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Center for Biologics Evaluation and Research (CBER)
173rd Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN PUBLIC MEETING

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

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TABLE OF CONTENTS

OPENING REMARKS: CALL TO ORDER AND WELCOME 6

ADMINISTRATIVE ANNOUCEMENTS, ROLL CALL, INTRO OF COMMITTEE, CONFLICT OF INTEREST STATEMENT 9

FDA INTRODUCTION 23

EMERGENCY USE AUTHORIZATION (EUA) REQUEST BY NOVAVAX FOR A VACCINE TO PREVENT COVID-19 IN INDIVIDUALS 18 YEARS OF AGE AND OLDER 25

CURRENT EPIDEMIOLOGY OF COVID-19 AND COVID-19 VACCINATION RATES IN THE UNITED STATES 37

OVERVIEW OF COVID-19 VACCINE ASSOCIATED MYOCARDITIS 59

EMERGENCY USE AUTHORIZATION (EUA) APPLICATION FOR NVX-CoV2373 INTRODUCTION 80

IMMUNOGENICITY AND EFFICACY 90

SAFETY 99

CLINICAL PERSPECTIVE 115

SPONSOR PRESENTATION CONCLUSION 123

FDA REVIEW OF EFFECTIVENESS AND SAFETY OF NOVAVAX COVID-19 VACCINE IN INDIVIDUALS 18 YEARS OF AGE AND OLDER 134

OPEN PUBLIC HEARING 170

ADDITIONAL Q & A REGARDING SPONSOR AND FDA PRESENTATIONS 206

COMMITTEE DISCUSSION AND VOTING 262

MEETING ADJOURNED 299

OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning, and welcome to the 173rd Meeting of the Vaccines and Related Biological Products Advisory Committee Meeting. I'm Mike Kawczynski and I will be helping to facilitate today's meeting, along with my colleagues and our guests.

Please note, this is a live public meeting, so we will be addressing any issues throughout the meeting and if anything does occur, we will make a momentarily stop to make sure that this meeting goes forth successfully. With that being said, I'd like to hand the meeting over to my colleague, Dr. Atreya. Dr. Atreya, if you are ready, let's have you take it away.

DR. PRABHAKARA ATREYA: Mike, I think you need to give it to Dr. Monto.

MR. MICHAEL KAWCZYNSKI: My apologies. All right. So, looks like I'm going to bring both you up here, and Dr. Monto, if you're ready, I'll let you take it away. Here we go.

DR. ARNOLD MONTO: Here I am. Thanks a lot, Mike. I'd like to add my welcome to the 173rd Meeting of the Vaccines and Related Biological Products Advisory Committee of the FDA. Today we are called into session to discuss one topic, Emergency Use Authorization requested by Novavax for a vaccine to prevent COVID-19 in individuals 18 years of age and older.

I'd like to welcome the members, the temporary voting members, including our new temporary voting members, and the interested public, to this meeting. We're going to have a long and very interesting day as we move to our voting questions, which will be acted upon at the end of the day. I'd like to turn the meeting over to our Designated Federal Officer, Praba Atreya, who will be making further introductions and handle some of our housekeeping issues. Over to you, Praba.

DR. PRABHAKARA ATREYA: Thank you, good morning, everyone, this is Praba Atreya, and it is my great honor to serve as the designated federal officer,

that is DFO, for today's 173rd Vaccines and Related Biological Products Advisory Committee Meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, and our Vaccines Advisory Committee I'm really happy to welcome everyone for today's virtual meeting.

Today's Committee will meet in open session to discuss the Emergency Use Authorization, EUA, request by Novavax for a vaccine to prevent COVID-19 in individuals 18 years of age and older. Today's meeting and the topic were announced in the federal register notice that was published on May 31, 2022. At this time I would like to introduce and acknowledge the excellent contributions of the staff and the great team I have in my division in preparing for today's meeting.

Ms. Christina Vert is my co-DFO providing excellent support in all aspects of preparing for and conducting the meeting. Other staff who contributed significantly are Dr. Susan Paydar, Ms. Joanne Lipkind, Ms. Karen Thomas, and Ms. Lisa Wheeler, who also provided excellent support. I also would like to

express our sincere appreciation and gratitude to Mr. Mike Kawczynski in facilitating the meeting today. Also, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one, like all the previous Vaccines Advisory Committee Meetings on the COVID topics.

Please contact in light of any press or media-related questions for today's meeting to the FDAs Office of Media Affairs at FDAOMA, one word, at FDA.hhs.gov. The transcriptionist for today's meeting is Ms. Linda Giles.

ADMINISTRATIVE ANNOUCEMENTS, ROLL CALL, INTRO OF COMMITTEE, CONFLICT OF INTEREST STATEMENT

DR. PRABHAKARA ATREYA: And we will also begin today's meeting by taking a formal roll call for the Committee members and the temporary members. When it is your turn, please turn on your camera and unmute your phone, and then state your first and last name,

and then, when finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slide in which we will begin with the chair, Dr. Arnold Monto. Dr. Monto, can we please start with you?

DR. ARNOLD MONTO: Yes. Thank you, Praba. I'm Arnold Monto. I'm at the University of Michigan School of Public Health where, over many years, I've been working on the prevention and control of respiratory agents, influenza in particular lately, until the coronavirus' came. And we've been looking at those over many years, and now our attention is directed towards these agents. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Monto. Next is Dr. Paula Annunziato.

DR. PAULA ANNUNZIATO: Good morning, my name is Paula Annunziato. I lead Vaccines Global clinical development at Merck. And I'm here today as the non-voting industry representative.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Adam Berger.

DR. ADAM BERGER: Hi, I'm Adam Berger. I'm at the National Institutes of Health and the director of clinical healthcare research policy here. I oversee all of our human subject protections and clinical trial policies. I'm a geneticist by training. Thanks.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Hank Bernstein. We can't hear you, Dr. Bernstein.

DR. HENRY BERNSTEIN: Good morning, my name is Hank Bernstein. I'm a professor of pediatrics at Hofstra/Northwell. I'm a general pediatrician with a special interest in vaccines.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Archana Chatterjee.

DR. ARCHANA CHATTERJEE: Good morning. My name is Archana Chatterjee. I'm the dean of Chicago Medical School and vice president for Medical Affairs at Rosalind Franklin University in North Chicago. I'm a pediatric infectious diseases specialist specializing in the area of vaccines.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr., Captain Amanda Cohn. Go ahead.

DR. AMANDA COHN: Thanks. Good morning, I'm Dr. Amanda Cohn. I'm a pediatrician and an epidemiologist at the Centers for Disease Control and Prevention.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr., Captain David Kim.

DR. DAVID KIM: Good morning. This is David Kim with the Division of Vaccines in the Office of Infectious Disease and HIV/AIDS Policy in the Office of the Assistant Secretary for Health. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Paul Offit.

DR. PAUL OFFIT: Good morning, my name is Paul Offit, I am an attending physician in the Division of Infectious Diseases at Children's Hospital Philadelphia, and a professor of pediatrics at the University of Pennsylvania School of Medicine, and my interest is in the area of vaccines. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Steve Pergam. Dr. Pergam?

DR. STEVEN PERGAM: Oh, sorry. This is Steve

Pergam. I'm a professor at the Fred Hutchinson Cancer Center. And I focus on adult infectious diseases, specifically in the immunosuppressed host.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Jay Portnoy, our consumer representative. Mike, is he available? If not, we'll move on to Dr. Eric Rubin.

DR. ERIC RUBIN: Good morning, Praba, I'm Eric Rubin. I'm at Harvard, the Brigham and Women's Hospital, and the *New England Journal of Medicine*.

DR. PRABHAKARA ATREYA: Thank you. Next, we will do the roll call for our temporary voting members. Dr. Fuller.

DR. A. OVETA FULLER: Good morning, I'm Oveta Fuller, I'm Dr. Oveta Fuller. I'm at the University of Michigan African Studies Center and Department of Microbiology/Immunology. I'm a virologist by training, and I do implementation science in the community.

DR. PRABHAKARA ATREYA: Thank you, Dr. Fuller. Next is Dr. Bruce Gellin.

DR. BRUCE GELLIN: Hi, I'm Bruce Gellin. I'm currently the chief of global public health strategies

for the Rockefeller Foundation. I'm honored to be back as a temporary member of the committee. For 15 years I was the director of what was then called The National Vaccine Program Office at HHS. Thanks.

DR. PRABHAKARA ATREYA: Thank you, Dr. Gellin. The next one is Dr. Jeannette Lee.

DR. JEANNETTE YEN LEE: Yes, good morning, I'm Jeannette Lee. I'm a professor of biostatistics and a member of the Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences. My area is multicenter clinical trials. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Ofer Levy.

DR. OFER LEVY: Hi, good morning, my name is Ofer Levy. I'm a physician scientist and pediatric infectious disease specialist at Boston Children's Hospital. I'm professor of pediatrics at Harvard Medical School, and I direct the precision vaccines program, which conducts research by applying precision medicine concepts to vaccinology.

