. The majority of these studies either did not include the target study population and/or did not use the final study product. These studies evaluated the safety and immunogenicity of RSV Pre-F in adults ranging from 18 to 85 years. From a safety database of an additional 1,982 participants enrolled in the four remaining studies, no safety concerns were identified after FDA review. Next slide.

As mentioned, study 1013 was designed as a Phase Three efficacy and safety study. Participants were enrolled and randomized one one-to-one to receive either RSV Pre-F or placebo administered intramuscularly. Of note, placebo used in this trial consisted of excipients matched to those used in the RSV Pre-F vaccine formulation, minus the active ingredients. The physical appearance of the RSV Pre-F vaccine and placebo were similar. The study was designed

to assess primary efficacy endpoints during the first RSV season and is planned to be conducted over two RSV seasons. Randomization was stratified by age, and the target enrollment was at least 6,000 participants that were 6 through 69 years of age, at least 6,000 participants that were 70 through 79 years of age, and at least 800 participants that were 80 years of age and older. Participants enrolled included both healthy adults and those with stable chronic diseases.

Starting 14 days post-vaccination, participants were actively monitored for acute respiratory illness, or ARI, and lower respiratory tract illness, or LRTI, symptoms. Regarding safety monitoring, a subset of participants in the US and Japan were included in the reactogenicity subset and monitored for solicited local and systemic reactions through seven days post-vaccination, whereas all participants were monitored through one-month post-vaccination for unsolicited adverse events and through the entire study duration for newly diagnosed chronic medical conditions and serious adverse events. The study used a data monitoring committee, or DMC, to review unblinded cumulative safety data throughout the study and the interim analysis for efficacy. The DMC was independent of the study team and included only external members. Next slide.

This slide shows the overall planned timeline for the study with highlights of key study dates. The study was initiated on August 31st, 2021. After informed consent, a subset of participants underwent a pre-vaccination blood draw, and all participants received the study of intervention as randomized on study day one. After vaccination, study monitoring was initiated with monitoring of local and systemic solicited reactions for seven days post-vaccination in a subset of participants, as described, and for unsolicited adverse events, or AEs, for one month in all participants. As mentioned, serious adverse events, or SAEs, and newly diagnosed chronic medical conditions, or NDCMCs, will be monitored throughout the study end.

Active surveillance of ARI and LRTI symptoms was initiated in all participants starting 14 days after vaccination. Additional blood sampling occurred in all participants at one month post-vaccination, and again in the immunogenicity subset at the start of season two. The red star on the timeline indicates the data cutoff for the analyses included in the BLA submission of July 14th, 2022. At the time of the data cutoff, 66.3% of study participants had completed season one surveillance. This included all participants enrolled from the United States, Canada, Finland, and South Africa. As of the data cutoff, the median duration for follow up for efficacy and safety was approximately seven months. Please note that the analyses of immunogenicity endpoints had not yet been conducted at the time of submission and were not yet reviewed. Immunogenicity analyses that were included in the end of season one analysis will be reviewed by the FDA at a later date. Next slide.

As shown in the previous slide, starting 14 days after vaccination, all participants were actively monitored for onset of acute respiratory illness or ARI symptoms. Participants met criteria for ARI if they experienced at least one of the following, new and increased sore throat, nasal congestion, nasal discharge, wheezing, sputum protection, cough, and shortness of breath. And participants who met criteria for ARI were instructed to self-collect midterm nasal swabs, optimally on day one to two after onset of symptoms. An illness visit was to be conducted within seven days of onset of symptoms. The swabs were collected by the study site and sent to the laboratory for RT-PCR testing for RSV. Lower respiratory tract illness associated with RSV, or LRTI-RSV, was defined as ARI with at least two or at least three LRTI signs or symptoms lasting more than one day during the same illness with confirmed RSV infection by RT-PCR. Signs or symptoms for LRTI included new and increased wheezing, sputum production, cough,

shortness of breath, and tachypnea. Note that the first four symptoms are also included in the criteria for ARI, as previously mentioned. Next slide.

The primary efficacy objective evaluated the efficacy of RSV Pre-F to prevent RSV-associated LRTI in the first RSV season. Vaccine efficacy against LRTI with at least two or at least three symptoms were the first and second primary endpoints, respectively, and evaluated sequentially. The primary efficacy objective for the study was considered met if the statistical success criterion was met for the first primary efficacy endpoint of vaccine efficacy against LRTI with at least two symptoms. Success criterion for the study was at the lower bound of the confidence interval for the vaccine efficacy against LRTI with at least two symptoms is greater than 20% at either the interim or primary analysis.

The study was designed as an event-driven study with a primary analysis plan to be conducted after accrual of 59 evaluable first episode LRTI cases with at least two symptoms. An interim analysis for this endpoint could be conducted after accrual of at least 29 first episode LRTI cases with at least two symptoms. If there were 15 or more first episode LRTI cases with at least three symptoms, the second primary endpoint would also be evaluated as part of the interim analyses.

The study specified that if success was achieved for the primary objective at the time of the interim analysis, the interim analysis will be considered the primary analysis for the study, and the planned primary analysis would not be conducted. For this stud, an interim analysis was conducted after 44 first episode LRTI cases with at least two symptoms had accrued in the first RSV season, using the cutoff date of July 8th, 2022. There were 16 first episode LRTI cases with at least three symptoms using the same cutoff date. Therefore, the interim analysis of the second primary endpoint was also conducted. Next slide.

A key secondary endpoint was to evaluate the vaccine efficacy against severe LRTI RSV, or SLRTI-RSV, starting 14 days after vaccination. SLRTI was defined as meeting LRTI criteria plus at least one of the following listed criteria, including hospitalization due to LRTI, new or increased oxygen supplementation, and new or increased mechanical ventilation, including CPAP. If there were at least 12 evaluable first episode SLRTI cases in the first RSV season, then this secondary endpoint would also be evaluated at the interim analysis. The minimum number of first episode SLRTI cases had not accrued as of the data cutoff, and therefore the secondary endpoint was not included in the interim analysis. Another secondary endpoint was to evaluate vaccine efficacy against ARI RSV starting 14 days after vaccination. A preliminary descriptive analysis of these endpoints was included in the interim analysis. Next slide.

At the time of the data cutoff and submission to the FDA, additional plan secondary objectives were to evaluate vaccine efficacy in preventing LRTI, SLRTI, and ARI at each RSV season and across two RSV seasons following the vaccination, to evaluate immunogenicity as measured by neutralizing and binding antibody responses from one month post-vaccination through the end of season two, and to evaluate the rates and descriptions of LRTI associated healthcare resource utilization. These analyses were reported to be conducted with the end of season one analysis and/or at the end of study analysis and will not be discussed in today's presentation. Of note, all participants in study 1013 currently remain in blinded follow up. Next slide.

The populations that were identified in the study included the safety population, which was the population used for analyses of safety, and included all enrolled participants who received the study intervention, the modified intent to treat, or efficacy population, which included all participants who were randomized and received study intervention, the valuable

efficacy population, which was the population used for analyses of efficacy and included all study participants who met criteria of being eligible for the study, having received study intervention to which they were randomized, having completed follow-up through 14 days post-vaccination, and having had no major protocol violations before the symptom onset date of the confirmed ARI or LRTI case, and the e-diary subset safety population, which was the population used for analyses of solicited safety. It included all participants from the reactogenicity subset who received the study intervention and had at least one day of e-diary data transferred. Next slide.

Now I will discuss the efficacy data submitted. Next slide. Of the 35,971 enrolled participants, 34,383 were randomized to receive RSV Pre-F or placebo. The MITT efficacy population included a total of 33,987 participants. The evaluable efficacy population used for the primary analysis of efficacy included a total of 32,614 participants with 16,306 RSV Pre-F recipients and 16,308 placebo recipients. The percentages of participants excluded and reasons for exclusion from the valuable efficacy population were similar between the two treatment groups. The most common reason for exclusion, occurring at a rate of 4% in both groups, was efficacy surveillance duration of less than 15 days, mostly due to participants receiving the vaccine after or less than 14 days before the efficacy cutoff date. Next slide.

This slide and the next few slides that follow will summarize the demographics of the participants in the evaluable efficacy population. Overall, the demographic characteristics were similar between the vaccine and placebo groups. As you can see, the study population was equally distributed between male and female participants. The majority of participants were 60 through 69 years of age. Approximately 32% were 70 through 79 years of age, and

approximately 6% were 80 years of age or older. Overall, the majority of participants were located in the US. Next slide.

With regard to race and ethnicity across both groups, the majority of participants were white and non-Hispanic or Latino. Next slide.

The majority of participants in the valuable efficacy population had one or more pre-specified at-risk condition, the most common of which was diabetes. Approximately 15% of participants had one or more chronic cardiopulmonary condition, the most common of which was asthma. Overall, the proportions and types of at-risk conditions were balanced between the RSV Pre-F and placebo groups. Next slide.

Shown here are the analyses of the primary efficacy endpoints of vaccine efficacy against LRTI with at least two or three symptoms. As of the cutoff date, there were 44 cases of first episode LRTI with at least two symptoms with onset starting 14 days after vaccination. The case split was 11 cases in the RSV Pre-F group compared to 33 cases in the placebo group, with a vaccine efficacy of 66.7% and the lower bound of the 96.66 confidence interval of 28.8%. This met the pre-specified study success criterion. There were 16 cases of first episode LRTI with at least three symptoms, with onset starting 14 days after vaccination. The case split was two cases in the RSV Pre-F group compared to 14 cases in the placebo group, with the vaccine efficacy of 85.7% and a lower bound of the 96.66 confidence interval of 32%. Again, meeting the pre-specified study success criterion. As mentioned earlier, as of the data cutoff, the median follow-up for efficacy was approximately seven months. Among participants in the evaluable efficacy population, 66.3% had completed season one surveillance, including all participants in the US. Next slide.

Here, the cumulative case accrual curve for LRTI with at least two symptoms starting the day of vaccination and the MITT efficacy population is shown. You'll note that starting approximately 25 to 30 days after vaccination, the curves diverge, with more cases occurring in the placebo group than the RSV group. Subsequently, cases accrue at a faster rate in the placebo group compared to the RSV Pre-F group through approximately seven months following vaccination, which was around the median duration for follow up of participants in the study at the time of the data cutoff. The cumulative case accrual curve for LRTI with at least three symptoms generally followed a similar pattern, as is displayed here, but was on based on a smaller number of cases. Next slide.

Although the study was not powered to assess vaccine efficacy by demographic subgroups, subgroup analyses were performed. Shown here are the subgroup analyses by age for the primary endpoint of vaccine efficacy against LRTI with at least two symptoms. Although the vaccine efficacy point estimates appear to trend higher with increasing age, the small numbers of enrolled participants in RSV cases in the older age subgroups, especially among participants 80 years of age and older, lets wide confidence intervals, which limits the interpretation of these results. Next slide.

Point estimates also appear to be preserved among participants with at least one at-risk condition for severe RSV. However, again, interpretation is limited by small sample size and a low number of cases for these subgroups. Subgroup analyses for the endpoint of LRTI with at least three symptoms generally followed similar trends as for those with two symptoms, though, the fewer number of cases, again, yielded wider confidence intervals resulting in less reliable vaccine efficacy estimates. Next slide.

Vaccine efficacy against RSV subgroups A and B were also individually calculated for each of the primary endpoints. The majority of LRTI cases accrued in the study were due to RSV subgroup B. Interpretation of the vaccine efficacy by RSV subgroup is, again, limited by the low number of cases, resulting in wide competence intervals. Next slide.

At the FDA's request, a post hoc analysis of medically attended LRTI associated with RSV was performed. A medically attended RSV case was defined as an episode of LRTI with any outpatient or inpatient visit. This included hospitalization, ER visit, urgent care visit, home healthcare services, primary care physician office visit, pulmonologist office visit, or any specialist office visit or telehealth contact. It did not include illness visits conducted at the study site. The analyses demonstrate that the vaccine efficacy point estimates were similar to those obtained in the primary efficacy analyses for the two LRTI endpoints. Next slide, please.

Because the pre-specified number of first episodes severe LRTI, or SLRTI, cases had not accrued as of the data cutoff date, a formal evaluation of the secondary endpoint was not conducted at the interim analysis. As of the data cutoff, there were two cases of SLRTI reported both among placebo recipients. Both participants were hospitalized, and one required supplemental oxygen. Next slide.

Vaccine efficacy against ARI was a secondary endpoint for the study. As of the data cutoff date, there were 8 first episode ARI cases reported starting 14 days after vaccination, with 22 cases in the RSV Pre-F group compared to 58 in the placebo group. In a descriptive analysis, the vaccine efficacy for this endpoint was 62.1%, with a lower bound of the 95% confidence interval of 37.1%. However, the FDA considered this vaccine efficacy estimate described to be preliminary. At the central lab, swabs from cases which met criteria for LRTI with at least two symptoms were prioritized for RT-PCR testing, which led to approximately one fourth of the

swabs meeting criteria for ARI not completing testing by the time of the data cutoff. Because the actual case count at the time of submission might have been higher than the number reported and the analysis displayed, at this time we consider these results incomplete. Next slide please.

Next, I'll summarize the safety data submitted. The next two slides summarize the demographics of the safety population. The demographics of the safety population, and the e-diary subset safety population were very similar to that of the valuable efficacy population, as shown earlier in the presentation. The median age of participants was 67 years with 16.3% of participants 75 years of age or older. Next slide.

Again, the race and ethnicity of participants in the safety population were very similar to that of the valuable efficacy population, with the majority of the participants identifying as white and non-Hispanic or Latino. Next slide.

In this ongoing Phase Three study, a total of 34,284, or 99.7%, of the randomized participants received study intervention and were included in the safety population. This resulted in 17,215 participants in the RSV Pre-F group and 17,069 participants in the placebo group. Of these participants, 77% had completed at least six months of follow-up post-vaccination at the time of the data cutoff. The e-diary subset safety population used for the analyses of solicited safety included 3,630 and 3,539 participants in the RSV Pre-F group and placebo groups, respectively. 5.3% of participants withdrew from the study after receipt of the study intervention. The reasons for withdrawal and proportions of participants withdrawn were similar between the RSV Pre-F and placebo groups. Common reasons for withdrawal from the study after vaccination were withdrawal by the participant, occurring at a rate of 2.6%, and lost at follow up, occurring at a rate of 1.9%. Death during the study led to withdrawal of 0.3% of participants in

each group. Study withdrawal due to non-fatal adverse events were rare and occurred in less than 0.1% of participants in each group. Next slide.

This is an overview of the proportion of participants in each group who reported adverse events during the study. Unsolicited adverse events within 30 minutes of vaccination were reported infrequently and at similar frequencies between the RSV Pre-F and placebo group at a rate of 0.2% in each group. These events consisted primarily of injection site reactions, and none of the events that occurred were clinically concerning for anaphylaxis. Rates of unsolicited diverse events within one month of vaccination were similar between the two groups. The types and proportions of newly diagnosed chronic medical conditions reported throughout the entire study period were balanced across the groups. Serious adverse events were reported by 2.3% of participants in both the RSV Pre-F and placebo groups, with three SAEs, all in the RSV Pre-F group, considered to be related to the study intervention. These three SAEs will be discussed later in the presentation. As mentioned, at the time of the data cutoff, deaths occurred at equal rates in both groups, with 52 deaths occurring among RSV Pre-F recipients, and 49 deaths occurring among placebo recipients. Next slide please.

