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

Participants

Chair	Hana M. El Sahly, M.D.	Professor, Baylor College of Medicine	Houston, TX
Voting Members	Adam C. Berger, Ph.D.	Director, Clinical and Healthcare Research Policy, NIH	Bethesda, MD
	Henry (Hank) Bernstein, D.O., MHCM, FAAP	Professor, Zucker School of Medicine	New Hyde Park, NY
	Amanda Cohn, M.D.	Chief Medical Officer, National Center for Immunizations and Respiratory Diseases, CDC	Atlanta, GA
	Holly Janes, Ph.D.	Professor, Fred Hutch Cancer Center	Seattle, WA
	David Kim, M.D., M.S., M.H.A.	Director, Division of Vaccines, HHS	Washington, DC
	Steven Pergam, M.D.	Professor, Fred Hutchinson Cancer Center	Seattle, WA
	Stanley Perlman, M.D., Ph.D.	Professor, University of Iowa	Iowa City, IA
Consumer Representative	Jay Portnoy, M.D.	Professor, University of Missouri Kansas City School of Medicine	Kansas City, MO
Alternate Industry Representative	Gregg Sylvester, M.D., M.PH.	Vice President of Medical Affairs, Seqirus Inc.	Summit, NJ
Temporary Voting Members	Daniel Feikin, M.D., M.S.P.H.	Respiratory Diseases Consultant	Coppet, Switzerland
	Marie Griffin, M.D., M.P.H	Professor, Vanderbilt University School of Medicine	Nashville, TN
	James Hildreth, Sr., Ph.D., M.D.	President, CEO, Meharry Medical College	Nashville, TN
Guest 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
FDA Participants/Staff	Peter Marks M.D., PhD.	Director, CBER, FDA	Silver Spring, MD

	David C. Kaslow, M.D. (Speaker)	Director, Office of Vaccines Research and Review (OVRR), CBER, FDA	Silver Spring, MD
	Goutam Sen, Ph.D. (Speaker)	Microbiologist, Division of Vaccines and Related Products Applications (DVRPA), OVRR, CBER, FDA	Silver Spring, MD
	Joseph Toerner, M.D., M.P.H.	Acting Deputy Director, OVRR, CBER, FDA	Silver Spring, MD
	Lucia Lee, M.D.	Lead Medical Officer, Clinical Review Branch I, DVRPA, OVRR, CBER, FDA	Silver Spring, MD
	Nadine Peart Akindele, M.D. (Speaker)	Medical Officer, DVRPA, OVRR, CBER, FDA	Silver Spring, MD
	Nicholas Geagan, D.O., STN (Speaker)	Staff Fellow, DVRPA, OVRR, CBER, FDA	Silver Spring, MD
	Santosh Nanda, DVM, Ph.D. (Speaker)	Microbiologist, DVRPA, OVRR, CBER, FDA	Silver Spring, MD
	Sudhakar Agnihothram, B.Pharm., Ph.D.	Biologist, OVRR, CBER, FDA	Silver Spring, MD
Designated Federal Officer (DFO)	Sussan Paydar, Ph.D.	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
Alternate DFO	Valerie Vashio, B. Pharm, RPh, RAC	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
Director	Prabhakara Atreya, Ph.D.	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
Committee Management Specialist	Lisa Johnson	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
Committee Management Officers	Joanne Lipkind, M.S.	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
	Karen Thomas	Division of Scientific Advisors & Consultants, CBER, FDA	Silver Spring, MD
External Speakers	Burton Eller	The National Grange	
	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	

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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

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.