DR. PRABHAKARA ATREYA: Thank you. Dr.

Marasco, Wayne Marasco. We can't hear you, Dr. Marasco.

DR. WAYNE MARASCO: Sorry, wrong button. I'm Wayne Marasco, professor of medicine at Dana Farber Cancer Institute at Harvard Medical School. I study antiviral antibody immunity to vaccines and natural infection.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Pamela McInnes. We can't hear you, Dr. McInnes.

DR. PAMELA MCINNES: Good morning --

MR. MICHEAL KAWCYNSKI: Give me one second, there we go.

DR. PAMELA MCINNES: -- Pamela McInnes. Retired deputy director of the National Center for Advancing Translational Sciences at the U.S. National Institutes of Health. Good morning.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Cody Meissner.

DR. CODY MEISSNER: Thank you, Praba. Good morning. My name is Cody Meissner. I'm a professor of pediatrics at Tufts University School of Medicine in

Boston. I specialize in infectious disease. As has been announced, Tufts will soon close the children's hospital at the end of this month, and I will have a new professional address. But I want to state that I appreciate the opportunity to participate in the VRBPAC Meeting this morning. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Meissner. Next is Dr. Michael Nelson.

DR. MICHAEL NELSON: I am Mike Nelson, I'm president of the American Board of Allergy and Immunology, and I'm chief of the division of asthma, allergy, and immunology at the University of Virginia. I'm an allergist/immunologist, as you might guess, with special expertise in vaccine adverse events and immune response. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Stanley Perlman.

DR. STANLEY PERLMAN: I'm Dr. Stanley Perlman, I'm a professor of microbiology and immunology, and of pediatrics. I'm a pediatric infectious diseases specialist, and I've been working with coronaviruses

here at the University of Iowa for 40 years.

DR. PRABHAKARA ATREYA: Thank you. Next is Dr. Arthur Reingold.

DR. ARTHUR REINGOLD: Good morning, can you hear me?

DR. PRABHAKARA ATREYA: Yes, yes, go ahead.

DR. ARTHUR REINGOLD: All right. I'm Art Reingold, I'm an infectious disease epidemiologist at the University of California, Berkeley School of Public Health.

DR. PRABHAKARA ATREYA: Thank you. Next is Dr. Mark Sawyer.

MR. MICHAEL KAWCZYNSKI: Sir, you have your phone muted.

DR. PRABHAKARA ATREYA: Can't hear -- yes.

MR. MICHAEL KAWCZYNSKI: You have your own phone muted.

DR. MARK SAWYER: Trying once again. This is Dr. Mark Sawyer, I'm a professor of pediatric infectious disease at the University of California, San Diego. And my expertise is in the public health

aspects of vaccines.

DR. PRABHAKARA ATREYA: Thank you. Last, but not least, Dr. Melinda Wharton.

DR. MELINDA WHARTON: Good morning. I'm an adult infectious disease physician by training, and I currently work as an associate director for vaccine policy at the Centers for Disease Control and Prevention.

DR. PRABHAKARA ATREYA: Great, thank you. So, overall, we have 23 participants in the meeting, 22 voting members and 1 non-voting member. And we have great experience around the table. Thank you so much, and I will now proceed with the reading of the Conflicts of Interest statement for the public record. Thank you. Hold on for a second.

The Food and Drug Administration, FDA, is convening virtually today, June 7, 2022, the 173rd Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC) under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Arnold Monto is serving as the acting voting chair for

today's meeting.

Today on June 7, 2022, the Committee will meet in open session to discuss Emergency Use Authorization request by Novavax for a vaccine to prevent COVID-19 in individuals 18 years of age and older. This topic is determined to be of particular matter involving specific parties. With the exception of the industry representative members, all standing and temporary voting members of the VRBPAC are appointed special government employee (SGEs) or regular government employees (RGEs) from other agencies and are subjected to federal Conflicts of Interest laws and regulations.

The following information on the status of this Committee's compliance with the federal Ethics and Conflict of Interest laws including, but not limited to, 18 U.S. Code Section 208 is being provided to participants in today's meeting and to the public.

Related to the discussions at this meeting, all members, RGE and SGE consultants of this Committee have been screened for potential financial conflicts of their own as well as those imputed to them, including

those of their spouse or minor children and, for the purpose of U.S. 18 Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements or CRADAs, teaching, speaking, writing assignments, patents and royalties, and also their primary employment. These may include interests that are current or under negotiation.

FDA has determined that all members of this Advisory Committee, both regular and temporary members, are in compliance with federal Ethics and the Conflict of Interest laws. Under the 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special government employees and/or regular government employees who have financial conflicts of interest when it is determined that the Agency's need for a special government employee's services outweighs the potential for a conflict of interest created by the financial interest involved. Or when the interest of a regular government employee is not so substantial as to be

deemed likely to affect the integrity of the services which the government may expect from the employee. Based on today's agenda and all financial interests reported by Committee members and consultants, there have been no Conflicts of Interest waivers issued under 18 U.S. Code 208 in connection with this meeting.

We have the following consultants service as temporary voting members. Dr. Oveta Fuller, Dr. Bruce Gellin, Dr. Jeannette Lee, Dr. Ofer Levy, Dr. Wayne Marasco, Dr. Pamela McInnes, Dr. Cody Meissner, Dr. Michael Nelson, Dr. Stanley Perlman, Dr. Art Reingold, Dr. Mark Sawyer, and Dr. Melinda Wharton.

Dr. Paula Annunziato of Merck will serve as the industry representative for today's meeting. Industry representatives are not appointed as special government employees and serve as non-voting members of the Committee only. Industry representatives act on behalf of all the regulated industry and bring general industry perspective to the Committee. Dr. Jay Portnoy is serving as the consumer representative for this Committee. Consumer representatives are appointed

special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the Committee.

The guest speakers for today's meeting are the following: Dr. Heather Scobie, Deputy Team Lead, Surveillance and Analytics Epidemiology Task Force COVID Emergency 19 Emergency Response Team at CDC, Atlanta and Dr., and CAPT. Tom Shimabukuro, Director in the Immunization Safety Office at the Centers for Disease Control and Prevention in Atlanta, Georgia. They are the guest speakers for today.

Disclosure of conflicts of interest for speakers and guest speakers follow applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including open public hearing speakers, to advise the Committee of any financial relationships that they may have with any affected firm and product and, if known, if direct competitors.

We would like to remind the standing and temporary members of the Committee that if the discussions involve any of the products or firms not

already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from the discussion and their exclusion will be noted for the record.

This concludes the reading of my Conflicts of Interest statement for the public record. At this time I would like to hand over the meeting back to our chair, Dr. Arnold Monto. Thank you very much and, Dr. Monto, take it away.

DR. ARNOLD MONTO: Thank you very much, Praba. First, we're going to hear from the director of CBER, Dr. Marks. Take it away, Dr. Marks.

FDA INTRODUCTION

DR. PETER MARKS: Thank you very much. So I just wanted to welcome everyone to today's VRBPAC Meeting. I'm not going to say very much right now, except to welcome everyone. This is our first meeting of a series of several this month to take up some

important topics. We'll look forward to working through these meetings.

We believe that we have done a fair amount of work to solve some of the technical glitches that have essentially haggled us in the past when we've had these meetings, and they hopefully will not be an issue today and we'll hopefully have a very good meeting today. I really look forward to and thank our advisors for their engagement and for our staff's hard work preparing for the meeting, and for everyone's participation today. I will turn it back over to Dr. Monto.

DR. ARNOLD MONTO: Thanks, Dr. Marks, first we're going to be going to hear some presentations from CDC, which will serve as background for our further deliberations. First, we hear from Dr. Heather Scobie, who's going to talk about the current epidemiology of COVID-19 and COVID-19 vaccination rates in the United States. Dr. Scobie.

DR. PRABHAKARA ATREYA: Dr. Monto, I think we need to allow Dr. Sen to speak from FDA before we hear from CDC.

DR. ARNOLD MONTO: Oh, excuse me, I jumped ahead. Thank you, Praba. We hear next from Dr. Sen. Dr. Sen is going to be telling us why we're here and the rules for Emergency Use Authorization. My apologies, Dr. Sen.

EMERGENCY USE AUTHORIZATION (EUA) REQUEST BY NOVAVAX FOR A VACCINE TO PREVENT COVID-19 IN INDIVIDUALS 18 YEARS OF AGE AND OLDER

DR. GOUTAM SEN: Good morning, Dr. Monto, and good morning, everybody. I would like to thank the Committee members for your time to convene here this morning to discuss Novavax COVID-19 vaccine Adjuvanted request for Emergency Use Authorization. My name is Goutam Sen, I'm from Office of Vaccine at CBER FDA. I'll give an overview of the product and today's agenda.