Data on solicited local and systemic adverse reactions within seven days following vaccination were collected from a subset of 7,196 study participants. You'll note that the ends provided are arranged, as only participants who completed the e-diary entry for the specified solicited reaction were included in the respective analyses. Within two days post-vaccination, the proportion of participants reporting grade one or higher local reactions was higher in the RSV Pre-F group compared to the placebo group. The most frequently reported local reaction in both groups was pain at the injection site, reported by 10.6% of participants in the RSV Pre-F group and 6.6% of participants in the placebo group. Severe or grade three solicited local reactions

were rare, reported by 0.2% and less than 0.1% of participants in the RSV Pre-f and placebo groups, respectively. Among those who received RSV Pre-F, the median day of onset of local reactions after vaccination was two to three days post-vaccination, and the median duration was one to one and a half days. Next slide.

This table includes the percentages of RSV Pre-F and placebo recipients who recorded any solicited systemic adverse reactions within seven days post-vaccination by maximum severity. The rates of solicited systemic adverse reactions were similar between the vaccine and placebo groups, and grade three systemic reactions were reported infrequently, in 0.7% of RSV Pre-F recipients and 0.6% of placebo recipients. Fatigue was the most frequently reported systemic adverse reaction, followed by headache and muscle pain. Next slide.

Fever was reported in 1.4% of participants in each group. Fever with a maximum temperature of 38.9 degrees to 40 degrees Celsius was reported by one and two participants in the RSV Pre-F and placebo groups, respectively. Fever greater than 40 degrees Celsius within seven days post-vaccination was only reported by one placebo participant, and it was measured at 40.1 degrees Celsius, occurring on the day of vaccination only. Among those who received RSV Pre-F, the median day of onset of solicited systemic adverse reactions was between two to three days post-vaccination, and the median duration was one to two days. Overall, subgroup analyses of solicited adverse reactions by age and sex were similar to the overall population. However, solicited reactions were reported more frequently in the younger age subgroup of 60 to 69 years of age as compared to the older age subgroups. Next slide.

Unsolicited adverse events were monitored in the entire safety population through one month following vaccination. During this monitoring period, the overall rates of unsolicited adverse events were similar between vaccine and placebo recipients. The most common

unsolicited adverse events by MedDRA system organ class, occurring at a rate of over 1%, were infections and infestations, respiratory, thoracic, and mediastinal disorders, and general disorders at administration site admissions. The rates of unsolicited adverse events within each of these SOCs were similar between the vaccine and placebo groups. Subgroup analyses of unsolicited adverse events by age, sex, race, ethnicity, country, or predefined at-risk condition identified no specific safety concerns.

Although there was no imbalance in the overall rates of unsolicited adverse events, there was a numerical imbalance noted in the events of atrial fibrillation within one month post-vaccination, with 10 events in the RSV Pre-F group and 4 events in the placebo group. Four of the events in the RSV Pre-F group and three of the events in the placebo group were reported as serious adverse events. None of these events were fatal. Among the 14 participants who experienced events of atrial fibrillation, a medical history of atrial fibrillation was reported by 6 RSV Pre-F recipients and 2 placebo recipients, and the event onset ranged from 18 to 30 days post-vaccination. Among all study participants, a baseline medical history of atrial fibrillation was documented at a rate of 0.3% in each group, with 60 in the RSV Pre-F group and 43 in the placebo group. When assessed through the data cutoff, events of atrial fibrillation were reported by 25 RSV Pre-F recipients and 22 placebo recipients, and the imbalance was no longer observed. None of the events of atrial fibrillation were considered related to the study intervention by the investigators. However, the FDA review of these cases is ongoing. Next slide, please.

As of the data cutoff, serious adverse events were balanced between study groups occurring at a rate of 2.3% in each group. Three SAEs, all of which were in the RSV Pre-F group, were considered to be possibly related to study vaccination by the FDA, in agreement

with the investigator's assessment. The first case was that of a 61-year-old female who had experienced hypersensitivity of moderate severity beginning eight hours after receipt of RSV Pre-F. The participant developed shortness of breath and chest pain, had loss of consciousness, and required hospitalization. She received a diagnosis of an allergic drug reaction, and her symptoms resolved five days after onset.

The second case was that of a 66-year-old male with a past medical history of hypertension who developed Guillain-Barre syndrome, or GBS, created as life-threatening in severity, with an onset seven days after receipt of RSV Pre-F. Prior to the onset of his symptoms, on day seven, the participant had experienced a non-SD elevation myocardial infarction not considered related to study vaccination. He was hospitalized from days seven to eight and underwent cardiac catheterization and angioplasty. On day eight, he developed lower back pain, and on day 14 he developed bilateral lower extremity weakness and had a fall, leading to his hospitalization. Physical exam and laboratory findings were consistent with the diagnosis of GBS. He was treated with intravenous immunoglobulin, and five sessions of plasma freezes. His symptoms improved, and the event of GBS was resolving at the time of the last available report, approximately six months after symptom onset.

The third case was that of a 66-year-old female with a past medical history of type two diabetes myelitis, who developed Miller Fisher Syndrome, a variant of GBS, and was graded at severe, with onset eight days after a seat of RSV Pre-F. The participant reported fatigue on day 9, sore throat on day 10, and ataxia on day 11. On day 19, she was hospitalized for severe fatigue and unstable movements, and later, diplopia, ataxia, and paresthesia of the bilateral palms and soles. Ophthalmoplegia was seen on exam. Her symptoms started to resolve on day 40 without treatment. On day 41, she was retrospectively diagnosed with Miller Fisher Syndrome based on

her clinical course. The participant's symptoms resolved completely approximately three months after symptom onset.

Through the data cutoff deaths occurred at a rate of 0.3% in both the RSV P F and placebo groups. In general, the causes of death among participants were representative of the most common causes of death among the elderly adult population. None of these deaths were considered related to study intervention. Next slide. Next, I will summarize the plans for pharmacovigilance. Next slide.

The applicant's pharmacovigilance plan includes passive and active surveillance activities for continued vaccine safety monitoring, including routine pharmacovigilance. The applicant has identified use in immunocompromised older adults as missing information and has proposed to conduct a post-marketing safety study in this population. Based on review of the submission to date, the FDA has requested that the applicant identify GBS and other immune mediated demyelinating conditions, as well as cardiac disorders, as important potential risks. The applicant has agreed to perform expedited reporting for all cases of GBS and other immune mediated demyelinating conditions and all cardiac disorders, aggregate analysis of GBS and other immune mediated demyelinating conditions and cardiac disorders in periodic safety reports, and to plan a post-marketing safety study to assess the risk of GBS and other immune mediated demyelinating conditions among individuals vaccinated with ABRYSVO. Next slide.

Finally, I'll close by summarizing the data from the submission and presenting the FDA questions to the advisory committee. In summary, based on a median follow up for efficacy of seven months, and with 66.3% of participants having completed season one surveillance, including all participants in the United States, vaccine efficacy to prevent first episode LRTI with at least two and at least three symptoms were 66.7% and 85.7%, respectively, with both

endpoints achieving lower bounds of the 96.66% confidence interval that met study success criterion. Additionally, descriptive vaccine efficacy estimates appear preserved among participants 80 years of age and older and among participants with at least one at risk condition, although these data were limited by small subpopulation sizes. As you'll soon see, we'll be asking for your vote today on vaccine effectiveness in the context of the primary endpoints against LRTI due to RSV.

Evaluation of the secondary endpoint of vaccine efficacy against ARI resulted in a vaccine efficacy es estimate of 62.1% with a lower bound of the 95% confidence interval of 37.1%. However, these data at the time of submission were considered preliminary by the FDA due to the need to complete the testing of the remaining nasals swabs meeting ARI criteria. Please be aware that although we are not asking you to vote on the secondary endpoint submitted, we would like to hear your opinion regarding the data presented on vaccine efficacy against ARI. Data are currently not available on the duration of vaccine effectiveness, the vaccine efficacy, and immunocompromised and frail elderly adults, and vaccine efficacy in preventing severe LRTI, as there were only two cases of SLRTI as of the data cutoff, both among placebo recipients. Data regarding concomitant administration with vaccines routinely recommended for use in this population are also not available. Next slide.

To summarize the safety data, the study included 34,284 participants, including 17,215 who received RSV Pre-F. Of these vaccinated participants, 77% have had at least six months of follow u. Solicited local and systemic reactions were generally mild to moderate and a short duration. The most frequently reported solicited reactions among RSV Pre-F recipients, at a rate of over 10%, were fatigue, headache, injection site pain, and muscle pain. Within one month after vaccination, a numerical imbalance was observed for events of atrial fibrillation. FDA

review of these events is ongoing. Serious adverse events were balanced between the RSV Pre-F and placebo groups. Three SAEs, including one case of GBS and one case of GBS variant, were assessed by the FDA as possibly related to the RSV Pre-F vaccine, in agreement with the investigator's assessment. Finally, review of the safety data from five supportive clinical studies did not reveal any other safety signals, including additional cases of GBS or other immune mediated demyelinating conditions post-vaccination. Next slide.

Today we will be asking you to vote on the following questions. Question number one, are the available data adequate to support the safety of ABRYSVO when administered to individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV? Please vote yes or no. Question number two, are the available data adequate to support the effectiveness of ABRYSVO for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older? Again, voting yes or no. Thank you for everyone for listening to me today, and thank you so much to my colleagues at the FDA who have helped to create this presentation and conduct the review of this vaccine.

Q & A

Dr. El Sahly: Thank you, Dr. Peart. I want to invite my colleagues to use the raise your hand function and so we can begin with questions. I see the first question by Dr. Portnoy. Dr. Portnoy.

Dr. Portnoy: Hello. Thank you so much for that presentation. It was very informative and very clear, and I appreciate it. I'm used to looking at vaccine data from drug vaccines that are being applied for emergency use authorization, like with the Covid. And so numbers like you're showing me are very familiar. But when the vaccine is being submitted for full approval and not just for emergency use authorization, usually the numbers are higher than what I've seen. And

this is still preliminary data. The studies are still ongoing. And I'm just wondering, does the FDA have any sense of whether these numbers are high enough to be considered useful for full approval, or is it this more emergency use authorization types of numbers? Do you have any sense?

Dr. Peart: Thank you for your question. Yes. The numbers that were submitted in the data that was provided by the applicant are acceptable for consideration for a BLA submission.

Dr. Portnoy: Thank you.

Dr. El Sahly: The second question is from Dr. Perlman.

Dr. Perlman: Yes. A great presentation. So I had a question to follow up with Dr. Portnoy. There's not data on what I would consider some of the most important things in the RSV world, death immunocompromised people, how, and we don't know how well the vaccine's going to work there. So if we give a BLA now, what's going to be the future if as data come in about those populations? Does the BLA get revoked if there's no protection, or how does the FDA deal with that?

Dr. Peart: That's an excellent question. Once the BLA, if the vaccine is approved, post-marketing surveillance will be conducted by the FDA as well as our colleagues from Pfizer. If there are new safety signals or new safety events, additional communications will be provided. But I will pass the microphone over to some of my colleagues at the FDA. Dr. Kaslow, who might be able to provide additional information on what might happen, should additional concerns be raised. Thank you.

Dr. Kaslow: Yeah. So as additional information is made available, it'll be submitted to the BLA and reevaluated. And if changes in the label are required, those will be undertaken. So data driven analysis through the part post-marketing studies.

Dr. El Sahly: The third question is from Dr. Bernstein.

Dr. Bernstein: Wonderful presentation. Thank you. So I also had the question about the efficacy against severe lower respiratory tract disease, which you just answered. My other question is that the epidemiology suggests that the older the subjects are, the worse or more likely to have RSV disease. And I wondered why the lower age group was down to 60, which then, but not enough in the 80 plus age group. It only accounted for I think 5% of the total population, where a third were in the younger age group. And it seemed that it would be better to have a larger sample size in the 80 plus age group.

Dr. Peart: Thank you for your question. Yes, this was a very large study, so although the proportion of participants 80 years of age and older does seem small, comparatively, the absolute number is reasonable. About 5,500 participants, 2,700 about of which were vaccine recipients, were 75 years of age and older. And the numbers of participants in this age population are comparable with those that we've seen in studies for other vaccines that have been used in older adults. Of course, if the vaccine is licensed, more data will then be more available on the age group, and we would be able to access that through real world evidence. Thank you.

Dr. El Sahly: The fourth question is from me. The issue of acute demyelinating disorders. There were two that were identified in the six weeks post-vaccination. However, there were a lot more SAEs in that umbrella not otherwise defined. Did the sponsor or the FDA look at this small subset and determine whether any of those could be remotely in the category of acute demyelinating disorders? Because, I mean, we're talking about a full order of magnitude in incidence here. It's more than a…

Dr. Peart: Yes. So absolutely, we definitely hear that concern, and we have been addressing that concern internally by conducting serial analyses of the participants who might have met

criteria for immune demyelinating conditions. We've reviewed all of these cases extensively, and so far, have only identified the two cases that we've reported to you that have met criteria for GBS or GBS variant.

Dr. El Sahly: Specifically ADEM as well, right?

Dr. Peart: Specifically ADEM as well. Yes.

Dr. El Sahly: All right, thank you. I see Dr. Griffin, question number five.

Dr. Griffin: Yeah. My question is about GBS's demyelinating diseases as well. And I'm interested in the post-marketing plan. What would be, sort of, I mean, because this is such a high rate, does FDA have an idea of what they would be looking for? How many new cases or, sort of… we've, FDA has considerable experience with this, and, you know, Shingrix, but that's like one in a hundred thousand or something. Yeah. So I'm just wondering how many cases would you have to see before something happened besides just a label change?

Dr. Peart: That's an excellent question. We might have to return to you with an answer on that exact question when our pharmacovigilance team is available. But I will turn the mic over to Dr. Kaslow who might be able to provide additional information.

Dr. Kaslow: Sorry. No. So thank you for the question, and it really is a quite important one. And I think, as you saw in the presentation, we're highlighting these post-marketing surveillance studies as being critically important in terms of monitoring the safety of these vaccines.

Dr. El Sahly: Okay. Question number six, from Dr. Janes.

Dr. Janes: Thank you. My question is about some of the subgroup analyses, and in particular, the one that caught my eye is the analysis of efficacy against RSV-A versus B. And you know, as you pointed out, there aren't very many endpoints here, and so the precision with which we can estimate how VE varies according to the type of viral infection is limited. But I'm

wondering if you can provide any additional context or help us to interpret what is, in my mind, sort of an intriguing potential difference in VE. Are there any additional data that can be brought to bear on helping us to interpret whether that's a real difference in VE or a statistical artifact?

Dr. Peart: That's an excellent question. We only have the data that was submitted with this an application currently at this time. So I would not be able to provide additional data, but I would invite our Pfizer colleagues to be able to provide any additional data that they might have to address that question.

Dr. El Sahly: Okay. Question number seven would be Dr. Feikin.

Dr. Feikin: Yes. Hi. A couple questions. The first is another question about the GBS. I'm wondering, when FDA considers a potential related SAE, how do you consider other potential causes of that SAE? Because we heard for both of those cases, there was another potential cause. One case was a viral upper respiratory tract infection, and the other was an acute myocardial infarction followed by angioplasty. So that's the first question, is, do you nuance your interpretation based on that?

And the second is, I was surprised in your presentation to hear about the imbalance and the atrial fibrillation, because I didn't see that in the briefing document for Pfizer. And so I'm just wondering why it wasn't there, what the disconnect is between what you presented and what we saw in the briefing document. Thank you.

Dr. Peart: Thank you for your question. In regard to GBS, how we determine whether or not the event is possibly related is first starting with whether or not there are imbalances. The severity of the condition, the likelihood of the condition being associated with the vaccine, as well as the background rates of the condition. We use all of these information and have several teams on board that help us to determine whether or not we have a concern about a

safety signal. And then once we determine there's a concern, we will, if a product is licensed, post-marketing additional data might be able to be obtained.