Here is my outline. I'll discuss about SARS-CoV-2 pandemic, then I'll discuss about Novavax COVID-19 vaccine, Adjuvanted and their EUA request for

immunization as a primary series two doses three weeks apart; considerations for EUA of a COVID-19 vaccine; COVID-19 vaccines available for use in the U.S.; overview of today's agenda; voting questions for the Committee.

Since the beginning of the pandemic in early 2020, SARS-CoV-2 has caused over half a billion confirmed cases of COVID-19 worldwide, including over six million deaths. In the United States, SARS-CoV-2 has caused over 84 million reported COVID-19 cases and over one million deaths. Surges in SARS-CoV-2 transmission and COVID-19 cases, hospitalizations, and deaths have been associated with emergence of SARS-CoV-2 variants. For example, Beta, Delta and, more recently, the Omicron, that are more infectious, more virulent, and are more resistant to natural or vaccine-elicited immunity than the prototype strain.

Each 0.5 mL dose of Novavax COVID-19 vaccine, Adjuvanted contains 5 micrograms of recombinant viral spike protein from SARS-CoV-2.1 strain expressed in Sf9 cells co-formulated with Novavax saponin-based Matrix-M

adjuvant 50 micrograms. Proposed use under the EUA: active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The dosing regimen is a two series of two doses of 0.5 mL each, administered intramuscularly three weeks apart. Novavax COVID-19 vaccine also referred to at NVX-CoV2373 during clinical development.

On February 1, 2022, FDA received Novavax's request for Emergency Use Authorization of their COVID-19 vaccine. EUA of Novavax COVID-19 vaccine, Adjuvanted would depend on clinical data to inform benefits and risks; manufacturing and product information to ensure the vaccines quality and consistency. The manufacturing process for Novavax COVID-19 vaccine, Adjuvanted has changed over time, and submission to FDA of complete manufacturing and product information to support the vaccine product intended for use under EUA is ongoing.

Novavax EUA request clinical package includes safety, immunogenicity, and efficacy data from a Phase 3 study protocol 2019nCoV-301 conducted in the U.S. and

Mexico with approximately 30,000 participants. FDA will be able to determine compatibility of the vaccine product evaluated in this study to the vaccine product intended for use under EUA. Novavax clinical package also includes safety data from approximately 10,000 subjects who received Novavax COVID-19 vaccine across three clinical studies worldwide: a Phase 3 Study 302 conducted in United Kingdom; a Phase 2 Study 501, which was conducted in South Africa, and a Phase 1 Study 101 conducted in Australia and U.S.

Available manufacturing and product information does now allow for a determination of compatibility between the vaccine product used in these three studies and the vaccine product intended for use under EUA. Therefore, FDAs review of these studies was limited to safety evaluation.

We would request the Committee members to focus their applications of clinical package only. Criteria for Emergency Use Authorization. FDA may issue an Emergency Use Authorization of an unapproved medical product following an EUA declaration if the

following statutory requirements' are met: the agent referred to in the EUA declaration can cause a series or life-threatening disease or condition; the medical product may be effective to prevent, diagnose, or treat the serious or life-threatening condition caused by the agent; the known and potential benefits of the product outweigh the known and potential risk of the product; there is no adequate, approved, and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

Currently, there are three COVID-19 vaccines available in the U.S. for use in individuals 18 years of age and older: Pfizer-BioNTech's COVID-19 vaccine, a mRNA vaccine, licensed as COMIRNATY; Moderna's COVID-19 vaccine, another mRNA vaccine, licensed as SPIKEVAX; Janssen's COVID-19 vaccine, not licensed, but available under EUA. Use of Janssen COVID-19 vaccine is limited to individuals for whom other FDA-approved or authorized COVID-19 vaccines are not accessible or clinically appropriate, and individuals who elect to receive the Janssen COVID-19 vaccine because they would

otherwise not receive a COVID-19 vaccine.

So, here is today's agenda, after my introduction Dr. Heather Scobie from CDC will give you an overview of current epidemiology of COVID-19 and COVID-19 vaccination rates in the United States. Followed by Dr. Tom Shimabukuro from CDC will give you an overview of COVID-19 vaccine-associated myocarditis, followed by sponsors presentation: Emergency Use Authorization request by Novavax for a vaccine to prevent COVID-19 in individuals 18 years of age and older.

There is a short break followed by Dr. Lucia Lee, the Lead Medical Officer from Office of Vaccine Research for FDA, will present FDAs Review of Effectiveness and Safety of Novavax COVID-19 Vaccine, Adjuvanted in Individuals 18 Years of Age and Older. Then we have 45 minutes lunch break, followed by open public hearing. Then a short break, and then additional question and answering session regarding the Sponsor and FDAs presentation. Followed by Committee's discussion and voting, and then meeting will be

adjourned.

Here is the voting question for the Committee. Based on the totality of scientific evidence available, do the benefits of Novavax COVID-19 vaccine, Adjuvanted, when administered as a 2-dose primary series, outweigh its risk in individual 18 years of age and older under EUA? Thank you for your attention.

DR. ARNOLD MONTO: Thank you, Dr. Sen, you've given us a good overview of the entire day's proceedings. We have a few minutes now and if the Committee has any questions about the guidance, about EUAs and the rationale for Emergency Use Authorization, you can raise your hands now. Okay, Dr. Rubin, is that your hand raised? I'm not seeing it in green here.

DR. ERIC RUBIN: Yeah, that's me, Doctor.

DR. ARNOLD MONTO: Okay. Go ahead.

DR. ERIC RUBIN: I know that it isn't our mission to interpret statute, but I am curious about the EUA justification. As you stated, Dr. Sen, there are three, two approved and one authorized vaccine out there so I'm curious as to how this meets the criteria

for a product for which there is a necessity given the existing products.

DR. GOUTAM SEN: Dr. Marks, would you like to respond?

DR. PETER MARKS: Yeah. I'm happy to, or Dr. Fink can. I'm trying to get my camera on here, there we go. Thanks very much for that question, Dr. Rubin. The statute says, it allows us some leeway because it gives us the ability to have products that are either, they would fulfill some unmet need. And, in this particular case, although we have mRNA vaccines out there, we have the Janssen vaccine out there, the Janssen vaccine is currently not being used as a frontline vaccine the same way as the mRNA vaccines.

Which leaves the issue of vaccines for those who might not want to take an mRNA vaccine because of concerns they might have with an mRNA vaccine. As needing potentially an alternative, having a protein-based alternative may be more comfortable for some in terms of their acceptance of vaccine. I will use this as a moment on the bully pulpit to say that we do have

a problem with vaccine uptake that is very serious in the United States. And anything we can do to get people more comfortable to be able to accept these potentially life-saving medical products is something that we feel we are compelled to do. Does that answer your question?

DR. ERIC RUBIN: That does, that's great. Thank you very much.

DR. GOUTAM SEN: Thank you, Dr. Marks.

DR. ARNOLD MONTO: Thank you. Dr. Levy.

DR. OFER LEVY: Hello, thank you for that helpful introduction. If I understood correctly, there have been some concerns with the manufacture of the protein that is the basis of this Novavax vaccine, and for that reason some of the data from some of the other international studies will not be considered with regards to vaccine efficacy and immunogenicity today.

My question is this, could FDA say a few words about what the nature of the manufacturing process was? And also, are we as a Committee to assume that these issues are completed solved now and that the latest

version of the way the protein is manufactured will not lead to any manufacturing problem?

DR. ARNOLD MONTO: Dr. Sen, I don't know if you would like to answer those questions or wait until later on because they are about the substance, so it's your choice.

DR. GOUTAM SEN: No, Dr. Monto, thank you. I think we'll discuss that during question and answer session. We can discuss a little more about that, so I'll pass it on now.

DR. ARNOLD MONTO: Okay, thank you. Dr. Gellin. We can't hear you.

DR. PRABHAKARA ATREYA: Dr. Gellin, muted.

MR. MICHAEL KAWCYNSKI: You're muted, sir, on your phone.

DR. BRUCE GELLIN: Okay, got it. Thanks, sorry. About dosing, we're asked to review the safety and efficacy of a two-dose schedule. If you wind back the clock that's how this all began, and we learned subsequently that two doses was not really the full need. And then, with this confusion about what's a

booster versus a third dose, we're likely to get into this later, but what are we going to be doing about more than a second dose?

And then a related piece is that this is entering a marketplace with other vaccines and while there may be some who've been waiting for this as their only vaccination, there are others who might want to think about how they optimize their own immunity with mixing/matching with other things, so hopefully we can hear something and learn something about that. Thank you.

DR. ARNOLD MONTO: Again, it's up to you whether you want to answer these questions now or later.

DR. GOUTAM SEN: Dr. Monto, Novavax has completed the booster dose data and once we complete these primary series, FDAs going to review those data and we'll discuss that in future.

DR. ARNOLD MONTO: Finally, Dr. Marasco, a very short question. We've run out of time.

DR. WAYNE MARASCO: Yes, it's really a

question to Dr. Marks and CBER really. It's a follow-up to Dr. Rubin's question. This vaccine that we're going to hear about today is Adjuvanted and I'm curious in terms of CBER have you guys really considered what the public is hearing and seeing, which is waning immunity. And is there any emphasis in this particular vaccine on the fact that it's Adjuvant and may change the durability of the response?

DR. ARNOLD MONTO: Dr. Marks?

DR. PETER MARKS: Yeah, no, thanks for that question. I think that'll be something for the Committee to discuss today and I think the Sponsor may be presenting some information on that as well. There's the issue of durability of response as well as the breadth of protection, which I think are both things that will be open for discussion.

DR. ARNOLD MONTO: Thank you, all. We've heard some questions which we need to park, and we can bring these up later on as we get into discussions of the substance that we're going to be handling today. Now, let's get back to the background, which I jumped

to before, and I'd like to reintroduce Dr. Scobie. Dr. Scobie, tell us about COVID vaccination rates in the United States.

CURRENT EPIDEMIOLOGY OF COVID-19 AND COVID-19 VACCINATION RATES IN THE UNITED STATES

DR. HEATHER SCOBIE: Good morning, can you hear me?

DR. ARNONLD MONTO: We can.

DR. HEATHER SCOBIE: Great. The Omicron variant has been shown to have increased transmissibility, a decreased severity relative to previous lineages. Omicron has many mutations in the spike gene, including 15 mutations in the receptor binding domain, as shown in the picture on the right. These mutations are associated with reduction and efficacy of some monoclonal antibody treatments. And a reduction in neutralization by sera from vaccinated or convalescent individuals.

This is a graph of the number of SARS-CoV-2

sequences submitted globally to the GISAID Public Genomic Data Repository since Omicron was first detected at the end of November 2021. The blue color shows the Delta variant being displaced as the Omicron BA.1 sub-lineages, in salmon color, quickly rose to predominance followed by the rise of the Omicron BA.2 sub-lineages in peach. The other Omicron sub-lineages like BA.4 and BA.5 are not readily apparent in the figure because they are still a relatively low proportion of submitted sequences. The total number of submitted sequences globally has shown a declining trend since January of 2022.

This stacked bar shows recent U.S. trends and the national weighted estimates of variant proportions and Nowcast projections of circulating SARS-CoV-2 lineages by week of specimen collection date from CDCs COVID data tracker. Omicron sub-lineage's depicted in different purple and pink shades have been over 99 percent predominant since late January.

The BA.1.1 sub-lineage in dark purple was gradually displaced by the BA.2 sub-lineage shown in

lavender and, more recently, the BA.2.12.1 sub-lineage, in pink, which was 59 percent of circulating lineages as of the week ending May 28th. BA.4 and BA.5 are not shown in this graph because they were less one percent for this period. But these sub-lineages will be shown in the variant proportion estimates released later today.

This map shows the relative proportions of BA.2.12.1 in pink, BA.2 in lavender, and other Omicron sub-lineages in the darker purple shade across the 10 health and human services subregions. You can see that BA.2.12.1 is at least 50 percent predominant in all regions, except region 10 in the northwest.

This graph shows the trends in daily numbers of COVID-19 cases reported in the United States since the beginning of the pandemic. The number of cases associated with the Alpha variant were relatively small compared with the Delta variant and then the Omicron variant. Nationally reported cases show increasing trends in April and May. Those trends may be starting to turn in the last week or so.

Reported cases still remain relatively high. I notice that the number of reported cases is likely underestimated due to the increased use of at-home tests whose reports are mostly unreported to public health departments. As of June 5th there have been over 84 million cases of COVID-19 reported in the U.S.

This is a graph from a recent MNWR on CDCs National Commercial Laboratory Seroprevalence Study and shows trends of infection-induced SARS-CoV-2 antibodies by age group. These results do not include anti-spike antibodies from vaccination, nor do they reflect the percentage of the population that might have sufficient antibodies to be protected from reinfection.

The percentages of people with previous infection noticeably increased following the rise of the Omicron variant. Greater seroprevalence was noted in younger age groups likely related to these groups being eligible for vaccination in later months and different exposure risk compared to older age groups. National seroprevalence during February 2022 was 58 percent.

This graph shows the trends in the daily number of reported COVID-19 deaths in the United States since the beginning of the pandemic. Including during the waves associated with the Alpha, Delta, and Omicron variants. Even though the Omicron infection is less severe overall relative to Delta, the number of deaths related to Omicron was relatively high because Omicron case numbers were very high. As of June 4th there have been over one million deaths due to COVID-19 reported cumulatively in the U.S.

These are the weekly trends in COVID-19 associated mortality rates by age group. The data show that higher mortality rates are consistently observed in older age groups. Most notably on this graph among ages 75+, 65 to 74, and 50 to 64, as shown in the purple and pink colors. These are the weekly trends in the rates of new COVID-19 in-patient admissions by age group. Similar to the previous graph, you can see higher hospitalization rates in the older age groups. With patients 70+ in purple, 65 to 74 and 50 to 64 years in the pink colors having the highest admission

rates, followed by other adult age groups in shades of blue.

As of June 2nd more than 221 million people in the U.S. have been vaccinated with a primary vaccine series, which is 71 percent of the eligible population aged five years and older. There are also over 103 million people, or 49 percent of the population, aged 12 years or older who have also received the first booster dose. And about 15 million people, or 23 percent of the population, aged 50 years and older who have also received a second booster dose.

This graph shows trends over time and by age group, and the percentage of people who have received at least a primary series on the left and a booster a dose on the right. In both figures vaccination coverage is higher in older age groups, indicated in the purple and pink colors. We can also see that coverage with the primary series for ages 5 to 11 years, shown with the yellow dotted line on the left, is still relatively low at 29 percent. Booster dose coverage on the right remains' under 50 percent for age

groups less than 50 years, shown in blues and yellows.

From data reported to COVID Data Tracker, over 230 million, or 89 percent, of U.S. adults ages 18 years and older have received at least one COVID-19 vaccine dose. Using these data and Census data, we can estimate that there are about 27 million adults who have not yet received a vaccine at this time. I'll also note that most adults aged 65 years and older have already received at least COVID vaccine dose.

This is data from the National Immunization Survey on adults who have not received a COVID-19 vaccine by age group, race and ethnicity. Across the age groups we can see that people of non-Hispanic, other, or multiple races, and non-Hispanic white people have the highest percentages remaining unvaccinated. While Hispanic and non-Hispanic black people have the lowest percentages remaining unvaccinated.

Next, we're going to shift to consider surveillance monitoring of rates of cases, hospitalizations, and deaths by vaccination status. CDC collaborates with 31 public health jurisdictions

representing 70 percent of the U.S. population. These jurisdictions actively link case surveillance, immunization registry, and vital registration data to monitor rates of COVID-19 cases and deaths by vaccination status. CDC also track's rates of COVID-19 hospitalizations by vaccination status using COVID-NET, which is a population-based sentinel surveillance system in 99 counties and 14 states representing 10 percent of the U.S. population.

In addition, CDCs vaccine effectiveness studies allow for more robust analyses as compared with surveillance, and a better understanding of how well vaccines are working. We also have detailed data on serious illnesses in vaccinated persons through COVID-NET, as well as electronic health record and vaccine effectiveness platform.

This slide shows the age-adjusted rates of COVID-19 associated deaths by vaccination status and receipt of booster doses. Unvaccinated people in all age groups have had higher mortality rates than people who received a primary series alone, and people who

also received a booster dose. Including after Omicron became the predominant variant. In March, unvaccinated people ages 12 years and older had 17 times the risk of dying from COVID-19 compared with people vaccinated with a primary series and booster dose.

This graph shows age-adjusted rates of COVID-19 associated hospitalizations by vaccination status and receipt of a booster dose. Hospitalizations for COVID-19 were higher among unvaccinated than vaccinated people over time. Including after Omicron became the predominant variant. In March, unvaccinated adults ages 18 years and older had five times higher risk of COVID-19 associated hospitalization compared to those fully vaccinated with a booster dose.

This slide shows age-adjusted rates of COVID-19 cases by vaccination status. In April, unvaccinated people ages five years and older had a two times higher risk of testing positive for COVID-19 compared to full vaccinated people overall.

Various studies have shown that severe COVID-19 illness is relatively rare among vaccinated people

compared with unvaccinated people. Compared with unvaccinated people, fully vaccinated people with severe COVID-19 illness are more likely to be older, be long-term care facility residents, and have underlying medical conditions, including immunosuppression, diabetes, and chronic kidney, lung, cardiovascular, and neurologic diseases. More than 75 percent of people who are fully vaccinated and get severe COVID-19 illness have multiple risk factors.

In summary, CDC continues to monitor emerging variants, like the BA.2 sub-lineage of Omicron, including their prevalence and impact on disease incidents and severity over time. Monitoring trends and rates of cases, hospitalizations, and deaths by vaccination status has been helpful for monitoring the impacts of different variants. And, finally, currently authorized vaccines offer protection against infection, severe illness, and death so it's important to stay up-to-date with vaccinations, including receipt of first and second booster doses in eligible populations. Thank you, and I'd like to acknowledge those people for

their contributions.