Regarding the question of atrial fibrillation I would have to defer that question to Pfizer. Thank you.

Dr. El Sahly: Okay. I mean, the last question, I think we have just a couple more minutes, is pertaining to an echo of what Dr. Perlman and Dr. Bernstein mentioned, in that the study recruitment kind of by design, or the way it happened, had only 1% CHF patients of all age ranges. And we heard this morning that of all comorbidities, in any age really, this seems to stand out as a risk factor for severe disease. So you know, especially what Dr. Talbot also mentioned, that frailty and comorbidity, are not just the number, the age that of the patient. So I wonder about the ability of the trial to answer that question. just by virtue of the population enrolled. It's a hanging question now, but.

Dr. Peart: Yes, that's a great question. So I will say, in addition to, as you mentioned, congestive heart failure, even our colleagues at the CDC, Dr. Havers had addressed that there were additional comorbidities such as COPD and diabetes that put you at higher risk for severe RSV disease. There were a higher proportion of participants, about 18% in the RSV Pre-F group, and about the similar amount in the placebo group, who had diabetes, and those who had had COPD at a rate of about 6.6% in both groups. So, although the study had a lower rate of congestive heart failure, it does seem as though, again, the point estimates for VE for those who have these at-risk conditions is preserved. However, again, that data does seem to be limited due to the wide confidence intervals that it had.

Dr. El Sahly: I do not see additional hands for questions. So with that, we conclude this portion of the meeting and allow everyone to stretch and have lunch. It's 12:29. We have 40 minutes. So 1:10 Central or 2:10 Eastern. Thank you all.

Open Public Hearing

Dr. El Sahly: Good afternoon, everyone. Welcome back to our 179th meeting for the VRBPAC discussing the safety and efficacy of RSV vaccine as presented by the sponsor Pfizer. We are in the Open Public Hearing session, and now I will be reading the Open Public Hearing statement.

Welcome to the Open Public Hearing session. Please note that both the Food and Drug Administration and the Public believe in a transparent process for information gathering and decision making. To ensure transparency at the Open Public Hearing session of the Advisory Committee Meeting, the 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'll not preclude you from speaking.

I will turn the meeting now to Dr. Sussan, who will moderate the Open Public Hearing session. Dr. Sussan.

Dr. Paydar: Hi everyone. 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 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 viewpoints of the individual speakers or their organizations and are not meant to indicate agency agreement. With the statements made with our guidance, I would like to begin. Every speaker will have only four minutes to make their remarks. I'll begin with our first OPH speaker, Mr. Burton Eller. Mr. Eller.

Burton Eller

Mr. Eller: Thank you for this opportunity to speak on a topic of great public interest and concern. Founded in 1867, the Grange is the oldest national organization advocating for the 22% of Americans living in rural and small-town America. Our mission is to work together to support and advance the safety, health, economic security, and wellbeing of those who have chosen a rural way of life. We are here today to continue our effort to highlight the vulnerability of our communities to respiratory disease and to speak to the urgent need for safe, effective, and accessible preventive measures to keep them from taking the lives of our families, friends, and neighbors.

For many years, the National Grange has worked with public, private, and nonprofit agencies and organizations to find ways to reduce the elevated risk public citizens face from respiratory diseases such as flu and pneumonia. Some aspects of that risk are quite harsh. Lack of access to care has been estimated to account for 55% of what could be preventable hospitalizations or deaths from all causes. Rural life expectancy is two years shorter than that of urban residents. In the past eight years, almost 200 rural hospitals have shut their doors, and recent studies project that one third of those who remain are struggling and are not likely to survive.

Just before Covid, it was reported that the rates for influenza and pneumonia were higher in rural communities than in urban areas. As a result of where we live, rural Americans must travel longer distances to obtain services from fewer available clinicians, diminishing numbers of hospitals, and more limited choices of pharmacies than our urban and suburban counterparts. In addition, the COVID-19 pandemic added an enormous new burden to the already fragile healthcare delivery system in rural America and even more danger to the respiratory health of rural patients.

As the pandemic began to ease, the unprecedented rise in RSV cases throughout the country during the fall and early winter of 2022 added yet another highly dangerous respiratory condition to the list of those that have already taken such a heavy toll on us. News outlets throughout the country once again, were reporting the challenges the remaining rural hospitals faced as they tried to cope with the influx of patients needing care but with no space to offer them. When fall arrives this year, we could once again face a quadruple respiratory threat from flu, pneumonia, Covid, and RSV. We must not let last year's crisis repeat itself. If there are resources available to prevent it.

We add our voice, those calling attention to the urgency and critical importance that safe, effective vaccine prevention can offer our communities from RSV. We have full confidence in the FDA's work to protect all Americans from these multiple respiratory threats and to do so as traditionally as possible, so that all segments of the healthcare delivery system are prepared before the next season is upon us. We appreciate the opportunity to present to the committee today.

Dr. Paydar: Thank you, Mr. Eller. I appreciate your opinions. Next is Robin Strongin.

Robin Strongin — National Consumers League

Ms. Strongin: Good afternoon. My name is Robin Strongin, and I direct health policy for the National Consumers League. Founded in 1899 by the renowned social reformer, Florence Kelly, the National Consumers League has long championed vaccines as lifesaving medical interventions. In fact, Kelly's support of vaccinations played a key part in mitigating a critical smallpox outbreak towards the end of the 19th century, and her tireless advocacy for immunizations has informed NCL's bedrock principles for increased access in vaccine confidence. 124 years later, we are honored to persist in our efforts to protect consumers from vaccine-preventable illnesses, and we extend our gratitude to this committee for the opportunity to present our public comments.

We know that despite decades of effort, no vaccine to protect against RSV disease in any population has been authorized, resulting in a very serious unmet need. The dramatic rise in cases this past fall was a wakeup call for us as a nation. As Americans faced the threat of contracting RSV, the flu, pneumonia, and Covid were circulating simultaneously. The difference, of course, is that vaccines for Covid, influenza, and pneumonia are widely available, and many

in the most vulnerable communities have embraced these tools to reduce their risk of serious illness and death. However, the lack of any such tool to protect against RSV made for a frightening reality for Americans already facing serious threats to their respiratory heath, especially among the very young and the elderly.

NCL is also concerned with the serious strain these viruses put on our healthcare system and its ability to provide quality and timely care for patients. From hospitals running at capacity to overtaxed healthcare providers and family caregivers, the prolonged burden such an uptick in cases can inflict is not sustainable. We are encouraged by the continued progress in the development of vaccines to help strengthen our ability to fight back against devastating diseases like RSV. Ensuring broad and equitable access to these vaccines is an important next step to improving the health of all communities while reducing the high burden these viruses place on our healthcare system.

NCL cares deeply about the health and wellbeing of our nation. We will continue to do our part to educate people about the importance of vaccines and the value they offer consumers. And society as a whole. Thank you.

Dr. Paydar: Thank you for your participation, Ms. Strongin. Next presenter is Meredith Whitmire.

Meredith Whitmire

Ms. Whitmire: Hi all. I have no financial disclosures to make. My name is Meredith Whitmire, and I represent the National Association of Nutrition and Aging Services Programs, also known as NANASP. Our organization's members collectively serve over 4 million older adults through nutrition and other community-based services. Since 2014, we have been at the forefront of

discussions on vaccines for older adults, beginning with our efforts to advocate for Medicare coverage of pneumococcal conjugate vaccines. We appreciate your examination of the safety of these RSV vaccines for older adults. We urge you to make your decision in a timely manner in order to hopefully continue the vaccine's overall consideration by the relevant federal committees and agencies.

We are living in unprecedented times with four respiratory threats, COVID-19, influenza pneumonia, and RSV, circulating in our environment simultaneously at elevated and deadlier levels than they have in previous years. While there have been vaccines than Americans can take to protect themselves against three of these threats, RSV has remained a dangerous condition for older adults. At the start of the COVID-19 pandemic, older Americans quickly stepped up and did their part to become vaccinated when safe and effective options were made available. To date, over 94% of older adults in the US have received the primary series of the COVID-19 vaccine. Similarly, the rate of uptake among older Americans is higher for the flu vaccine as well. Recent CDC data showed that flu vaccine coverage for adults 65 years and older is 36% higher compared with adults 18 to 49 years.

Not only does this generation value vaccines as an important aspect of protection for their own health, but they also understand that they can help to protect the younger generations, as well. Many older adults care for grandchildren, so approval of RSV vaccines for older adults would help protect babies and younger children, as well. Since we know that RSV can be quite serious and even deadly for the youngest and oldest in our population, it stands to reason that we should be doing everything we can to provide the most vulnerable with these vaccines before the next round of respiratory threats comes our way in the fall.

We are grateful for this committee's tireless work on behalf of older Americans to evaluate new and innovative options for vaccines and to provide expert guidance on their use. We also know that the true value of vaccines relies not in the science alone, but in connecting the science to the people who would most benefit from it. NANSP, our members, and our partner organizations all connect with older adults in the state, cities and communities where they live when new vaccine options are available. We also work to ensure, ensure broad and equitable access to these vaccines for all who would benefit.

Though we are still in February, we are already looking ahead to how we can best serve our communities in helping them to prepare for yet another fall of an unpredictable deluge of threats to our respiratory systems. We are encouraged by the prospect that a major aspect of that planning could be ensuring access to these new and much needed protections against RSV. In short, older Americans are eager for the ability to strengthen their immune systems against this virus before we face yet another season of elevated respiratory threats in the fall. They are ready and willing to take the vaccines if approved. Thank you.

Dr. Paydar: Thank you so much. Ms. Whitmire. Next speaker is Martha Nolan.

Martha Nolan

Ms. Nolan: Good afternoon. My name is Martha Nolan. I am the Senior Policy Advisor for Healthy Women, a women's health online resource dedicated to educating women to make informed health decisions, advocate for themselves, and prioritize their health and wellness. And I am not participating today in this meeting at the direction of the sponsors, nor have I or my organization been paid to be participating in this meeting.

Much of our focus on women's health is centered around educating and empowering women to take control of their health and to know the facts about what resources are available to support their overall wellness and prevent serious illness. Vaccines are one of those essential resources, and therefore, we routinely share information and updates on available vaccines to keep women and their families informed. History has proven time and time again that vaccines help society keep dangerous diseases in check.

Pre-Covid, many Americans may have thought of vaccines as primarily a tool for infants and young children to build up their immune systems to fight off disease and illness throughout the rest of their lifespan. However, Covid illustrated for all of us how the strength of our immune systems wanes as we age, along with our ability to fight off illness. RSV is one such virus that many have associated with impacting young children, but we know it can also be dangerous for older adults. Each year, an estimated 177,000 adults are hospitalized with RSV, and 14,000 will die.

As cases of RSV dramatically rose this past fall, a virus many people had never even heard of quickly became a very serious threat to our communities as it coincided with the now predictable spike in COVID-19 and the annual threat from the flu and pneumonia seasons. It has reinforced the lesson we all learned at the start of the Covid pandemic, which is how interconnected we all are as a community. The intergenerational nature of our society, while so important in many ways, also lends itself to an environment in which viruses can spread among those most vulnerable from the youngest to the oldest.

The societal costs of RSV are considerable, as well. RSV costs the US more than a billion dollars in healthcare costs and lost productivity each year. Women are often the caretakers of the family, responsible for the health and wellbeing of both younger and older generations in our

society, and they are very much feeling the burden of this increased threats as well. And given that women have longer lifespans and are more likely to reach an older and more vulnerable age than men, we believe it is critical that they have access to effective vaccines to protect against serious illness and preserve their long-term health.

That is why Healthy Women supports the continued innovation of vaccines and is encouraged by the prospect of safe and effective vaccines for RSV in older adults. We are hopeful that as we enter into fall of 2023, we can do so with this added protection against RSV strengthening our immune systems. We appreciate this committee's role in ensuring that Americans have access to these vital technologies, and we will continue to share the FDA's updates on the newest approved vaccines and ensure that women are informed about the value they offer to our overall health and wellbeing. Thank you for this opportunity to speak before the committee.

Dr. Paydar: Thank you, Ms. Nolan. I appreciate your participation in VRBPAC. The next speaker is Mr. Kenneth Mendez.

Kenneth Mendez — Asthma and Allergy Foundation of America

Mr. Mendez: Great. Thank you. Good afternoon, members of the committee. Thank you for the opportunity to provide this testimony. Disclosure, AAFA receives financial support from Pfizer and other vaccine manufacturers, but I'm here to represent our organization. I'm President and CEO. We are the oldest and largest nonprofit patient advocacy group, representing the 65 million Americans with asthma and allergies. Our mission is to save lives and reduce the burden of disease through support, advocacy, research, and education.

I'd like to express our perspective using some statistics from the asthma world and why an RSV vaccine for older adults with asthma is so important. We know that RSV can be particularly dangerous for older adults with asthma. RSV can trigger asthma episodes or asthma attacks. Being over 65 and having asthma are factors for greater risk of RSV-related hospitalization or death. Our hope is that an RSV vaccine for this age group will reduce hospitalizations and death for people with asthma.

Let's look at some statistics on asthma and age. 7.8% of the US population, or 4.2 million adults older than 65, have asthma. There were 4,100 deaths in 2020 from asthma, and 41% of these deaths were from those aged 65 and older. This age group has the highest death rate of any age group, 31 deaths per million, more than twice the rate of the death in the next highest age group. An RSV vaccine has the potential of reducing the negative impact of RSV on those who have asthma and their unique challenges for the 65 and older age group. Evidence suggests that elderly asthmatics are more likely to be underdiagnosed and undertreated. Physical changes from aging, reduced motor and other skills, lower income, and the demands of other comorbid conditions can all exacerbate older adults' asthma and create barriers to care.

Asthma also impacts older adults of certain racial and ethnic groups more severely. For example, older adults with asthma who are black, Hispanic, and/or low income are at a heightened risk of frequent hospitalization for asthma. Because of these factors, we ask the advisory committee to take into account not only the overall potential impact of RSV vaccines for older adults, but the potential importance of such vaccines for older adults with asthma, including those subpopulations most burdened by the disease. A vaccine for RSV could reduce asthma exacerbations, improve quality of life for older adults living with asthma, and reduce

mortality, particularly among older adults with asthma. Thank you for your time and thank you for the work that you do as a committee.

Dr. Paydar: Thank you, Ms. Mendez. We appreciate your participation, sharing your perspective. Last but not least, our last speaker is Lindsay Clarke.

Lindsay Clarke - SVP Health Education & Advocacy Alliance for Aging Research

Ms. Clarke: Good afternoon. Thank you to the committee for this opportunity to comment. My name is Lindsay Clark, and I'm the Senior Vice President of Health Education and Advocacy at the Alliance for Aging Research. The Alliance received some industry funding for non-branded health education campaigns on older adult vaccination.

One of those campaigns that I lead at the Alliance is the Our Best Shot Campaign. Over the years, this campaign has produced dozens of educational resources, focused on raising awareness about the importance of vaccines in older adults, how they work, and which ones are recommended by the CDC's Advisory Committee on immunization practices, how the Medicare program covers vaccines, and more. The educational resources have included a focus on influenza, pneumonia, shingles, and Covid, and this past year we produced an educational campaign and film on RSV in older adults, emphasizing to viewers that RSV is not just a pediatric disease.

We know that the reported 14,000 deaths in 177,000 hospitalizations in older adults each year due to RSV are likely underestimated due to under-testing and reporting of the disease. We also know that in those older adults who are infected with RSV but don't have serious complications, they can still pass the virus on to vulnerable children and infants in their lives. In addition to adults ages 65 and older adults ages 60 to 64 living with asthma, congestive heart

failure, or COPD are at high risk for RSV-related hospitalizations and deaths. Studies from the CDC and others presented at the Resonant conference last week demonstrate that a higher proportion of adults ages 60 to 64, who were hospitalized and/or experienced severe outcomes due to RSV, were black, Hispanic, or American Indian, or Alaskan Native.

These racial and ethnic differences are critical for the FDA and CDC to recognize as they consider labeling and vaccine administration recommendations by age. Earlier and higher rates of asthma, COPD, or congestive heart failure in communities of color due to structural racism leads to earlier RSV onset and higher risk of hospitalization and severer outcomes, including deaths. We ask both agencies to heed the still raw lessons of COVID-19 and work together to collect and analyze data by race ethnicity, as well as age, to better ensure RSV vaccine equity and equity for all other vaccines.

Additionally, please do not layer on a shared clinical decision-making recommendation for this vaccine as a utilization management technique. It is not needed and will only reinforce known disparities. Effective vaccines for RSV and older adults clearly have the potential to make a tremendous impact and save tons of thousands of lives. We call on the CDC's advisory committee on immunization practices to meet and vote on recommendations within a week or two of any FDA approval and to publish the recommendations in the MMWR without delay.

While respiratory surges are no longer limited to the traditional cold and flu season, we know that the surges of influenza, covid, pneumonia, RSV, and other respiratory illnesses continue to flood and overwhelm our healthcare system in the fall, winter months. That gives us six months to approve, recommend, and start administering these vaccines while simultaneously educating older adults and clinicians about their benefits and availability.

Lastly, we urge the federal government to make sure that the safety of co-administering multiple vaccines, like RSV and influenza, Covid, or pneumonia, is clearly communicated. We know from our education and outreach that misinformation about the safety of receiving multiple vaccines at once persists, and clear communication from the FDA, CDC, and other agencies is critical in the distribution of reliable and trustworthy information on vaccination, and specifically on co-administration.

We are excited by the fact that RSV vaccines could be available for older adults before the start of the serious cold and flu season. While general awareness and prevention will remain a priority for the Alliance, we look forward to being able to encourage older adults and all adults at high risk to receive an RSV Vaccine to protect themselves and their loved ones. Thank you for this opportunity.

Dr. Paydar: Thank you, Ms. Clark. I appreciate your participation. This concludes our Open Public Hearing session for today. I now 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: Sure. Thank you, Dr. Paydar. Our next agenda item is the Q&A session. During the session, the committee members will have the opportunity to ask questions to the presenters this morning. It would be the CDC, the FDA, the sponsor, and additional presenters. To that end, I invite the committee members to use the raise your hand function in the Zoom. So we can begin without delay. No hands so far. I'll get us started. The reminder, please use the raise your hand function. It's under reactions in the ribbon below, so you can raise your hand for questions to all of our presenters from this morning.

So the first question I have is for the sponsor. In the briefing document you presented, the antibody response at one month and the antibody decay at 12 months was superimposed when we looked at 60, 120 and 240 microgram, give or take. Moving forward, the program went with 120 microgram. What was the rationale?

Dr. Gurtman: Yeah, so Alejandra Gurtman again, here from Pfizer. The rationale for the dose selection was that we did not see much difference between the 100 and 240 micrograms, and it was a little bit of a dose selection with the 60 micrograms. And based on the totality of the immunogenicity data and the safety that we observe with the vaccine, although the vaccine was safe at all doses, we selected the 120 micrograms.

Dr. El Sahly: Okay. So, alright. I see Dr. Kaslow.

Dr. Kaslow: So, Dr. El Sahly, I wonder if it would be helpful for the advisory committee to hear at a very high level, the vaccine safety review process during the BLA regulatory review process, kind of where we are now in considering those safety signals, what steps remain, and how the post-approval information will be assessed. Seems like there's great interest around that. And if so, our colleague from the Office of Biostatistics and Pharmacovigilance, Dr. Alimchandani, is on standby to do so, if that would be helpful.

Dr. El Sahly: Definitely. Hi, this is Meg Alimchandani. Can you hear me okay?

Dr. El Sahly: We can hear you.

Dr. Alimchandani: Okay, great. So I just wanted to take a couple of minutes. So Pfizer has proposed a post-marketing active surveillance study in Medicare beneficiaries to further assess the risk of GBS. This post-marketing study is under discussion between FDA and Pfizer at this time, and Dr. Kaslow asked that we provide an overview of our process at FDA with regards to review of post-marketing safety studies.

We are currently reviewing Pfizer's study proposal. Our next step is to discuss the study and taking into account the comments from VRBPAC today at a CBER safety working group. This is an internal safety working group, which includes members from the center leadership. Our review will consider the study design, including the study objectives, the data source, study feasibility, and also the timeline for conducting the study, when the study would be completed in the submission of the final study report. So FDA will be providing our comments on aspects of the study design to Pfizer for them to include FDA recommendations as they prepare the final study protocol.

And we wanted to remind the VRBPAC that post-marketing safety studies can be conducted as post-marketing requirements or commitments. And FDA has the regulatory authority to require the sponsor to conduct a post-marketing study to assess a serious risk. So following our internal discussions with central leadership, FDA would issue a sponsor notification for a safety study that would be either a PMR or a PMC. So that's all I had just to provide a high-level overview of things.

Dr. El Sahly: Thank you, Dr. Alimchandani. I see Dr. Cohen has a question.

Dr. Cohen: Great, thank you. This is a question for FDA. I am curious about the rationale regarding setting up the study with Pfizer originally to be a whole of two seasons, and then doing this interim, that analysis. And what is FDA's plan, for example, if during the next season, as this study continues, efficacy is very different? What would the approach be, given that originally this was meant to cover two years or RSV seasons?

Dr. Peart: Hi. Thank you for that question. It's a great question. We are of course monitoring the study, the ongoing study as it's being conducted. And if new data becomes available that changes our current opinions on the vaccine and its efficacy, of course, we would reevaluate at

that time and likely request another meeting with the committee to determine further plans. Thank you.

Dr. El Sahly: The committee is a little quiet. Any additional questions? Dr. Cohen, you have a second question?

Dr. Cohen: Sure. I have a follow up question if nobody else has raised their hand . Thanks for that response. I guess I was wondering if there are any other examples of vaccines that have been meant to cover cyclical… Like, so influenza vaccine, we have annual with changing strains, and that's where it looks like Covid is going. But do you have any examples where you want to have long-term protection and you required a longer duration of protection before licensing a product, or a vaccine specifically? Or do you always use that short term immunogenicity or effectiveness for your determinations?

Dr. Peart: Thank you. As you mentioned, influenza is a great example of that. It's a respiratory virus that changes annually and requires updates annually to the vaccine schedule. We do have that model if we do need to address this vaccine in that, in that manner. But again, until we have additional data, I will not be able to further comment on that. Thank you.

Dr. El Sahly: Dr. Griffin.

Dr. Griffin: Yeah, I'm also concerned about the vaccine that could be recommended for all adults but has been tested in a relatively healthy adult population, where the number of hospitalizations has been pretty low. So how would FDA, how are we going to find out if it really works for frail elderly and nursing home patients? And is that going to rely on observational studies, like we had to do for influenza vaccine for years and years? I mean, and would that change the labeling at all if an observational study showed that it wasn't effective in nursing home patients? I'm just wondering if it's possible to get more efficacy data.

Dr. Peart: Again, an excellent question. So I do want to also just readdress that the study, while we did ask for a post hoc analysis on medically attended cases, and there were 64.6% of medically attended cases in the RSV pre-F group as compared to the placebo group for those who had LRTI of at least two symptoms. But that medically attended definition was broad and did include hospitalization, inpatient hospitalization, but also outpatient hospitalization data. So I just wanted to make sure to bring that up again to the committee.

And then going to the question that you asked about if new data or how the efficacy would be assessed in the frail elderly population. In previous vaccine trials and studies, that specific population has not always been taken out to study and to study the efficacy in. And in the same circumstances as what would happen with this vaccine potentially, real-world evidence and data would be a supplement to the data that we have already to help in establishing and in understanding the vaccine efficacy. Now, when that data becomes available, yes, we would definitely readdress that by whether or not we need to come back to a committee to re-discuss it. And then, if needed, to update the label accordingly. Thank you.

Dr. El Sahly: Dr. Kim. Oh, thank you. When Dr. Gurtman presented her information, there were certain cutoff points for age groups, for example, age 60 and another at age 80. And then and you also went into a little bit of a discussion into age 65. And I'm looking at this RSV vaccination from a policy perspective on this. And we have vaccination recommendations for people 65 or older. And Pfizer is obviously very in tune with the Prevnar vaccine recommendations at age 65. And there's also, of course, the influenza vaccination for those 65 or older to receive either the high dose influenza vaccine or an adjuvanted influenza vaccine. So given that we have certain age process for routine immunization schedule for adults at age 65, and we don't have one for age 60, and from an implementation perspective, a 60 there would add

a layer of complexity to the to the overall larger immunization schedule. So for our Pfizer colleagues as well as our FDA colleagues, is there some consideration for age 65 to really dive into the data for age 65 and look at the benefits from 65 on and compare that to those age less than 65 and determine whether a policy consideration can be made for 65 and older as opposed to 60 and older?

Dr. Gurtman: So thank you, Dr. Kim, for the question. Our program is seeking an indication in adults 60 years of age and older, and as it was mentioned this morning, immunosenescence is hard to define, but it starts probably at age 50. The final recommendation of how the vaccine will be recommended will be up to the CDC, but we have shown data. Our study includes all the age groups between, as I said, the youngest 60 to 97 years of age, and we have shown consistency on vaccine efficacy across the different decades of life. So the submission put together for the BLA actually supports the request for the age 60 and older. And recommendations at the end will be made by CDC and ACIP.

Dr. El Sahly: Dr. Perlman.

Dr. Perlman: So I have a question, going back to the safety issues. So with this vaccine, is the thought that this is going to be given yearly, every other year? And how does that affect the risk of GBS if one gets multiple in inoculations? Do we have any information about that?

Dr. Gurtman: Yeah, so thank you for the question. The revaccination data that we have is in a very small cohort of subjects in this age group, but not to support a response to your question. However, as it was mentioned by the FDA expert, we will be crafting and designing a study to clearly investigate the incidence of GBS in this age group. And that study, as it was mentioned before, it has been currently discussed with the FDA. And in addition to the study, we will have also our enhanced pharmacovigilance that we will do to ensure that we detect cases of GBS or

other immune demyelinating conditions. And that is an expedited report that is done to the FDA, regardless of the severity of the syndrome or regardless of any relationship. So it will be the study design as it was mentioned, but also enhanced pharmacovigilance activities, which we have done for a long time. And we can really, we have the whole system to support detecting cases if they're presented and reporting them to the FDA.

Dr. El Sahly: I have a question to the FDA. And it pertains also to the safety. The sponsor did indicate that there is interference when this vaccine is co-administered with influenza vaccine. In this particular population, with the VE of influenza every year being so closely monitored and being so vital for our public health efforts to decrease hospitalizations and death each year, in the absence of data to the contrary, that it does not interfere, because all we see in the briefing is that it does interfere. In the absence of such data to the contrary, what would be the post-marketing, or what would be a piece of information that would help alleviate this particular concern?

Dr. Alimchandani: So I think in terms of the post-marketing safety surveillance study, we can do sensitivity analysis, and that will be under consideration as we look at the protocol. I think for any sort of specific questions about the study design, I would defer back to Pfizer if they have additional comments on that.

Dr. Gurtman: So if I may, Dr. El Sahly, we truly didn't show interference. We should show a trend in decreased responses in the flu vaccine in a study that was not powered to look at really non-inferiority. And that's why we are conducting, and now completed, a study with flu vaccine, actually, to see if there is interference or not. So the data is not available yet but will be available very soon. And as I think I mentioned in the morning, we will be submitting that data to the FDA for potential inclusion in the label.

In terms of coadministration with flu vaccine and ISV in terms of detecting GBS in our pharmacovigilance studies or activities, actually, we collect when the information is available, but not always is available. But we made an effort to collect that concomitant administration once the vaccine will be approved and recommended.

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

Dr. Bernstein: Yeah, I wanted to follow up, Dr. El Sahly. I think the co-administration is very important, and I was wondering whether there was a study to do this with Covid vaccine as well. Because those are certainly the population that we're dealing with, 60 and above, or 65 and above, are well vaccinated but also very vulnerable. And then the other vulnerable population that I wanted to ask about was, what plans are there for the immunocompromised populations or those that have not so stable chronic medical conditions?

Dr. Gurtman: Yeah. So thank you for the question. In terms of concomitant or administration or the future of vaccines, I think that I'm very excited to say that Pfizer will continue to try to bring vaccines that actually can make a difference in public health. This is one of the vaccines and we are evaluating, actually different respiratory combinations that are included, as the ones that you mentioned in the future. Because it might be the way that some of these vaccines might be given based on the seasonality and based on the fact that they're, in this case we're talking about all respiratory pathogens. Clearly, combination vaccines have made a difference in the pediatric population, and hopefully that will be the case in the future as well. And I apologize because I did not, could you please repeat your second question to me?

Dr. Bernstein: Yeah, I was interested the immunocompromised and those with the not so stable chronic medical conditions who both would be very much at risk for problems getting RSV.

Dr. Gurtman: Yeah. So thank you for the question. We're currently evaluating to a study, not a post-marketing commitment study, but a study to assess actually those who are immunocompromised, and that will be all ages, from 18 all the way to older adults. But also, we are looking at doing in the same study, actually having a different population for at risk in those who are 18 to 60, to address some of the comments that were made today in terms of higher disease and higher hospitalization and mortality in those who have chronic cardiopulmonary conditions, regardless of age. So that's something that I am also looking forward to start very soon and have the data available for additional information for the question that you're asking.

Dr. El Sahly: Dr. Janes. My, my question is very related to the last question, but maybe I'll pose it a bit differently. And to the FDA, the epidemiologic overview earlier really characterized a number of impacted populations, including older adults, but also including individuals with preexisting conditions. And importantly, I was struck by the racial and ethnic disparities in terms of burden of disease. And so I guess I wonder what FDA's perspective is on the pursuit of data on safety and efficacy in these other populations. Is that part of the post-marketing requirements that have been worked out with the sponsor?

Dr. Peart: Thank you for that question. I think we might ask Dr. Alimchandani to comment a little bit on if it's related to a post-marketing question. Thank you.

Dr. Alimchandani: Sure. This is Meg Alimchandani again. So, for the PMRs that's at the safety, those are really focusing on safety. We have the regulatory requirement to have these PMRs under FEDA for safeties purposes. For the efficacy in a portion, we sometimes have post-marketing commitments if we have agreed upon studies with the sponsor to look at efficacy. But I would really defer that to OVRR for any, any questions related to post-marketing efficacy studies.

Dr. Peart: Thank you. We'll take that under advisement and we'll be considering that as we discuss with the sponsor. Thanks.

Dr. El Sahly: Dr. Kim.

Dr. Kim: This is partly a follow up for Doc from, from Dr. Janes' question, as well as what Dr. Hildreth had asked in the near the beginning of our discussion today. And that has to do with racial and ethnic disparity. The data that you presented Dr. Gurtman, on the demographics of the Phase Three, as well as previous phases, indicated that there was a significant amount of Latinos as well as African Americans and Asians. But the study studies took place in Japan, South Africa, and elsewhere, in Argentina, and so on. So, the question I have is, the data that you showed were aggregates from all these countries in addition to the United States. And if so, then, for example, the Japanese social determinants of health and the Argentinian social determinants of health will be very different from what we would see in the United States, in terms of African-Americans in the United States versus Africans in South Africa. So the data we have are more of a national difference. So for the US, do you have any additional information on how the how the vaccination impacted the American population with regards to this intervention?