DR. ARNOLD MONTO: Thank you, Dr. Scobie. We have a few minutes for questions specifically concerning the presentation about where we are with COVID, with the variants, and with vaccination. Let's stick to those topics. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thank you, Dr. Monto. Dr. Scobie, my question is in regard to long COVID and whether you have any data to share with us on the impact of the vaccines on long COVID?

DR. HEATHER SCOBIE: No, unfortunately I don't have data on that today, but I might ask Lieutenant Commander Ruth Link-Gelles, so she's on the line, if she has any data from vaccine effectiveness studies or any other related data that she wants to share. Are you there Dr. Link-Gelles?

MR. MICHAEL KAWCZYNSKI: I'm sorry, who are you looking for, Heather?

DR. HEATHER SCOBIE: Ruth Link-Gelles, do you see her on the line?

MR. MICHAEL KAWCZYNSKI: No. Go ahead, Praba.

DR. ARNOLD MONTO: Okay, I think we'll just move on. Sorry, Dr. Chatterjee, but this'll probably come up later today. Dr. Perlman.

DR. STANLEY PERLMAN: Yeah, I just had a question about one of the first figures that you showed. The data showing the high mortality in people over 75 with the Omicron. Do you know if those people were vaccinated? Would this be justification for different vaccines? Or were those people mostly unvaccinated? Or were they just people that had many, many comorbidities? Do we know about antibody titers in them? Trying to get a sense for how the Novavax vaccine could fit in this.

DR. HEATHER SCOBIE: Yeah, that's an interesting question. The data I showed are actually surveillance data, so we don't have detailed information in that system on vaccination status. And we don't have titers, like you were asking about. There are studies, like vaccine effectiveness studies, that would have more detailed information. And the data that I showed you on vaccine breakthrough

surveillance, the rates of cases, hospitalizations, and deaths by vaccination status, those data are collected by age groups. And even in the older age groups we do see a very large disparity in unvaccinated people having higher rates of hospitalization and death regardless of age group.

Although it may be true that, as I was saying, that if you are of older age and you have underlying conditions and you happen to have a breakthrough infection, you will be more likely to have a serious event compared to people who don't have those risk factors. It's still very much the case that adults and children alike are protected against serious illness with these vaccines.

DR. STANLEY PERLMAN: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Reingold.

DR. ARTHUR REINGOLD: Can you hear me?

DR. ARNOLD MONTO: Yes.

DR. HEATHER SCOBIE: Yes.

DR. ARTHUR REINGOLD: Thanks' for that. Arthur Reingold. Quick question, I know you depressed

the most recent data, you don't have quantified yet, but the eyeball test looking at those graphs of rates of either hospitalizations or deaths by vaccination status would suggest they're converging more recently. And that the VE is in fact shrinking in the most recent time period. I'm just curious if you have any thoughts about that of whether the eyeball test --

DR. HEATHER SCOBIE: Yeah, I mean -- so the eyeball test is challenging in this situation because the Omicron peak at the beginning of the year was so high, so it's really throwing the Y axis off. It's scaling everything down. And then, in the data that I showed you on more serious outcomes, that was during a period of relatively low incidents in the U.S. so it's pretty hard to see what's going on in those graphs.

But it is true what you're saying, that as different variants have come through, notably the Delta variants and then the Omicron variants, we have seen evidence in our rate data that suggests a decrease in vaccination effectiveness. We don't choose to calculate vaccine effectiveness using those data

because of our inability to control for other factors besides age.

It's definitely true what you're saying that vaccine effectiveness has been reduced related to different variants. I don't, Ruth Link-Gelles, I don't know if you're able to connect her now, but she was my expert that I had on about VE if she wants to say more.

DR. ARNOLD MONTO: Let's, for technical reasons I think it's very difficult to link other people on, so --

DR. HEATHER SCOBIE: Okay.

DR. ARNOLD MONTO: -- let's go on and Dr. Gellin has his hand raised.

DR. BRUCE GELLIN: Heather, thanks' for that, can you hear me?

DR. HEATHER SCOBIE: Yes.

DR. BRUCE GELLIN: Two things, you used the term fully vaccinated several times, I wanted to know how you define that. And maybe this is for later when we think about epidemiology of COVID infection, will we be hearing either now or later background rates of

myocarditis from natural infection? Thanks.

DR. ARNOLD MONTO: We have a talk coming up, Bruce, on myocarditis.

DR. HEATHER SCOBIE: Yes, that's the next talk about myocarditis. Let's see, and fully vaccinated is a term that still exists that's defined as vaccinated with a primary series. And it's challenging to understand, so we make attempts to not use it, but for whatever -- it still exists in the literature, and it still exists on my slides, so apologies for that. But it means vaccinated with a primary series.

There's another term called up-to-date that means vaccinated with a primary series and whatever booster doses were indicated for the particular individual according to minimal intervals specified in the guidance. That term is challenging to implement from a surveillance and monitoring perspective. It's often not what's used in our measurements for surveillance data.

DR. ARNOLD MONTO: Thank you, and Dr. Nelson, final question in this series.

DR. MICHAEL NELSON: Thank you, Commander Scobie, for that great overview and very informative presentation. One of our considerations for an EUA authorization is the availability of treatments for the disease in which we are trying to prevent with the vaccine. So, in scouring the agenda today, I didn't really see the impact of available treatments for disease on the epidemiology of the disease itself. And I wonder if you care to comment at this time or save it for later discussion. Thank you.

DR. HEATHER SCOBIE: Yeah, so unfortunately, so I have a variant's expert also on the line, but I'm not sure that that person could be connected, Dr. Natalie Thornburg, so I didn't prepare for certain questions because I believed they would be able to be connected. It's true what you're saying that this is definitely a concern when we're talking about vaccination and these variants.

Whether there are other treatments that can be used when people become infected to protect them against serious illness. And it's definitely true that

when Omicron became predominant this was a major thing that the healthcare system had to deal with because there was essentially only one monoclonal antibody that was effective against Omicron. And there wasn't enough of it, and it was a major problem. Natalie is writing me now. But --

DR. PRABHAKARA ATREYA: Dr. Monto can we have Dr. Natalie speak?

DR. HEATHER SCOBIE: Were you able to connect her?

DR. ARNOLD MONTO: Well, yes, if she's available.

DR. PRABHAKARA ATREYA: Yes, she is available, thank you.

DR. ARNOLD MONTO: Then we'll have to move ahead. And, Dr. Nelson, this is an important point which I think you may wish Dr. Mark's group to weigh in on, but later on this afternoon.

DR. MICHAEL NELSON: Understood. Thank you.

DR. ARNOLD MONTO: Is Natalie available?

DR. HEATHER SCOBIE: Dr. Thornburg, are you

there?

DR. PRABHAKARA ATREYA: Yes, Mike, can you connect Natalie please?

DR. ARNOLD MONTO: Let me suggest --

DR. HEATHER SCOBIE: She said she is muted.

DR. ARNOLD MONTO: -- that we not have too many link-ins. The technology is not all that able to handle this.

MR. MICHAEL KAWCZYNSKI: Natalie, hold on a second, I will unmute you right now. Hold on, I just had to know who it was. Thank you. Go ahead, Natalie, take it away.

DR. HEATHER SCOBIE: I believe you may have unmuted Dr. Link-Gelles, it's Natalie Thornburg.

DR. NATALIE THORNBURG: I am unmuted now, thank you.

DR. HEATHER SCOBIE: Oh, you're there. Okay, great.

DR. NATALIE THORNBURG: Yes, I'm here. Yeah, so I believe the question was use of therapeutics. You sort of summarized the question, it was use of

therapeutics and how that has impacted the variants, with variants circulating, is that the correct question?

DR. HEATHER SCOBIE: Concerns about Omicron probably specifically, and the use of monoclonal antibodies and other treatments.

DR. NATALIE THORNBURG: Yeah, on the monoclonal antibodies, use of those treatments and those prophylaxis, because there's so many changes in the receptor binding domain of Omicron, Heather said there's 15 in the receptor binding domain, that's the part of the spike protein that binds to the cell and, therefore, that is also the same region that neutralizing monoclonal antibodies bind. So Omicron has indeed lost activity, or the monoclonal antibody therapeutics, several of them have lost potent activity against Omicron.

And we don't have as many of those available. Those same problems won't exist for small molecule inhibitors, fortunately. And new monoclonals can be developed, but when a variant emerges like Omicron,

that have a lot of changes in the receptor binding domain, it does reduce the toolbox clinicians have to use when people get infected.

DR. MICHAEL NELSON: And I guess for Committee's consideration and one clarifying question, would it be fair to state that the availability of these various treatments have had little impact on the overall course of the epidemiology of the disease in the U.S. at this time?