Dr. Gurtman: Yeah. So thank you, Dr. Kim, for your question. And you are correct. The data that I presented is aggregate data for all the countries. About 63% of the participants came from the United States, and most of the cases actually came from the United States. So I think that vaccine efficacy that I presented today is highly representative of the US population, but also we saw consistency of vaccine efficacy across the other countries had sufficient cases for us to be able to evaluate that.

I want to emphasize that we really strive at Pfizer to enroll a diverse population. We understand how critical it is to have participants that are representative of every ethnic and race group to ensure that the data as an aggregate actually is representative of the population. For the US, as I mentioned, because most of the cases came from the US, I do think that it is representative.

Dr. Kim: Thanks for that additional information.

Dr. El Sahly: Dr. Feikin.

Dr. Feikin: Yeah. I have a question for FDA and a question for Pfizer. For FDA, I want to circle back to the atrial fibrillation question. I was able in the break to go back, and I realized I was looking at an earlier briefing document, and in a later briefing document it, it did mention the atrial fibrillation imbalance. So my question is to the safety follow up post-marketing, whether FDA has considered also looking at atrial fibrillation, potentially, given the possible class effect for this type of vaccine, RSV Pre-Fusion vaccine in elderly. I think we'll be seeing some other data tomorrow. So that's the first question is to FDA about that.

My question to Pfizer is, many of us have noted that the lack of efficacy data for severe disease, which is ultimately what we want to prevent. And I think there were only two cases that met the severe case definition. I'm wondering if that is lower than you expected. I don't know the exact rates, but it, it seems to be quite low given the size of the study that there were only two severe cases of RSV LRTI. And I think maybe only one of them was hospitalized, but I'm not sure about that. But just wondering if that is lower than you expected, and if so, why?

Dr. Gurtman: So I can start with the Pfizer or the FDA first and then second. Well, maybe I will start. So thank you for the question. So couple of things. We have very high vaccine efficacy, right, of 85.7, and with the new data I show you about NF system, one of about 89% against

three plus symptoms. And those participants clearly had a much more compromised clinical presentation. There is no reason for us to think that if the vaccine was so highly effective on those who had three plus symptoms will be as high or even higher, present higher efficacy for those who have severe disease. And we have seen this recently with the Covid vaccine, for example, where we have been able to prevent the most severe cases such as death and hospitalization. And similar for the flu vaccine with, for example, ICU admissions.

With respect to the question, so we have we have four pneumonias out of the cases that I presented today, and two of those were hospitalized. And the two hospitalizations were in the placebo group, and the four pneumonias were in the placebo group. The reason why we didn't see more severe cases is probably multifactorial. One of the reasons is potentially related to the Covid pandemic and how are speaking back. And actually we are detecting probably five to six fold lower in the study than we would have seen prior to the pandemic.

The other piece, which was mentioned this morning is that the protocol accepted actually PCR testing if it was done at the hospital level. But it was mentioned this morning. We don't have great RSV testing when patients are hospitalized. So some of with, of, I can tell you that two cases of hospitalization, actually, one was a local PCR testing and the other one was a central one. So it is multifactorial. So I think it's the pandemic, the rate, the lack of RSV testing. Patients who are very sick usually don't get to self-swab before they go to the hospital. They just go to the emergency room. And, but I, having said all of that and having seen such high vaccine efficacy in the three plus symptoms, I think that hopefully we'll have the opportunity to see the true impact of the vaccine on post licensure studies.

Dr. Feikin: Did you collect information on all cause respiratory hospitalizations? We did not. We did not collect that information in the study, and we only did PCR testing for RSV centrally.

Dr. Alimchandani: Okay. Hi, this is Meg Alimchandani from FDA. So I think your first question, Dr. Feikin, was about a-fib and what we're going to do for post-market safety. Correct? So we are, under our post-market safety regulations for certain adverse events of special interest, we can implement enhanced pharmacovigilance. So we are discussing that with the applicant, and we want them to submit reports to us for all a-fib and supraventricular tachycardias as expedited reports and provide sort of aggregate analysis in their periodic safety reports. So that's our plan for now to do the enhanced vigilance, and if there is new safety information in the post-market survey post-market period, that may trigger additional actions.

Dr. Feikin: Thank you.

Dr. El Sahly: Any additional questions? I see Dr. Janes.

Dr. Janes: Yes. If it's all right. I have one more question for FDA, and it's somewhat of a rephrase of a question that's been asked before, but I wonder if our FDA colleagues can help us gauge the importance of the strength of evidence here. So, what we've been presented is evidence from a single Phase Three trial that has a fairly modest number of primary endpoint events, 44 primary endpoint events. And admittedly, it was done in a global context and enrolled a large number of individuals in order to accrue that number of events. But I'm wondering if FDA can provide us a little bit more background and rationale in terms of the strength of evidence that they deem is needed to justify approval for a product such as this. Again, on what basis would a single Phase Three efficacy trial with data as of an interim analysis be deemed adequate for a licensure recommendation? Thank you.

Dr. Peart: Thank you so much. So as we've mentioned, the data that the applicant has submitted, it was acceptable for BLA submission. And so now at this point, that's what we are looking to hopefully generate conversation about today. Whether or not the advisory committee

agrees that the data presented demonstrates adequate safety and efficacy. So we're looking forward to the conversation. Thank you.

Dr. El Sahly: Any additional questions to the FDA, the sponsor, or the CDC from the committee members? I don't see any hands, but I hope I didn't miss any.

Okay. So that concludes this portion of the meeting whereby we ask questions to the presenters and the FDA. We take a 10-minute break. And we reconvene, during which we will deliberate as a committee on the two questions and then vote on the two questions. So now it's 2:14. So we will reconvene at 2:24.

Committee Discussion and Voting — Pfizer RSV Vaccine

Dr. El Sahly: Dr. Paydar, can we resume?

Dr. Paydar: Yes, please go ahead. We will have the voting question number one for the committee. So we will discuss that first before we go into voting session.

Dr. El Sahly: Very good. And are you going to put it on the screen?

Dr. Paydar: Yes. There it is.

Dr. El Sahly: There we go. Welcome back dear committee members. For this next portion of the program, we will go over two voting questions. The goal is to divide our time 50/50 between both questions, or close to it. The way we envision this going is that we discuss question one. Dr. Paydar will ask us to vote, and after we vote, we go around the virtual table and ask for final comments from each voting member. So I'll read the voting question, and I ask that everyone use the hand function again in Zoom so I can call on your name to discuss your viewpoint pertaining to the first question.

Voting Question #1

Dr. El Sahly: So the voting question number one, are the available data adequate to support the safety of ABRYSVO RSV Pre-F when administered to individuals 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV? And to start us off will be Dr. Portnoy.

Dr. Portnoy: Great. Thank you. See, I've learned the trick of hitting the raised hand early, so I get in early. I just wanted to make a few comments before we vote on these two questions, and this one in particular. I'm a pediatrician. Every year during the fall and in the winter I see epidemics of kids in the emergency room and in the hospital with RS. It's a total disaster. This year, the emergency room was completely filled. So I'm very aware of the importance of getting a vaccine for this disease. It's been the scourge for as long as I've been in practice. As an older adult, I wasn't aware that it affects older adults as much as it apparently does. So it's a little bit eye-opening.

My comment is that I would've liked Pfizer to have completed all of the studies before submitting it for licensure. I'm used to emergency use authorizations from Covid. I've seen the data there. It is urgent. That's why it was submitted and approved before all of the data were in. This is not an emergency. This thing has been around for as long as I've been in practice. I would like to see it, but I think it's a little premature. I would really like to have seen them complete all of the studies before submitting it. I have to admit, I'm reassured that there are no major safety signals, including enhanced disease. I wasn't aware that it wasn't a problem in adults, but in pediatrics, it's going to be an issue that we'll have to discuss. We definitely need a vaccine. This

is a good start, but I really would've liked to have seen them complete all of the studies before they submitted it for full licensure. So thank you very much.

Dr. El Sahly: Thanks, Dr. Portnoy. Dr. Griffin.

Dr. Griffin: Yeah, I'd say I think there are safety concerns, and I think when you talk about safety, it's always a benefit risk. So I think I would be less concerned about safety in a population that had a very high, if we knew the population was a very high hospitalization risk, we're going to receive a benefit. So unfortunately, the population that was studied was underrepresented with these frail people. And so it's really hard to make a, when there's this huge safety question of Guillain-Barre, to say that's not a concern. Because I think the benefit for relatively healthy older people is not, you have to consider that is not that great compared to a possible high risk of a very severe outcome.

Dr. El Sahly: Okay. Thank you, Dr. Griffin. I do not see hands risen, but this is the portion where even if you have minor or no consideration, I'm going to ask your opinion. I see Dr. Bernstein.

Dr. Bernstein: Yeah, thanks Dr. El Sahly. So I don't know. I'm a bit challenged by this. I mean, after decades of scientific study, this RSV vaccine really shows incredible promise. And an RSV vaccine could have immense impact on a really very common respiratory pathogen. But I do think that there are a lot of concerns that I think we probably need a little bit more data. I'm concerned about the safety signal with GBS, or inflammatory neuropathy. I think there's only a modest amount of data on the most vulnerable populations. I think there's limited co-administration experience with this vaccine with high dose influenza and Covid vaccines. The VE for hospitalization and death is unknown or not documented well at this point. And the data, at least most that was presented, only reflects the one RSV season. And maybe we should be

waiting for the year two data and look at it all in total, especially with the fact that there was inter-season RSV during the pandemic. And so I don't know whether the seasonal pattern will continue or whether we'll need to be concerned about inter-season play. So those are my real concerns, why I'm challenged about voting on this at the moment.

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

Dr. Pergam: Yeah. I have similar concerns to what have been raised by others. It feels as though a lot of the responses that we were expecting are wondering about, that study's done, the data hasn't been analyzed yet. The data that year two data's there, but we don't have it. There's the finalized flu and RSV combo study that's completed, but the data hasn't been analyzed. These are big questions that are important as we get into this season about who should be getting this and why. I think the safety signals, I'm not overly concerned, but I think there's a really good plan of action for how to approach this. But I think, following Covid where there's been so much pushback around myocarditis and other complications and how that's had a larger effect on the vaccine confidence. I think it's critically important for us to make sure that we're making a decision that also includes these safety evaluations. So I think the additional data would be helpful in terms of understanding that.

I do think there are some aspects of this that are intriguing, of course, because this does look to have good efficacy. I think it's very interesting that the data also suggests there's longer potential benefits of her, maybe even up to 12 months and potentially additional protection. But that's still not super clear yet. My biggest concern, as others have talked about, is that the population that was studied is really not those who are high risk patients. And these were very stable patients, very selected to be healthy with potential to produce good immune responses, but

really were not ones that had the efficacy endpoints that were so necessary for decision making, I think for all of us. So those are my specific concerns.

Dr. El Sahly: Thank you. I do not see raised hands, so I'm going to start asking for your opinions. Oh, Dr. Cohen.

Dr. Cohen: Thanks. I echo much of what's already been said. I struggle with this a little bit, because this is such amazing data that we have on efficacy for an RSV vaccine in this population, in this age group. So it's both amazing to see that it looks like we have a vaccine that may work, but I also feel like this is a little, I would love to see more time, more efficacy data, and have a better sense of a, whether or not this vaccine will protect those who are at most risk, as well as whether or not this is going to inevitably become an annual vaccination, or if we'll get more than one season from a single dose.

Dr. El Sahly: Okay. Thank you all. Thank you, Dr. Cohen. Dr. Feikin. If we can also focus on the safety question, it'd be great, because we're going to have also another session dedicated to voting question two, which centers around efficacy of the product.

Dr. Feikin: Okay. Well, thanks for saying that because I do have more comments about the efficacy, but I do have a couple about the safety. I agree with others that the GBS signal is potentially there. I do feel like it was only two cases. You know, if you look at the rate, it would be on the high end of what would be expected. But given the fact that it's only two cases, both of which had a potential other explanation for the GBS, I'd feel a bit more comfortable in doing a detailed safety follow up post-marketing.

I don't think the second season data is going to help us much with the safety aspects, because the vaccination, if I understand, is finished. And you wouldn't expect to see to see vaccine related GBS in the second year of follow up. So I'm not sure how we're going to get

more data on a GBS signal. I mean, this was a study of you know, 30, 35, 40,000 people. So I'm not sure where that data would come except in a post-marketing setting over.

Dr. El Sahly: Okay. Thank you. I mean, I know the issue of the MI has been invoked as a trigger, but to my knowledge, this is not an important trigger for GBS, having cardiovascular events. I mean, is it distress? I don't know. Dr. Berger.

Dr. Berger: So we don't have an answer for the question you just posed, but I'll just go forward. I think I agree with exactly what Dr. Feikin just relayed. I think there are some concerns around the safety signals that we've seen, particularly around GBS and a-fib, even though that is a numerical differentiation.

You know, I will say, I also agree though that there is this post-marketing surveillance study that's being agreed to where those types of signals will be muted out. You know, if I'm ignoring all the vaccine efficacy questions that we'll get to, from a safety standpoint, I agree. I mean, this was 35,000 people involved in this study. I'm not sure we're going to see it in a different way. So I think the post market surveillance studies are going to be essential to move forward here. You know, if this does get approved.

Dr. El Sahly: Okay. Let's see. I do not see any hands, so I'm going to ask Dr. Holly Janes to weigh in.

Dr. Janes: I don't think I have much to add in terms of safety. I agree that, really, the place to definitively nail whether there's a concern with these very rare events is in the post-marketing surveillance. So I'll reserve further comments for the efficacy.

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

Dr. Hildreth: Thank you. I agree with my colleagues, and my main concern is that the immunity seems to wane fairly, I don't know, relatively quickly for these vaccines. So they're up to be boosters, probably every year. And so, would the safety profile for the revaccinated be different than it is for the primary? So that would be my, my concern.

Dr. El Sahly: Thank you. Okay. Dr. Perlman?

Dr. Perlman: Yeah, I think what I was thinking has been well discussed by previous people on the call on this meeting. I'm pretty concerned about the GBS after having the swine flu in the seventies, since I'm old enough to remember that. And also living through all the COVID-19 vaccine stuff where we have abysmal booster rates because of people's concerns. Most are not valid. So I just don't... I'm very nervous about having any safety feature come up even in post-marketed surveys, because it'll affect both this population and then uptake of the vaccine for babies, where we know already that the COVID-19 vaccine is not taken up particularly well for the little children. But on the other hand, I also appreciate the argument that we're never going to get the data to know whether the GBS and atrial fib are really issues until we do a post-marketing survey. So, I guess I would vote in favor of saying that safety is okay, but with a really, really careful post-marketing evaluation.

Dr. El Sahly: Okay. Dr. Kim, I think.

Dr. Kim: You know, given the voting question one here, we don't have any more data that we're going to be presented with, now or in the immediate future, because the safety data are what they are. So therefore, is that enough to make a decision on the safety issue on this? And concerns aside, further post-marketing analysis pending and those other things in place, I think given the task at hand on voting question one, it's actually, I appreciate that the other committee members have expressed concerns regarding Guillain-Barre syndrome and other

adverse events. But given the available data, is that adequate? I think, to me, I think the answer is fairly straightforward on this. Given the safety on this, is that going to be beneficial in the long run and provide the protection that people need? So it's obvious other things need to take place down the line as far as the continued product evaluation is concerned. So that's the reassurance that I need. Thank you.

Dr. El Sahly: Thank you, Dr. Kim. I think everyone had an opportunity to discuss the issue of the safety. I'm going to read the question. Are the available data adequate? Reading the briefing document and listening to the presentation today, two issues rise to the top when it comes to safety.