DR. NATALIE THORNBURG: Well, I think that the transmission of the virus, most people are most transmissible in the day or two leading up to symptom onset, and a few days after symptom onset. Often, they can't get access to treatment until their transmissibility is already beginning to wane. And therefore, vaccines are a really key tool in reducing transmission. But we have to use all of the tools in our toolbox.

DR. ARNOLD MONTO: Right, thank you. Dr. Marks, for a final comment before we go on to the next presentation.

DR. PETER MARKS: I think it's very important for us to step back here for a moment and just recognize that vaccines are a unique public health tool that is relatively inexpensive. The safety of vaccines in terms of the benefit/risk is often much better than the safety of some of the therapeutics that might be used post-facto after one is infected. And so, one of the really important things here about vaccines is they have been wonderful public health interventions, and that's why we use them.

They can give protection to many, many, many more people than we can come up with courses of oral therapies or intravenous therapies. And the cost of actually, and the complexity and the potential complications of delivering intravenous therapies or even some of the oral therapies are much greater than the simplicity of giving vaccines. Not that vaccines have zero risk associated with them; we'll hear about potential side effects of vaccines later today. But that overall the benefit/risk is quite favorable as a public health intervention.

DR. ARNOLD MONTO: Thank you, Dr. Marks. Now we are moving ahead to the next discussion, which is about myocarditis. We will hear Captain Shimabukuro from CDC giving us this update. Thank you.

OVERVIEW OF COVID-19 VACCINE ASSOCIATED MYOCARDITIS

DR. TOM SHIMABUKURO: Hi, can you hear me okay?

MR. MICHAEL KAWCZYNSKI: Yeah, you're fine.

DR. TOM SHIMABUKURO: All right. Next slide, please, or, I'm sorry, I'll control. So today topic I'm going to cover is a background on classic myocarditis and myocarditis associated with mRNA COVID-19 vaccination. And then I'll give an update on myocarditis following mRNA COVID-19 vaccination with a focus on people ages 18 and older that will include data from the Vaccine Adverse Event reporting system, or VAERS, and the Vaccine Safety Datalink, or VSD.

Classic myocarditis usually has an infectious cause, typically viral or presumed to be viral.

Although infection with a pathogen is frequently not identified. It can be due to direct microbial infection of the myocardial cells. I'm having some technical difficulties with the slides. They keep on reversing order here. I don't know if that's on my end or your end.

MR. MICHAEL KAWCZYNSKI: We're not touching your slides, so go ahead, sir.

DR. ARNOLD MONTO: We're okay.

DR. TOM SHIMABUKURO: Okay. It can also be toxin-mediated or in a setting in systematic infection or infection of non-cardiac tissue. Rarer causes include autoimmune, hypersensitivity, or giant cell myocarditis. Incidence is higher in males compared to females starting after age five years. And, as I mentioned, it's common to not identify a pathogen or possible infectious etiology for myocarditis. And some studies, when they do testing in a minority of cases do they find a possible infectious etiology.

These are graphs showing the epidemiology of myocarditis with children on the righthand side, and

adults on the lefthand side. This is from the published literature. If you focus on the lefthand side, with the exception of very early in childhood when there may be factors like genetic factors in play incidence is relatively low in early childhood. And then begins to increase in adolescence. And if you move over to the right graph, you can see peaking in adolescence and then gradually decreasing incidence with age. Most of these cases are male, and by the time you hit middle age the male to female predominance goes away.

This is a table showing the characteristics of myocarditis associated with mRNA COVID-19 vaccination in a comparison with viral myocarditis. For vaccine associated myocarditis, mRNA COVID-19 vaccination is the inciting exposure. And then, for viral myocarditis, it's viral, although many of these cases can be asymptomatic. For vaccine associated myocarditis, most cases have been in adolescence and young adults, with more cases in males compared to females. Then for viral myocarditis incidents in males

greater than females. Male incidence peaking in adolescence and then gradually declining. Onset for vaccine associated myocarditis has typically been within a few days after vaccination, with most cases occurring within a week. And then, for viral myocarditis, onset is typically one to four weeks after viral illness.

The next set of characteristics get at clinical severity, but just in general vaccine associated myocarditis following mRNA COVID-19 vaccination has been relatively mild when compared to viral myocarditis which can frequently be severe.

So, now I'm going to move on to data from the Vaccine Adverse Event Reporting System, which is the national spontaneous reporting system that's comanaged by CDC and FDA. The key limitation, VAERS is a passive surveillance system. We generally cannot determine cause and effect from VAERS data alone. This is a flow diagram showing U.S. reports to VAERS of myocarditis after mRNA COVID-19 vaccination among people 18 and older following primary series and first booster. We

have observed 1,836 reports in this age group. Eleven remain under review, 504 did not meet case definition, and that leaves us with 1,321 reports in this age group that met CDC case definition. To put that number in context, there's been an estimated 491.9 million primary series and first booster doses administered in this age group.

This is a figure showing time to onset of these cases. And you'll notice that there appears to be clustering within a few days after vaccination. Many of these cases occurring in the one to four day period. When we get to the vaccine safety data link, I'll show you some additional data that also supports this clustering of onset within a few days of vaccination.

Of these 1,321 verified reports that met CDC case definition, the median age in this age group 18 and older was 28 years. Median time to onset symptoms after vaccination is three days. Most of these occurred after dose two, and most occurred in males. This is a table of VAERS reporting rates of myocarditis

per million doses administered after mRNA COVID-19 vaccination in the 0 to 7 and 8 to 21 days post-vaccination.

I know this is a busy slide, but there's a few key takeaway points from this. If you look, the peach colored slides are where the observed reporting rates to VAERS exceed the expected background rates based on what's in the published literature. So you can use that as a proxy of risk, that's where the O to E ratio exceeds background. If you look in the 8 to 21 days, you'll see that there are no peach shaded cells, and that reinforces that the risk is concentrated primarily in the zero to seven days.

If you look at males versus females you see that reporting rates are generally higher in females, and reporting rates for both males and females are higher after dose two compared to dose one. I have the children in there for reference, but if you start at the 18 to 24 year old age group you see that the reporting rates decrease with time. And, at least for males, by the time you hit 50 years old we do not see

an increased risk.

So, of these 1,321 reports, where we had information on healthcare utilization most were hospitalized. And most of these reports that were hospitalized had a known outcome at the time of the report. And 73 percent of these had recovered from symptoms at the time of the last follow-up, according to the VAERS report. There were 21 reports of death involving myocarditis. When we evaluated the reports and accompanying records, in one report myocarditis was attributed to causes other than vaccination, and four potential alternate etiologies were present. In 15, cause of death was not attributed to myocarditis, and then one adequate information was not available to fully evaluate the case.

So I just want to spend a little bit of time talking about CDCs enhanced surveillance of myocarditis outcomes. And this is currently in an age 12 to 29 years. The purpose was to assess functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination.

And it's a two component survey conducted at least 90 days after the onset of symptoms. It included a patient survey and a healthcare provider survey.

When the analytic period close in November 2021 VAERS had received 852 reports in this age group that were at least 90 days that met case definition. They were at least 90 post-myocarditis diagnosis. We're able to complete 360 patient surveys and 398 cardiologist or other healthcare provider surveys that these patients were seeing in aftercare. The main finding from the cardiologists or healthcare provider survey was that based on the provider assessment most patients appeared to have fully or probably fully recovered from their myocarditis.

Roughly 82 percent of patients, according to the cardiologist, were classified as fully recovered or probably fully recovered, but pending more information. The majority of the remainder had improved but did not report being fully recovered. So some key findings from this enhanced surveillance activity. On patient follow-up with the patient surveys at least 90 days

after diagnosis, most patients who were reached reported no impact on their quality of life and most did not report missing school or work. As I mentioned, 82 percent of healthcare providers indicated that the patient was fully recovered or probably fully recovered.

Notably there was substantial heterogeneity in the initial and follow-up treatment and testing of these patients. And there did not appear to be a single test that was indicative of recovery. Some additional next steps we're doing is we're going to follow-up on patients who were not yet fully recovered at the time of the survey to further assess the recovery status at least 12 months after myocarditis. And we're also following up on children and evaluating myocarditis cases in children ages 5 to 11 years.

So now I'm going to move on to data from our Vaccine Safety Datalink system, which is our electronic health record-based system for surveillance and research. We conduct rapid cycle analysis in the Vaccine Safety Datalink. The aims are to monitor the

safety of COVID-19 vaccines weekly using pre-specified outcomes and to describe the uptake of COVID-19 vaccines over time among eligible VSD members.

Here's a table of the pre-specified outcomes that we are monitoring in VSD and the settings in which we are monitoring them. I'm not going to go through this slide, this is methods. I'll just mention that the primary analytic method for VSD rapid cycle analysis is a vaccinated concurrent comparator analysis. It basically compares vaccinated individuals to other vaccinated individuals looking at cases in a risk interval compared to cases in a comparison interval. For the outcome of myocarditis and pericarditis, all cases were chart confirmed and verified using the CDC case definition.