Guillain-Barre Syndrome, of course. The 1976 influenza program is still fresh in our minds. I know Dr. Perlman said it's old, but it's really not. It's part of the reason why we follow GBS so closely on every clinical trial. And the disease has an incidence of one in 100,000 in this population, but what we are seeing here is more like one in 9,000. So this is major in terms, if we take it at this level, given that, because it's two events, the confidence interval around this estimation would be wide. But nonetheless, it's significant in terms of incidence.

The other issue is, and I know I brought it a couple of times, but it does pertain to safety. The study that evaluated the co-administration of influenza and ABRYSVO is a 1200+ person study. And individuals were administered different doses of the RSV vaccine with or without influenza. There was no interference with the RSV antibodies, but there was trend of interference with the HAI. We are not presented with the magnitude of that interference. So that is also, even if there's a follow up study and that study is better powered to answer this question, I mean, we've seen a lot of data where we see it and we say that, well, probably there is, we can't say either way. But I also find it intriguing that neither the data from the 1200 person study were

shared. And there are outstanding data that can definitely inform this question, which has important safety implications for the population in whom ABRYSVO will be given. We do know for a fact that influenza vaccine in this population prevents hospitalization and death by virtue of how this study population on this trial were enrolled, meaning 1% CHF, 5% COPD, and these are the two subgroups in whom the majority of the events would've happened. So they are a minority, so we could not learn more about the hospitalization and death in this trial. We are left with an outstanding question for which data exists elsewhere. And that weighs a lot in how we can, at least for me, answer this question.

Any final thoughts from any of our committee members or from the FDA before we turn over to Sussan for the voting? We have one raised hand. Let's see. Dr. Cohen.

Dr. Cohen: Thanks, Dr. El Sahly. So are we going to vote on this question before discussing the second question?

Dr. El Sahly: Yes. So the way, the way the flow is, we discuss, we vote, we explain the vote, and then we move to question number two.

Dr. Cohen: Okay. I guess, so first of all, I agree with you.

I think that, and I apologize for messing up my thoughts last time, but there's available data here that we haven't seen yet, and I feel like we, if this large outbreak hadn't occurred last fall, I don't know that we would be in a place where we're being asked about this without the co-administration and other available data, or data that will be available in the next several months. I think the timing feels rushed. I don't think that this is a viable vaccination program if we have to administer flu vaccine and this vaccine and maybe even Covid vaccine separately. So as you

were saying that. it struck me that I agree. This is a safety issue, because it would be potentially interfering with influenza vaccine effectiveness.

And it does seem like inevitably this vaccine will be co-administered if it is recommended and authorized. So it, it does feel like unlicensed, but it does feel like I would love to hear from the FDA, like what would happen if we needed to wait for some of that additional data to be presented?

Dr. El Sahly: Yeah, that would be a great question. Those two studies would be very informative. Anyone from the FDA to answer Dr. Cohen's question and my concern?

Dr. Kaslow: Can you hear me? It's David. No question, I just think that this discussion is absolutely essential in terms of our regulatory review process and incredibly helpful. And you're delivering exactly what we wanted, which was a robust discussion around both the safety topics and the efficacy topics.

Dr. El Sahly: Okay. Thank you, Dr. Kaslow. We have time for more comments, if anyone has any. Oh, there's one hand. Let's see. Dr. Perlman.

Dr. Perlman: Yeah. So I just want to ask Dr. Kaslow if he can give a more definitive answer on whether we can postpone this and get more information.

Dr. Kaslow: Yeah, I knew what you were thinking. Going to make some changes there.

Dr. El Sahly: Dr. Kaslow, your very your microphone is very distant. We can't hear you.

Dr. Kaslow: So again, I think we're looking to the advisory committee to provide input to the FDA in terms of the timing of this approval. And these voting questions have been crafted specifically to ask that question. And so, yeah, I think your input would be considered, as will the vote.

Dr. El Sahly: Okay. Dr. Portnoy.

Dr. Portnoy: Right. I guess my last comment, given our recent exposure with experience with Covid, I think we have to be really careful before we send a vaccine out to cover large groups of patients, given the hesitancy that occurred surrounding Covid vaccine, which turned out to be a very safe vaccine. The public is very skeptical, and in order to maintain the trust that the FDA gets from the public, and perhaps to rebuild that trust, we need to make sure that we're really careful about the safety of a vaccine before we send it out to immunize a large population of people. We just need to be very careful that we have all of the data that we need in order to confidently say that this is a safe vaccine and that the risk of getting the vaccine is less than the risk of having the infection. Thank you.

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

Dr. Bernstein: Yeah. This is just a question, and then maybe I should know the answer, but was the submission for BLA, was it a surprise to the FDA? Or is this normal that people, that industry would present interim data that's to some extent incomplete at the moment given their original study that they've been working on. Is that, was this initiated by the company? Was the FDA asking for an interim analysis? I was just wondering what the logistics were.

Dr. Peart: That's a great question. So as a standard for all submissions, companies are required to meet specific criteria before they can submit to the FDA their application. Once we receive their application, we then review their application. And the application submission is typically based off of predefined criteria that the company has established and has discussed with the FDA. Now, the question of whether or not companies have come in previously with interim analyses, the answer is yes. There have been examples of vaccines in the past that have used case driven and interim analyses to meet their specific endpoints. And so that's exactly what. Dr. Kaslow was mentioning is that, while this application has met criteria for submission and for our

review, we really are eager to continue this discussion that the advisory committee is to help guide us in our decisions going forward. Thank you.

Dr. El Sahly: Dr. Cohen.

Dr. Cohen: Thank you. I'm sorry, Tippi. this is a little bit of an off-base question, but I'm wondering if anybody from the FDA can remind us what happened with the, I believe it was the two dose hepatitis B vaccine, where there was a similar, very, very small but important signal in the original safety trial. I think my question is, has there been an example of FDA asking for additional safety analysis or increasing the size of the safety analysis with these small but potentially important signals, or have you always relied on post-marketing data, which is obviously going to be the fastest and easiest way to detect an increased risk?

Dr. Peart: Hi, can you please repeat that question? One second. Can you repeat that question for us please?

Dr. Cohen: Sure, sure. I think I'm asking if there's ever been a time where, regarding a small but potentially very important safety risk in a large clinical trial, if there's ever been a time when FDA has gone back and asked the company to expand the size of their vaccinated population just to assess safety.

Dr. Toerner: Yes. Hi, good afternoon. My name is Joe Toerner. I'm the Acting Deputy Office Director of Office of Vaccine Research and Review. In my previous roles at FDA, I have been involved in post-marketing activities. And I don't have a specific example in response to your question, but just to say, in general, when FDA is considering a post-marketing requirement — and as you know, FDA now has the authority to require post-marketing studies. I can tell you that when FDA is discussing with applicants about the context of post-marketing studies, that the answer to the safety question really should, should the, in other words, the post-marketing study

should be able to answer and best characterize the safety signal in the post-market setting. So in addition to routine pharmacovigilance, that's done for any post licensure vaccine.

There is also an ability for FDA to require post-marketing studies specifically to best characterize an adverse event signal. And so I think, you know what? We want to hear from your vote and your discussion today is your opinion of this of the safety data that we're under reviewed by FDA currently, and what is your best opinion so that FDA can move forward with the BLA review of safety and efficacy in this application. Thank you.

Dr. El Sahly: Thank you, Dr. Toerner. So, as I understand it is weighing on the data as is not on the data as might be in the future. Right? Okay. Dr. Feikin?

Dr. Feikin: Yeah, hi. I asked some questions around this issue of co-administration with influenza vaccine. And here, and maybe to get some clarity from FDA on sort of what the difference is between what we vote on and what ACIP votes on. You know, I take Dr. Cohen's comment that, in practice, this vaccine would likely be given at the same time as an influenza vaccine.

But in theory, it doesn't have to be given at the same time. And whether we are, certainly as ACIP when they make recommendations on policy, they would consider the practical features of how the vaccine would be optimally used. But for us voting for VRBPAC, are we to consider the policy and the implications of how these vaccines will be used, or rather, how they work, given the data that we've seen today? Because it is possible that we could just evaluate the efficacy data given what we've seen today. And that ACIP could then say, well, we don't have enough co-administration data to recommend use with influenza vaccine. So just to get some clarity on how we should be viewing this, as a strictly sort of vaccine performance type vote, or are we actually to consider policy here?

And I do notice from the report that the data on the co-administration study should be available by Q2 2023. So I guess the question there is, if were to wait to get that data, what would be the timelines for the next RSV season? Would that be too late? Which I think is of some consideration here. Dr. Peart: Yes. Thank you. So thank you for that clarifying question. So exactly as you stated, our goal for this committee is that you vote on the data as is. Our job as the regulators would be to determine whether or not the vaccine is safe and effective. And we are hoping for your advice in that regard. The ACIP would do additional voting subsequently to determine who, when, and et cetera might receive the vaccine. I hope that answered your question. Did you have a follow up question? Sorry, I might have missed it.

Dr. Feikin: It was just a comment that the data on the immunogenicity, sorry, on the co-administration would be available by Q2 2023. And what that would do to the timelines for a potential approval of this vaccine.

Dr. Peart: I can only speak to the data that we do have available at this time. However Dr. Marks is also on the line, and I'd like to turn the microphone to him for a moment. Thank you.

Dr. Marks: Thanks. And I'm sorry that I'm not able to be on camera. I think again, we have to judge this on its own. And we are not in a position that at this point to require a co-administration study. We have to essentially look at what we have in front of us and look at the benefits and risk for this particular vaccine given a problem that… You know, I think the issue here that, and this goes back to the question about why are we talking about this now, it's because obviously RSV is a pretty serious respiratory infection. And so this was the reason for trying to, I think where the sponsors tried to move forward with this given the earlier part of this season where there was a pretty big scare with RSV. So I think there is some rationale of what's going on in the background here for some urgency to having an RSV vaccine. And the Agency, based on your

feedback, can use a variety of different tools including different approval strategies and as well as potentially requiring post-marketing studies to help clarify remaining uncertainties. Over.

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

Dr. Janes: Thank you. I have two data questions that are prompted by this discussion that could provide a little more evidence on the issue of potential interference with the immune responses to the flu vaccine. I wonder, for the sponsor, whether or not there is a sort of broad ILI endpoint that was captured in this study that would include both potentially RSV infections as well as influenza infections? That might shed some light in terms of the overall impact the vaccine on influenza-like illness. And relatedly, whether there's data in the Phase Three study on the extent of flu vaccination? That might help interpret that overall endpoint. Thank you.

Dr. Gurtman: Yeah. Is Alejandra Gurtman. I just want to check that you can hear me.

Dr. El Sahly: We can hear you.

Dr. Gurtman: Yeah. Okay. Thank you. So the study was designed, since we didn't have information about the flu vaccine, to not allow co-administration of the vaccine at the same time. So we have a temporary delay criteria, for which the two vaccines could not be given together. And if they were given together, that will consider the protocol violation. In terms of collecting information, we tested PCR for RSV, and we collected information if the testing was done for medical care and not as part of the study. And at this time, I do not have information about the flu. I do have some information about Covid, how prevalent Covid was when we're doing the study. But we can go back definitely and look at diagnosis of flu, influenza, in participants in the study.

Dr. El Sahly: Any final thoughts, additional thoughts, questions. Dr. Paydar, should we be voting now? I don't see any raised hands, unless anyone from the FDA needs to make a final comment, then we can proceed.

Dr. Kaslow: And Dr. El Sahly, so no, thank you. Thank you to the committee for a very robust discussion on the safety topic. I do think it would be useful to vote on the question now.

Dr. Paydar: Right. Hana, I'll go ahead and read the instructions for the voting, and then we will begin. Only our nine regular members and three temporary voting members, a total of 12, will be voting in today's meeting. With regards to the voting process, Dr. El Sahly will read the final voting question for the record, and afterwards, all regular voting members and temporary voting members will cast their vote by selecting one of the voting options: yes, no, or abstain. You'll have one minute to cast your vote after the question is read. Please note that once you have cast your vote, you may change your vote within the one-minute timeframe. However, once the poll is closed, all votes will be considered final. Once all the votes have been placed, we'll broadcast the results and read the individual votes aloud for the public record. Does anyone have any questions related to the voting process before we begin? Anyone? We're good. Okay, Dr. El Sahly, if you could please read the voting question number one for the record.

Dr. El Sahly: Sure. Are the available data adequate to support the safety of ABRYSVO RSV Pre-F when administered to individual 60 years of age and older for the prevention of lower respiratory tract disease caused by RSV?

Dr. Paydar: Thank you. At this point Derek will move all the non-voting members outside the main room. For folks who are non-voting, please do not log out of Zoom. We'll be back in few minutes. Thank you so much.

Voting Question #1 Results and Explanations

We are ready to display. Great. Thank you, Derek. So there are 12 total voting members for today's meeting. 58%, 7 out of 12, have voted yes. 33% have voted no, and 8% have abstained from voting. If I could see the Excel to read for the recording and for the public record. Okay. So at this point I'm going to read the votes one by one for the public record.

David Kim voted yes. Marie Griffin, no. Steven Pergam, yes. Henry Bernstein, no. Stanley Perlman, abstain. Dr. El Sahly, chair, no. Jay Portnoy, yes. Adam Berger, yes. Holly Janes, yes. James Hildreth, no. Daniel Feikin, yes. Amanda Cohen, yes. Dr. El Sahly, if you would like to begin the voting explanation for voting question one, that would be great. Thank you.

Dr. El Sahly: Sure. I will go down the list as displayed. Dr. Kim.

Dr. Kim: Thank you. I voted yes. And as I indicated earlier, we have the data that we have, and then were asked to make a decision based on the data that we have. So I was interpreting the question very narrowly. So I wasn't necessarily taking into consideration what ifs or taking the consideration other data that might be forthcoming. So for what we have today, and given the charge that we are given today, I felt compelled to say yes, because the information we have does encourage us to be able to proceed with the with the use of vaccine based on its safety data.

Dr. El Sahly: Dr. Griffin.

Dr. Griffin: Yeah, I had, you know, the data we have today, I guess. There's 1 in 9,000 people had GBS, which is really concerning. We don't have administration on data on co-administration,

which is a safety issue, and we don't have information on repeat vaccination, which is also a potential safety issue. So I feel like we don't have… I'm not assured of the safety of this vaccine.

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

Dr. Pergam: Yeah, I'm sort of in the same camp as Dr. Kim, where I sort of looked at the data we had available. I'm concerned about the flu vaccine, at least what has been discussed. But without seeing data, I didn't feel like I could include that as part of my discussion and my thought process. I think in order to really get the, the crux of the GBS, it's almost an impossibility without post-marketing data for the small number of cases that would be seen. And even if we did another 40,000 patients with this study and we saw no cases, would that still mean there's no potential risk? I think that's a hard decision to make. So I felt compelled that the data was safe, although clearly more work needs to be done in that post-marketing surveillance, which I think they outlined well and would work really closely with the FDA to accomplish.

Dr. El Sahly: Dr. Bernstein.

Dr. Bernstein: Yes. Thank you, Dr. El Sahly. I voted no because I am concerned about the safety signal. And if it was really just the safety signal, I might have been convinced based on the data discussed today, that we could have, that the safety data was adequate. But I am really concerned about the co-administration, as well, with flu vaccine and with co-administration with Covid vaccine. These respiratory viruses, we need as many of the public vaccinated as possible, and I would not want to take two steps forward and three steps back if there was a real problem with co-administration.

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

Dr. Perlman: Yeah, I think I had the same opinions as other people, and I ended up more wishy-washy. So abstaining. Yes. I think that I'm most concerned about these things like the GBS and

maybe the atrial fib. On the other hand, I also don't think we're going to get the information without a post-marketing study, so that's why I came out as an abstain.

Dr. El Sahly: Dr. Portnoy.

Dr. Portnoy: I kind of agree with the other people who voted yes. I felt comforted that there was a pretty large number of people who were exposed to the vaccine, and there were no obvious, or were significant signals that occurred in those individuals. There always is a possibility that less frequent adverse events like GBS could show up over time. But you can go for a very long time before you can identify those very infrequent events, and I don't think that it's necessary to wait for that. They'll show up if they're going to show up. The data that we have right now to consider, though, did not show any significant adverse problems, so I felt comfortable voting yes on this question.

Dr. El Sahly: Dr. Berger.

Dr. Berger: I'm not sure I can add any more than what everyone else who's voted yes before me has already stated. You know, I think I agree with where everyone is. I think I do have concern, clearly, about the safety signals that were detected in the studies. I do think the post-marketing surveillance studies are where we're going to get better answers to that. You know, the fact is, and I think a couple people have already stated this, that data is not going to be coming from a trial. It is going to be resting on that post-marketing surveillance. So at this point, I think in terms of whether the safety, the data we have is going to be adequate. It is the data we have.

And at this point, I think I agree with Dr. Portnoy, he stated nicely that the signals that we're seeing from other types of scenarios are not seen in the data itself. The limited signals we do have, we definitely need a much larger population to be able to see whether those are real or what the actual amounts are that they're going to be. There are ratios that will come out for those.

So you know, from that, I felt that I could vote yes at this point, with a heavy lean towards the real requirements of that post-market surveillance study.

Dr. El Sahly: Dr. Janes.

Dr. Janes: I agree with the comments that were just made and my rationale for the safety determinations as it pertains to the Guillain-Barre and additional potential safety signals in terms of the potential interference with flu vaccine immune responses. I guess I came down on interpreting quite literally the safety package that was presented here, which basically pertains to safety and efficacy of the vaccine when not administered concurrent with flu vaccination. And in that context, I felt that this was a reasonable package of safety, and ultimately that the potential interference is a very tricky and complicated question. But I guess I view it more as an implementation question as opposed to pertinent to our considerations here.

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

Dr. Hildreth: Thank you. I voted no, because I'm concerned about the Guillain-Barre signal. I'm also concerned that the public is hypersensitive to using post-marketing to answer some of these questions because it makes it feel like they're being experimented on. And that's a real concern about the trust that the public has for the FDA. So that needs to be protected. So I think we need to do everything we can to make sure the vaccines are safe before we send them out to the public in large numbers. So that's why I voted no. Thank you.

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

Dr. Feikin: I voted yes. I feel like as others have stated, for GBS being a rare complication, that we're just not going to be able to the data we need to make a decision, except for post-marketing surveillance where we need millions of people to detect a safety signal there. And even though this is all about safety, I can't help but think about the risk benefit analysis and ratio

of the amount of disease, severe disease potentially, that could be prevented by this vaccine. I also agree with Dr. James that, to me, the co-administration is really a question of implementation and optimal use policy rather than one of safety. So I think that would not concern us here today in this vote. Thank you.

Dr. El Sahly: Dr. Cohen.

Dr. Cohen: Thank you. This was actually a very challenging vote for me today. I did land at yes. I think if you take what Dr. Hildreth and Dr. Feikin said, I felt both of those things very strongly. And I think Dr. Hildreth just Illustrated the concern I have about post-marketing surveillance. But also understanding that it really is going to be the only way to get at the GBS question quickly, and at the same time, be able to use a vaccine that will protect against what can be a very serious disease and older adults. I do hope and know that FDA will do a really strong job at both ensuring that the post-marketing surveillance is good for this vaccine if it is approved.

But I tried to take myself out of this question of, what will this do for vaccine confidence? Because I know we're in this moment of significant lack of vaccine confidence, and we need to maintain that. But I also think we need to maintain our same scientific perspective that we did prior to some of these real challenges we're having with vaccine confidence in order to most effectively use vaccines. So it was a struggle of for me, but I voted yes.

Dr. El Sahly: Well, thank you all. I will explain my vote Dr. Bernstein and Perlman expressed my viewpoint precisely. And Dr. Griffin. It was a 1 in 9,000 risk of GBS, which is concerning. And while the issue of co-admin is an implementation question. We were given information in the briefing document that there is some type of interference. We don't know the magnitude, we don't know the extent of it the confidence interval around that particular interference, and the data were not shared, so we can make at least maybe dismiss, maybe, this data. I don't know. I

was left with the idea that there is interference, and whether we like it or not, this vaccine is going to be given in the fall around the time of administration of influenza. So knowing that there are outstanding data that maybe can inform this safety question well, but we don't have it, I said, no, the data are not adequate to reassure of the safety. I guess I interpreted it narrowly, just in the opposite direction.

Voting Question #2

Dr. El Sahly: Well, thank you all. We now move to the next question. Are the available data adequate to support the effectiveness of ABRYSVO RSV Pre-F for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older? We will do the same process whereby each committee member will share their viewpoint of the interpretation of the data we saw today pertaining to effectiveness. And I see hands. We begin with Dr. Griffin.

Dr. Griffin: Yeah, I want to share other people's sort of amazement at how well this vaccine does work for preventing disease. And to finally have an effective RSV vaccine is really great. You know, it would be nice to have data on hospitalizations, but even the data on prevention of medical care visits is really important. And about, I guess 4 or 5% of us get RSV every year. And so, yeah, it would be great to have a vaccine that could prevent those more mild illnesses as well as hospitalizations. So, and I think they did meet their primary endpoint. So I think there's a lot of, the data does support the effectiveness of this vaccine. It's just the population was underrepresented by people who could most benefit from the vaccine, but the data that we see is great.

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

Dr. Pergam: I think I sort of stated a lot of my comments before in the prior question, but I'll just reiterate. I think the data's exciting in terms of what it shows and the potential for an RSV vaccine is highly exciting. Primarily the data we have in front of us for adults, but also the potential that a vaccine of this potential could have a major effect in children. Obviously, that's not what we're talking about today. But I think what's troubling is just the inability to really assess true efficacy in the population at highest risk. I just don't feel like that is well linked in the data, I think as you pointed out, 1% with CHF, 5% with COPD. Those are the high-risk populations that are really going to develop complications, and you would expect to see with hospitalizations and major morbidity. There's obviously no immunosuppressed patient patients in this population who are very at risk for developing complications.

And then, you know, I think there's a lot more data for this second year to find out how long this efficacy lasts. And it feels like that data is literally like a week away from being made available, but we just don't have it. And some of this feels like we're voting on this prematurely without all of the information in front of us. And that goes for the flu vaccine and RSV vaccine combination. So I'm struck because I know how important this vaccine is to prevention, but I don't feel like the timing of this vote is necessarily the right time for me to fully be supportive this efficacy. And I'd like to see more data.

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

Dr. Portnoy: Thank you. I pretty much agree with what Dr. Pergam says. I'm desperately eager to have a vaccine that works for RSV. This has been terrible disease my whole career. I would love to see it. No doubt about it. My concern is that so few patients were actually infected by RSV in this study that if just a few of the placebo patients, right, I guess a few of the actively vaccinated patients had actually developed RSV, the confidence interval would've gone past the

20%, and this would've been statistically insignificant. The numbers of patients are so small in this study that I just don't have confidence in the statistics, even though they're statistically significant. I'm very skeptical about that. I'm concerned that there could be a type one or two error, whatever kind of error that would be. And I think that it would be much better if this vaccine could be considered after the study was completely done, because I think more patients would've been included. There would've been time for more complete analysis. It would've been more robust numbers. The confidence intervals might have been a little bit narrower, which would've given me more comfort that this vaccine actually works.

This is not an emergency use authorization. If we were in the middle of Covid and we needed a vaccine immediately, or people are dying, and I know that people are dying from RSV, but it's not like Covid. It's not an emergency use authorization. We can take the time to finish the studies and get the information we need before licensing this product going forward. And so I remain a little bit skeptical given the data that we have. Thank you.

Dr. El Sahly: Thank you, Dr. Portnoy. I do not see… Oh, here we go, Dr. Cohen.

Dr. Cohen: I will just reiterate what everyone has said so far. I feel like this is not great timing to be asking this question right now, whereas with the safety data, you weren't going to get more safety data. This data is actually on the cusp of being available and will be incredibly influential in terms of both increasing the confidence of the efficacy estimates, as well as potentially helping us understand any sort of duration of protection issues, at least through this time. And so it feels like there is not a reason to… it feels like we are not in a state of crisis, and we can wait for this additional data to be presented or shared. At which time, I'm really hopeful that the data will support that the vaccine is as effective as it appears to be so far.

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

Dr. Bernstein: Thanks. I agree with what my colleagues have said. I kind of feel that it's a little premature to be moving in this direction so quickly. I kind of feel we waited decades to come up with an RSV vaccine, and I feel that there's a modest amount of data on the most vulnerable populations. There's not efficacy as far as preventing hospitalization and death in those that are most vulnerable. And I just think there's more data that's, as Dr. Cohen said, that's on the cusp. And I just think that it's a little early for us to be suggesting that we have adequate data to support the effectiveness of the vaccine at this point.

Dr. El Sahly: Okay. Thank you. I'm going to go down the name list. I don't see any more hands, Dr. Berger.

Dr. Berger: Thanks, Dr. El Sahly. I think I'm in the boat with everybody else. I would love to see more data available to be able to make this decision at this point. But it also is an unmet need. You know, we've not had an RSV vaccine at all. This would be potentially able to protect older individuals. Again, we're missing a lot of the data to show that it really is effective. But, I mean, the data that we've seen though is, from a preliminary standpoint, it does look great. You know, I think I do agree with Dr. Griffin in terms of that assessment. The efficacy rates above 66%, above 85% for greater than three symptoms you know is very exciting to see.

Should we be voting at this point? I think that's really the question that everyone is coming to, and I guess I do have a question that might be better addressed by FDA. But I guess where I'd be interested is, depending on what happens, is there a potential of having this pushed out? To hold on this question until the data actually is finished? I mean, I think, as others have pointed out, it's just around the corner. And I guess the question is whether or not, could this question just be held until that data is available? And then the committee actually can discuss. I

don't obviously know the answer to that question, but again, I think that's really an FDA question at this point.

Dr. El Sahly: Dr. Kaslow, are you available to answer the question, or Dr. Peart, maybe?

Dr. Kaslow: Thank you, Dr. Berger, for that question. That's exactly the question we're asking in this voting question, and we do take it literally. Are the available data adequate to support the effectiveness for the pre, for today? That's the question we're asking.

Dr. El Sahly: Okay. So I guess the answer is, as before, just vote on the data as presented to you, even though we know the study's incomplete.

Dr. Kaslow: That's correct.

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

Dr. Janes: Again, I guess just one comment and follow up to some of the perspectives that have been shared. I guess it's not clear to me that, or to what extent, additional follow up of this study through the second season would address all of the remaining questions around efficacy. It seems to me that many of these questions are sort of baked in by the trial design and by the population that's been enrolled here. As Dr. El Sahly has pointed out, there are very few individuals that were enrolled that were immunocompromised, had the eligibility criteria dictated not enrolling individuals without stable preexisting conditions, there are, I think, just about 5% of participants above the age of 80. And so those questions I don't think will ever be addressed with this study population. The question around durability of vaccine efficacy is one that could be addressed with additional follow up. I guess I was somewhat reassured by the data that the sponsor shared that have not been FDA reviewed, but were preliminary data, suggesting that the vaccine efficacy estimates were stable and not appreciably different when one included all the data to date.

And in terms of the severe endpoint, I don't recall precisely how many severe disease endpoints there were that accrued, except that there weren't the 12 that would've been required to meet the criteria for performing the interim analysis. Again, I question whether or not there would be sufficient numbers of severe disease endpoints, even with the second season of data, to reliably evaluate efficacy against that critical endpoint. So I guess that's all I'll share for now.

Dr. El Sahly: Thank you. So Dr. Janes, I just want to clarify that the additional data shared by the sponsor included a few more cases from season one.

But, you know, we had a very early, very intense RSV season and definitely way more than 44 cases. But yeah, I just want to clarify that.

Dr. Janes: Thank you.

Dr. El Sahly: Thank you. Okay. Keep going down the list. Dr. Feikin.

Dr. Feikin: Yes. I mean, to me, if I just read the voting question, which is I think what we're being asked to vote on, I feel like there was sufficient data presented to answer this question in the positive. Do I wish that they had enrolled more people in their eighties, where the real risk of hospitalization goes up? Yes. Do I wish they had enrolled more people with underlying illness? Yes. But I think we do have some signals that, for 80-year-olds, that the trend in the efficacy was in the right direction along the lines of the other age groups with wide conference intervals. And the same with those who are in a severe risk group. I think we saw a similar. And I do think that the primary efficacy analysis was stated to be the first RSV season, not the second RSV season. So while I think it will be interesting and useful from a programmatic standpoint to see if there's durability of protection into that second season, I don't think that is the primary question in the way that the data was analyzed here.

And the last point I wanted to make is I think it's unfortunate that this happened during the Covid pandemic. And we all know that rates of RSV were decreased because of all the non-pharmaceutical interventions. I think it's unfortunate because they didn't get enough severe cases because of that. I think we do know from other respiratory viral vaccines that they do tend to have higher efficacy against the more severe cases. And if this vaccine works similarly to those other vaccines, we would expect that for severe disease, hospitalization, we should see at least similar efficacy, if not greater, rather than lower efficacy. Over.

Dr. El Sahly: Dr. Hildreth.

Dr. Hildreth: Thank you. I agree with my colleague who just spoke that I think there's sufficient data to vote yes on this question. I also wish there were more enrollees, participants, who are 80 years or older to have more data in that age group. But I think there's sufficient data to say that the efficacy of the vaccine is sufficient to prevent lower tract disease. So my vote will be yes.

Dr. El Sahly: Okay, Dr. Kim.

Dr. Kim: Well thank you. No, for the clinical trial here, I'm looking at looking at the question of was the primary point addressed and met? And the answer is yes. FDA analysis confirmed that. And with that said, whether it's preliminary or final, I have to ask a question, what is the alternative? And that is, if the vote is no, and a vaccine, which admittedly I think we say is it's a good vaccine that can and perhaps should be used, is not available for the, let's say, for the upcoming RSV season or perhaps even sooner.

And the off chance that it might be injected inter-season. Then we have in terms of public health implication, we would have people who were unnecessarily impacted adversely by not having the vaccine available. So considering that other possibility, how should we go?

If we rephrase the available data to say, if this is a final data and the only data that we have, then how would we vote? And honestly, if the data that we currently have is preliminary, and it's not like we're going to get additional study subject enrolled, and there, there are certain projections, of course. It is not going to be... Do we expect reasonably a vastly different outcome than the analyses that have been completed? And so weighing all those possibilities, and again, thinking about this voting question as narrowly as what's been written then I think that there is evidence to support the support the notion that the effectiveness of the vaccine against RSV is rather profound. So that would lead me to the decision that I will make when we take the vote.

Dr. El Sahly: Okay. Dr. Perlman.

Dr. Perlman: Yeah, so I agree with what my colleagues have said up until now. I am going to vote yes for this, because I think about a couple of things. So first, when the COVID-19 vaccine was being first put out, were hoping for efficacy of 50%. And here this vaccine is above 50%. Now it's a not the ideal population to have been studied. But as opposed to safety, if it turns out that this isn't quite as effective as we thought, I don't think that anyone is going to be hurt, which is what I was worried about with the biosafety. And I think a lot of people will be helped. And if there's no safety issues, I think we'll find out if people who are really compromised can mount a decent response to this vaccine. Because we don't even know that really. And we want to find that out. But I think that the data we have right now is adequate for this general population, which isn't the ideal population. But that's what I'm thinking.