Here's the mRNA COVID-19 vaccine doses administered in VSD in the age group 18 to 39 years old, which is the age group that I'll be presenting data for. There were about 950 patients who received a primary series dose one and dose two for Moderna. And about 1.5 million who received a primary Pfizer series.

There's about 574 million people who received a Moderna booster dose one and about 812,000 people who received a Pfizer booster dose one.

This is a figure showing the day of onset of verified myocarditis and pericarditis cases in the age group. And you can see similar to what I showed in VAERS, these cases following vaccination tend to cluster shortly after vaccination. In this case, statistically significant clustering in the day zero to three and zero to four. Reinforcing the biological plausibility of this zero to seven day risk interval that we use for our main analyses for myocarditis after mRNA COVID-19 vaccination.

This is a table showing verified myocarditis and pericarditis cases in the zero to seven day risk interval compared to outcome events in vaccinated comparators and risk. This is basically looking at the risk in the risk interval compared to the comparison interval. This statistic is the adjusted rate ratio, and this table is for males 18 to 39 years old. And you can see whether it's a combined analysis of both

vaccines or looking at the Pfizer vaccine or looking at the Moderna vaccine, the adjusted rate ratios are all elevated. Many of them statistically significantly elevated with the dose two rate ratios tending to be the highest. And then you see, on the far righthand side there, how that translates into the excess cases in the risk period per million doses, which, depending upon the analysis, range from about 40 to 60 additional cases in the risk period per million doses administered.

This is the same table, but for females. And you can see that the case counts are substantially lower. The adjusted rate ratios tend to be elevated, some statistically significantly elevated. And some of these adjusted rate ratios are comparable to those observed for males, but I want to caution you, this is based on relatively small numbers. And so, these can be impacted by those small number effects, and then you see the excess cases in the risk period on the righthand side there. I'm going to go back to the previous slide, you'll see that the excess cases in the

risk period there. Like I said, in the highest risk strata ranging from about 40 to 60, and you'll see they're substantially lower here for females. So even though some of the adjusted rate ratios may be elevated in females, because of the lower case counts the excess risk tends to be quite lower in females compared to males.

This is a table showing the level of care and status of the cases in VSD. And these are the cases after a primary series dose of mRNA COVID-19 vaccine. Most of these cases are admitted to the hospital. A relatively small minority are treated in the emergency department. The length of stays tends to be short. The median length of stay is one. The overwhelming majority of these cases have stays of three days or less. And 100 percent of these case patients were discharged home.

This is the same slide, it's a similar table, but it's showing the cases following the first booster dose of an mRNA COVID-19 vaccine. And this, I think, just demonstrates that the level of care and status is

similar for the cases following the booster dose compared to the cases following the primary series.

So, just to sum up, the current evidence supports a causal association between mRNA COVID-19 vaccination and myocarditis and pericarditis. Cases following vaccination cluster within the first week of vaccination. The risk is greatest in adolescents and young adults, higher after dose two compared to dose one of the primary series. And higher in males compared to females. Some risk estimates for females in VSD are comparable to males, but case counts are small and excess risk in females is substantially lower than for males.

The risk appears to decrease with age and the male to female predominance of cases attenuates with age. Reporting rates in VAERS are highest following dose two, reporting rates following dose one and first booster dose tend to be lower. Incidence rates in VSD of verified myocarditis and pericarditis zero to seven days following vaccination are generally highest following dose two. In a minority of age and sex

strata, notable males aged 16 to 17 years, the incidence is highest following the booster dose.

And, based on our follow-up of VAERS cases reports, available information suggests that most persons with myocarditis after mRNA COVID-19 vaccination recover from myocarditis by three to eight months after diagnosis. I'd like to acknowledge the following groups for their contributions. And I'll be happy to answer questions.

DR. ARNOLD MONTO: We have only a few minutes for questions right now. I'm sure that the topic will come back. Remember, to our Committee, that this is background information on mRNA vaccines in basically observational studies. I see a lot of hands raised and we're not going to be able to get all of them. I'm going to have a couple of questions, maybe two or three, and then we're going to be going on to the Sponsor presentation. If you are disappointed, my apologies. Dr. Rubin.

DR. ERIC RUBIN: Hi, sorry about that. Thanks Dr. Shimabukuro. One of the hypotheses is that the

antigen itself and cross reactivity that's leading to myocarditis, is there any evidence, and I realize a lot of it might be international, of an association between myocarditis and the viral vectored vaccines?

DR. TOM SHIMABUKURO: I don't know if anyone could hear me.

DR. ARNOLD MONTO: No, I couldn't.

MR. MICHAEL KAWCZYNSKI: Tom just disconnected his audio inadvertently, so I'm just going to reconnect Tom's audio here. Here he comes. There he comes. There you go. Tom, you there?

DR. TOM SHIMABUKURO: Sorry, I lost audio there for a second and missed --

DR. ERIC RUBIN: That's okay.

DR. TOM SHIMABUKURO: -- the questions.

MR. MICHAEL KAWCZYNSKI: Go ahead, Eric, will you repeat that quick?

DR. ERIC RUBIN: The quick version, is there evidence that this is the antigen rather than the method of delivery? In other words, do you see the same thing with viral vectored vaccines?

DR. TOM SHIMABUKURO: There have been case reports after the Janssen vaccine, but the data are pretty sparse. There hasn't been much vaccine administered, and there hasn't been much vaccine administered in these high risk groups, namely adolescents and young adults. So I don't think we have sufficient evidence to rule out or establish a risk. And I'm not aware of any surveillance or epi data from the Astra-Zeneca vaccine that would indicate a risk, but I think right now the data are really not sufficient for Janssen to draw hard conclusions on that.

DR. ERIC RUBIN: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Gellin. We can't hear you.

MR. MICHAEL KAWCZYNSKI: You have your phone muted again, Dr. Gellin.

DR. BRUCE GELLIN: Sorry. This is about natural history of myocarditis and recovery from it. You talked about recovery in the vaccine associated cases. Does that mean in the natural history, is fully

recovered meaning people don't have to worry about it ever again, or are there long-term consequences that might come up later? Over.

DR. TOM SHIMABUKURO: I'm probably not the best person to talk about the natural history of myocarditis. I think that there can be long-term effects, residual effects of myocarditis. There is not, as I said, there appears to be a lot of heterogeneity, both in the treatment and in the follow-up care, and not really a standard to determine whether a patient has recovered. There's a bit of a lack of standardization.

What I can say about the cases that we have followed up on is that overwhelming, either when you survey the patient or you survey the healthcare provider, they report generally having favorable outcomes. There's a small number which have improved but have not fully recovered, and that's why we're going to follow-up on these case patients at 12 months or more to try to get a better idea of the recovery status of these vaccine associated cases.

DR. ARNOLD MONTO: Thank you. Dr. Meissner.

DR. CODY MEISSNER: Dr. Shimabukuro, thank you so much for your work in this area over the past year or two, it's been very helpful. The question I have for you first is a follow-up to Dr. Gellin's question, and that is, gadolinium uptake of children or adolescents who have had myocarditis has been a helpful marker to address this question of longer term inflammation in the heart muscle.

Do you have any more data regarding, in the groups that your following, regarding results of studies to look at gadolinium uptake? If I may, a very quick question, the numbers from Israel regarding myocarditis following the mRNA vaccines is a little bit different than from VAERS. Probably reflecting the means by which the data is collected. Can you comment on that? Over.

DR. TOM SHIMABUKURO: I'm don't think I'm going to be able to comment on the comparison between the Israel data and the U.S. data because I'm not, at least off the top of my head, not as familiar with the

Israeli data. To get to your question on the recovery status. For patients that we followed up on that did receive an MRI during outpatient follow-up, some of those patients did have this late gadolinium enhancement on cardiac MRI. And from speaking to our cardiologist consultants, the clinical significant of the late gadolinium enhancement, especially in patients who report having recovered their cardiac function and are otherwise feeling well, is unclear. So I think there still needs to be some more work in that area about what is the significant of that finding in these patients months after the initial diagnosis.

DR. CODY MEISSNER: Has it been --

DR. ARNOLD MONTO: Thank you.

DR. CODY MEISSNER: -- possible to collect the figures?

DR. ARNOLD MONTO: We're going to have to move ahead, Cody. Dr. Bernstein, the final question.

DR. HENRY BERNSTEIN: Yeah, Tom, a very clear presentation, as always. I was interested to know whether the number of cases following booster doses

appeared to be notably lower than after dose two. Can you comment about the length of interval between doses as possibly further lowering the rate of myocarditis in patients?

DR. TOM SHIMABUKURO: In many cases the rate of myocarditis after the booster dose is lower than after dose two, although I would say not in all age and sex strata. I believe there is some evidence in other countries where they have had some different recommendations or at least operationalized the vaccination program so there were longer spacing between vaccines. Maybe not necessarily the booster, but maybe the primary series. And some evidence that that spacing may mitigate the risk of myocarditis. In the United States, there tends to be a fairly close following of the immunization schedule, so we don't, unfortunately, we don't have that kind of data.