Dr. El Sahly: Thank you, Dr. Perlman. I'm trying to see if I skipped anyone. No, I think everyone had an opportunity to weigh in. Correct? So, okay, it's my turn at the end. As presented, yes. The vaccine does prevent lower respiratory disease in a generally healthy 60-year-old and older population. I know on the issue of safety, everyone said these are the data

we're going to get, but to me it's on the efficacy. These are the only data we're going to get. Unfortunately the populations enrolled was not enriched for COPD and CHF, and these are the individuals who would've had significant disease with this virus. I know that these statistics are predefined in terms of how many cases would lead to the analysis, and that we have utilized this approach with other vaccines, but also in a disease as prevalent and as ubiquitous as RSV, also making decisions based on 44 cases kind of feels also just too small a number of cases. But it was preset with the Agency in advance.

The issue of durability is very important, and the RSV season is complete almost, so we should have those data from season two. What happens when antibodies wane? Do we lose the efficacy? Is it maintained against the outcomes of interest? You know, this has to do with the fact that the study was not completed prior to the submission. But then again it seems that it was negotiated, or acceptable. So these are the thoughts in my mind when I'm looking at the effectiveness of this product. I see one hand. Dr. Bernstein.

Dr. Bernstein: Yeah, I just had a question, because one of the struggles that I'm having, and maybe colleagues around the table can weigh in. I kind of feel that the way this has been presented is that there's a large unmet need, but the unmet need is for vulnerable populations. And this study really does not answer that question. And although the efficacy is rather high, there are some wide confidence intervals. But I just, I kind of feel the unmet need, this is the wrong population necessarily, that the VE is addressing. So I'm sort of wrestling with that.

Dr. El Sahly: I agree with you, Dr. Bernstein. The population where the vaccine is going to potentially have the biggest impact is less represented in this study. Dr. Griffin.

Dr. Griffin: Yeah, I just want to say I agree with that. And it’s really concerning because, I mean, my answer to this will be yes, but I feel like it's pre-licensure that we are able to get our

best data. And it's really, we're playing catch up if we have to get efficacy data post-licensure, or post-recommendation, is even harder. And this is a vaccine that would potentially be recommended for every older person for every year. I mean, it's a huge market for forever, maybe. So I just feel like, wow, it would be really, we played catch up with flu vaccine forever, because we never had the clinical trials. And I feel like this is an opportunity to have more information before licensure, before recommendations. So.

Dr. El Sahly: But, if I may ask, how would that be? In a new trial that enriches for individuals older than 70 and individuals with COPD, CHF, for example, or?

Dr. Griffin: Yeah. I don't think that would be unreasonable for a vaccine that's going to be used for every, or going to be recommend, could be recommended for every older person every year.

I don't think that's, and I think, yeah, maybe it makes sense to do a trial in the healthier people first. But I think the risk benefit would be much, much better for people 70 and older people who are frail, in a nursing home, CHF, COPD, people who have had pneumonia, who are going to get pneumonia again. Yeah, I think there's another study, is not unreasonable.

Dr. El Sahly: But however, that doesn't… I guess I'm sharing the same concerns, of course, as you have expressed, but that doesn't help us with how we're going to answer the question on hand based on the trial we have. Knowing that the population that's going to get the vaccine is going to be different, and the unmet need, as Dr. Bernstein put it, is in a different population.

Dr. Griffin: Yeah. Well, I think FDA needs to listen to these other comments and not just the answers to the voting questions.

Dr. El Sahly: Yeah, I agree. Thank you, Dr. Griffin. Dr. Cohen.

Dr. Cohen: Thanks. Yeah, I totally agree with Dr. Griffin. It does feel like there's this… This is not an EUA, this is a BLA that's being looked at right now. So this is a permanent sort of decision, unless — I know FDA can always change. I know they can always adapt to changing data. But I do feel like this is a pretty large decision to license this vaccine.

And I know that we don't always have the right group of people in our studies, and that that needs to change. I believe that the risk benefit in those groups that Dr. Griffin just discussed will be good for this vaccine. I'm concerned about what happens next year, for example, if we vaccinate a whole population of people this year and we have no data on what they're going to need next year, if they're going to need a vaccine. We're going to be very stuck without the completion, or we'll have just had the completion of this data, but we won't be able to look at a booster dose. I just feel like we're going to constantly being playing catch-up from a boosting perspective, or an annual vaccination perspective. And we're always going to have limited data, because we pushed ahead with vaccinating based off of this interim analysis. But I also do agree that this vaccine looks like it works really well based on the available data.

Dr. El Sahly: Dr. Kaslow?

Dr. Kaslow: So I just wanted to be clear with everyone that this is the primary analysis for the primary endpoint of this study. Because I'm hearing interim analysis and preliminary, just wanted to be crystal clear that, as specified in the study, this is the primary analysis for the primary endpoint. Over.

Dr. El Sahly: Dr. Cohen.

Dr. Cohen: Sorry that was from earlier. Thank you for that helpful clarification though, Dr. Kaslow. Dr. El Sahly: Okay. I think I don't see any additional requests or hands. We can proceed with the voting.

Dr. Paydar: Okay, so just again, this is for the public record. I have to say this. Our nine regular members and three temporary voting members, a total of 12, will be voting. Dr. El Sahly will read the voting question number two for the record. You have one minute to vote. And voting options are yes, no, or abstain. So if Dr. El Sahly, if you would be kind to read the second voting question for the public record.

Dr. El Sahly: Voting question number two, are the available data adequate to support the effectiveness of ABRYSVO RSV Pre-F for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older? Great. Thank you. At this point, Derek, we'll move all the non-voting members out of the main room. Please do not log out of the Zoom. We'll be back in few minutes. Derek, let us know when all the voting members are present.

Voting Question #2 Results and Explanations

Dr. Paydar: Great. Thank you, Derek. So what we have is we have 7 out of 12 members who have voted yes. 4 out of 12 have voted no, and 1 out of 12 has abstained. For the public record, here I go reading the one by one.

Okay. Dr. Jay Portnoy, no. Dr. Stanley Perlman, yes. Dr. Marie Griffin, yes. Dr. Holly Janes, yes. Dr. James Hildreth, yes. Dr. Henry Bernstein, no. Dr. David Kim, yes. Dr. Hana El Sahly, yes. Dr. Adam Berger, abstain. Dr. Daniel Feikin, yes. Dr. Steven Pergam, no. Dr. Amanda Cohen, no. That concludes my reading of the votes. Dr. El Sahly, I'll hand the meeting back to you for discussing the voting questions.

Dr. El Sahly: We'll go down the list. Dr. Portnoy.

Dr. Portnoy: Great, thanks. I had a split vote. I voted no for this question because, as I said before, there are such small numbers that one or two cases in the opposite direction could have changed the results. And I'm very concerned about that. I think it's rushed. I would really like to have seen them complete the study, get at least another year's worth of RSV data, and then I would feel more comfortable about the results. Given that fact, I'm okay with these results, because statistically speaking, it did show efficacy. So I'll leave it at that. Thank you,

Dr. El Sahly: Dr. Perlman.

Dr. Perlman: I don't have much to add beyond what I said just a few minutes ago. I think that for the primary goal of this study, I think the endpoint was met. I also think that I wish also we had more numbers, that we had more different kinds of people in the study. So it's imperfect, but I think it met its primary endpoint.

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

Dr. Griffin: Yeah, I agree with that. The primary endpoint was met. It prevented lower respiratory tract disease. I do want to point out that in the study population, there were only two RSV hospitalizations prevented, and there were two GBS hospitalizations that were caused. So as far as serious outcomes in this study, it's really tough, you know? So.

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

Dr. Janes: Thank you. I voted yes. First, on the population, I guess I interpreted the question quite literally to be whether or not this supportive data regarding efficacy in the population of adults aged 60 or older. And so on that basis, for that population, I thought that this was a reasonable data package.

Notwithstanding the questions have been raised around potential efficacy in other key populations with the burden of RSV-associated disease. And then in terms of the strength of the statistical evidence, I also share some concerns raised by others in terms of there being relatively few primary endpoint events and just one single trial here. And an analysis based on interim analysis that sort of turns into the primary analysis once efficacy is established, but nonetheless an interim analysis. But I guess I was swayed by the high estimates of efficacy, the consistent estimates of efficacy across subgroups, and the fact that the lower bounds of the confidence intervals were not just above 20%, but above 30%, I think in all cases. So gauging the balance in terms of benefits and risks, I voted yes on that basis.

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

Dr. Hildreth: Thank you. I don't have much to add to my colleagues. I think that, based on the question we're asked to address and the data put in front of us, I think the criteria are met. And so I voted yes. Thank you.

Dr. El Sahly: Okay. I guess someone should take note of the enthusiasm of the yeses. Dr. Bernstein.

Dr. Bernstein: Well I'll be enthusiastic about the no. Because I still believe that the vaccine is created to meet unmet needs for vulnerable populations, not healthy people. Yes, it's impressive, the VE against lower respiratory tract disease, but it really didn't do anything for hospitalization or death, which is one of the major things I suspect that we would want from a vaccine in protecting against or preventing respiratory disease. And I think some of the confidence intervals, even for the healthy ones, were kind of wide in my mind. So that's why I voted no.

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

Dr. Kim: Well, I don't have anything more to add than what I said earlier and what I heard from other committee members, I think. But I will say that I look forward to additional data coming in to review, hopefully to further add to the to the guest vote that I just cast.

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

Dr. Berger: So I voted to abstain because that was the one that made sense to me for saying, I'm leaning yes, but I want to see the other data that's about to come out. And it wasn't clear to me which answer actually got you that from the question that was posed. So you know, the abstain here, like I said, is more of a lean yes. But I do have concerns about the 44, that there's only 44 patients we're making these decisions on. And I do understand that still met the pre-specified primary endpoint. I fully understand that. But it's still like the idea that data is just going to be available shortly, you know, I'd like to be able to see that, to make sure that still pans out, as others have stated. The confidence intervals are quite wide in many of these, as I think a couple of people have already pointed out, but a couple of swings the other direction may change the efficacy numbers.

You know, that being said, I do want to just explicitly say, I find the data exciting. I think the idea that we'd be looking at a vaccine efficacy rate of 85% is fantastic. And I certainly hope that pans out. And I, as Dr. Kim just stated, I too look forward to seeing the rest of the data that as it comes in. So that's why I voted abstain.

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

Dr. Feikin: I voted yes. I think the primary endpoint was clearly met. I do feel, like others, that it's disappointing that we don't have more data on the high-risk groups and the severe outcomes, partly by design and partly by circumstance. And I think, like with the post-marketing safety surveillance, it'll be critical to get, if this vaccine does get licensed, that there is robust

post-introduction vaccine effectiveness data and impact data in those high-risk groups against severe outcomes. Because I think how this vaccine will optimally be used is going to be the more challenging question. And I think that will be a work in progress that could take perhaps years and a lot of post-introduction evidence to shape what that looks like. So I think that will be critical.

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

Dr. Pergam: Boy, I'll tell you, this was, considering how we voted on all the Covid vaccines, I think this was probably the most difficult decision I've made in a while. I voted no because I feel like there are too many lingering questions in the data set. Yes, it did meet the primary endpoint per the letter of the law, but there's so much data that is just waiting on the other edge that I think will be informative. I lean no, only because of that information, but in terms of the data that's presented, I'm very much interested in this being a yes. But I think with additional data that becomes an easier decision for me.

I'm really struggling with this because of the importance of what this vaccine means to public health. But I would really encourage the FDA to rethink how they developed this vaccine question and this design of this trial. Because what you hear from all of us is that this did not target the population of interest. And this was in some ways set up to be a population that was maybe a little bit easier to approach and easier to collect data on. But the real importance is the population that is at risk. And I think there was a missed opportunity to develop and design this trial in a way that would make this decision easier for us moving forward.

And it's unfortunate from my view, because I think there's some lingering questions that I think, even with the additional data, we will not get answers to and will lead to a lot of additional work in the post-licensure period.

And then I just want to say, you'll see where I am on the list of voting, and that's how long it took me to think about this. And I think part of that is also because of what Amanda Cohen said, and I imagine she'll probably feel the same, is this is a BLA, it's very different. We're approving this vaccine. And that means it goes to production, it goes out to the public. And I think I want to be very cautious about how we do that. With the EUA and Covid vaccines we were in a pandemic and a very different situation. I think we need to be cautious when we think through this. So that's the reason my vote was no.

Dr. El Sahly: Thank you. Dr. Cohen.

Dr. Cohen: I think I echo Dr. Perkin's comments almost precisely. I also believe that, had we had a little bit more time to see the data that is on the cusp, I would've been a confident yes. And the data that was presented today, I do believe met the endpoint, as we all do. But I feel like we… I think I voted no to try to take a step back and get into our sort of pre-pandemic approach towards vaccines. And I do know that we had a bad RSV season last year, but we've been waiting for these vaccines for decades, and I think the time we could have had to really be confident in this data and get the complete first season data and potentially even understand second season would really… I feel like we're going to get very stuck trying to sort through lots of post-licensure data. When, with a little bit more time, we may have understood the clinical trial data better.

Dr. El Sahly: Thank you, Dr. Cohen. And last, I'll say my rationale for the vote. Again, it took me a while to cast my vote, as well. The as agreed upon with the Agency, and as agreed upon in the statistical analysis plan, the answer is yes. However, I'm going to revisit Covid like some of my colleagues did. When we were designing and implementing the Covid vaccine trials, we had to stop some of the enrollment for a while in order to allow for the at-risk populations to be

represented because when we do a clinical trial, invariably, the healthier, the non-minorities, the ones living in certain areas are the ones who are going to enroll. But they are not necessarily the population in whom the vaccine needs to be implemented. And we followed at the time, actually, FDA guidance that the trials have to mirror the populations at risk. And for this particular trial, I think everyone hears an agreement that this did not take place. And this should be taken into account as the analysis of our discussion takes place at the level of the Agency. Okay. Anything else from any of our members or from the FDA?

Dr. Kaslow: No, not at this time. I think we turn it back to Dr. Paydar to close. I'll have some closing remarks after it goes back to her.

Closing Comments

Dr. Paydar: Thank you, Dr. Kaslow. Please go ahead with your closing remarks,

Dr. Kaslow: Thank you. I'd like to thank the advisory committee for the critical and probing questions in the subsequent voting discussion today. It was quite helpful to hear the discourse on the safety topics, including GBS and other demyelinating disorders, the concomitant vaccine use, atrial fibrillation, and the importance of robustness of the post-marketing studies and surveillance. And also on the efficacy topics, including the durability, the at-risk populations, the post-approval vaccine effectiveness, and correlates of protection.

Input from experts qualified by scientific training and expertise in evaluating evidence on effectiveness and safety of products is really a critical part of the regulatory review process and the advisory committee has served us well today. We look forward to further discussions tomorrow. In the meantime, let me thank the advisory committee meeting staff and also the

technical staff that ran a meeting today for re remarkably flawless meeting today in this virtual environment. Let me also thank the FDA BLA review team and the invited and Open Public Hearing speakers. And finally, we greatly appreciate the time and diligence of the advisory committee members and of our chair, Dr. El Sahly. We'll see everyone tomorrow.

Adjournment

Dr. Paydar: Great. Thank you. Dr. Kaslow for closing comments. I wanted to thank the committee and CBER staff for working so hard to make this meeting a successful meeting as always. I now call the meeting officially adjourned at 4:14 PM Eastern time. Have a wonderful evening. Bye-bye.