But, I mean, it is an interesting finding that when you have that longer interval between that booster dose, we tend to see lower reporting rates or lower risk. I would just caution that it's possible that

there could be some self-selecting out of the population. For example, if a person got myocarditis after dose two, they may not get a booster dose. So that may also be impacting the findings as well.

DR. HENRY BERNSTEIN: Yeah. I just mention that because of the 21 days between the doses of Novavax as well.

DR. ARNOLD MONTO: Right, thank you. We're going to have to move ahead. Dr. Shimabukuro, I'm sure we're going to be coming back to these issues and ascertainment and rates later on, so please stick with us to the afternoon. Now I'd like to turn the floor over to the Sponsor, to Dr. Dubovsky, who is going to take the lead in the presentations on the Emergency Use Authorization by Novavax for a vaccine to prevent COVID-19 in individuals 18 years of age and older. Over to you.

EMERGENCY USE AUTHORIZATION (EUA) APPLICATION FOR NVX-CoV2373 INTRODUCTION

DR. FILIP DUBOVSKY: Thank you, and I'll just wait for the slides to load up.

MR. MICHAEL KAWCZYNSKI: Are you sharing on your end?

DR. FILIP DUBOVSKY: It should be coming from --

MR. MICHAEL KAWCZYNSKI: Yep, we gave the share to Justin.

DR. FILIP DUBOVSKY: Justin.

MR. MICHAEL KAWCZYNSKI: There you go, sir.

DR. FILIP DUBOVSKY: I'm still seeing a lag here.

MR. MICHAEL KAWCZYNSKI: They're up on our end, sir.

DR. FILIP DUBOVSKY: Excellent. Good morning, after that delay, my name is Filip Dubovsky, and I'm the chief medical officer at Novavax. We're pleased to have this opportunity to present our data for NVX2373. Our vaccine provides an important new approach in the fight against COVID-19. We believe its authorization will improve vaccine availability and accessibility,

with the ultimate goal of increasing vaccination rates in the U.S. and throughout the world.

As we will show you today, NVX2373 leverages a well-defined platform offering a different vaccine option to fulfill an unmet need within the U.S. and globally. Our vaccine is a recombinant protein subunit vaccine formulated with a natural malleable adjuvant. It induces robust immune responses and provides high levels of protection against mild, moderate, and severe COVID-19. The vaccine is proven to be generally well-tolerated and has a positive benefit/risk profile across a large and diverse patient population.

Our COVID-19 vaccine is based on Novavax's platform technology. A recombinant protein antigen formulated as a particle and our Matrix-M adjuvant, which is a saponin-based adjuvant. Our recombinant proteins represent a tested and well-understood vaccine technology. Currently approved examples include influenza, hep-B, HPV, MenB, and shingles. There are also approved vaccines for malaria and shingles that includes saponin-based adjuvants.

Here's a brief overview of our vaccine. The NVX2373 antigen is a recombinant SARS-CoV-2 spike protein. The spike protein is based on the following sequence from the original strain, including a transmembrane domain. We've engineered changes into the sequence to inactivate the (inaudible) and stabilize its structure. It's manufactured in the baculovirus SS9N60 expression system, a well-defined approach which has been used for decades. And then the full length protein is expressed and self-assembled into a trimer, which is locked into a state of confirmation.

These recombinant protein trimers are purified and further processed to form nanoparticles around a polysorbate core, shown on the slide in blue. The adjuvant, Matrix-M, is purified from the Soapbark tree grown in South America. During processing and purification, the saponin forms cage-like structures. The antigen and adjuvant are co-dispensed into a vial where they form a ready-to-use suspension.

Let's talk a bit about the mechanism of

action, or the Matrix and adjuvant. The mechanism of action of saponin-based adjuvants has been evaluated in a number of animal models. Matrix-M is just a transient effect at the injection site and a more sustained immunostimulatory effect in the draining lymph nodes. It does not contain alum, it does not form a depo at injection site, nor does it engage the total (inaudible) receptor pathways. Injection of Matrix-M increases the magnitude and breadth of immune response. It induces a rapid transient activation of innate immune cells and increases cytokine and chemokine production at the injection site.

This peaks at 5 to 48 hours after injection and rapidly drops by 72 hours. This results in a local influx of activated antigen-presenting cells, which the antigen is delivered and triggers and antigen specific immune response. Subsequently, there's enhanced antigen presentation by MHC class one and MHC class two molecules in the draining lymph nodes. The result is the induction of high levels of neutralizing antibody, polyfunctional CD4 T cells, and a TH1 biased cell-

mediated immune response.

Now let's shift to the vaccines presentation and profile. Our vaccine has key attributes that support the increased access and ease of use. It's dispensed in a 10-dose vial as a preservative-free, ready-to-use liquid suspension. It can be transported and stored through refrigerator temperatures, making it easy to ship, store, and administer. Each dose contains 5 micrograms of antigen and 50 micrograms of Matrix-M adjuvant. Two doses are administered 21 days apart of a 0.5 mL intramuscular injection using standard needles and syringes. The proposed medication under discussion for today's meeting is for adults 18 years of age and older.

Our clinical development program includes four studies. These studies constitute the body of data used for global regulatory approvals. The initial Phase 1/Phase 2 Study established the 5 microgram dose level, confirmed the total of the adjuvant, and a two-dose schedule in both younger and older adults. The study also defined the immunologic phenotype and

described the preliminary safety profile. Subsequently, our Phase 2 Study in South Africa did include a small subset of medically-stable participants living with HIV evaluated preliminary efficacy and safety.

Pivotal safety and efficacy was initially evaluated in a Phase 3 Study in the UK followed by an even larger study in the U.S. and Mexico to (inaudible) within the U.S. As part of the U.S./Mexico Phase 3 Study effectiveness and clinical efficacy was established in adolescents 12 to 17 years of age. Now, after discussion with the FDA, today's efficacy presentation will focus on our largest study in the U.S./Mexico Phase 3 Study, Study 301.

Study 301 is most relevant for today's discussion because it was conducted in a diverse U.S. population and the vaccine used in the study was manufactured in the commercial scale that's consistent with the vaccine we are distributing globally. Relevant safety data from all studies will be discussed.

Okay, let's briefly review the 301 topline results. Our U.S./Mexico Phase 3 Study met it's prespecified primary efficacy endpoint. Study 301 demonstrated an overall efficacy of 9.4 percent against protocol-defined symptomatic disease. And achieved 92 percent efficacy in the highest populations with medical comorbidities, and 100 percent efficacy against moderate and severe disease. All events of moderate and severe disease, and hospitalizations occurred in a placebo group.

Additionally, matched strain efficacy was 97 percent. Matched strains are strains that are considered genetically similar to the original virus on which the vaccine is based. As far as variants go, our vaccine demonstrated high levels of protection against the Alpha variant, as well as against all of the variants of interest and concern that circulated at that time. And a number of variants circulated and caused disease during our study. In fact, the majority of cases were caused by variants of concern and variants of interest. The most commonly observed were

Alpha, Epsilon, and Iota.

Displayed here are our global regulatory approvals. As of today our vaccine has been granted authorization for use in over 40 countries for individuals 18 years of age and older, including those over 65. In December 2021, we received our first authorization in the European Union granting access to all 27 countries. This was followed by the World Health Organization granting Emergency Use, listing for global use. Subsequently approval was achieved in the countries listed on the slide. I should note that the indication in India and Thailand includes adolescents and adults, and our vaccine has been approved as a booster dose in Japan.

Our clinical development plans are ongoing and will continue following EUA. We've submitted the results from the adolescent expansion of Study 301 and are completing safety follow-up in our Phase 2 and Phase 3 studies to support whole BLA. And we have additional ongoing studies in adolescents, and soon we will initiate a pediatric HDS (inaudible) study

beginning in school-aged children. We believe one approach to optimizing protective efficacy may include the use of vaccines engineered against emerging variants.

We're collecting data on homologous and heterologous boosting for continued vaccine use. And, finally, we have post-authorization plans which include additional studies for real-world effectiveness and safety monitoring. Here's the agenda for the remainder of our presentation. Dr. Raburn Mallory will review the immunogenicity and efficacy data. Dr. Denny Kim will present the safety data, followed by Dr. Gregory Poland with the Mayo Clinic to provide his clinical perspective for NVX2373.

I will then return to conclude the presentation, and my colleagues and I will be available to answer questions from the Committee. We also have additional experts with us today. All outside experts have been compensated for their time to prepare for today's meeting. Thank you. I'll turn this presentation over to Dr. Mallory to review the

immunogenicity and efficacy data.

IMMUNOGENICITY AND EFFICACY

DR. RABURN MALLORY: Thank you, Dr. Dobovsky. I'm the senior vice president and head of clinical development at Novavax, and I'm pleased to review our FDA data for the EUA application today. As I'll share with you, our data demonstrates the vaccine induced high levels of neutralizing antibodies in both younger and older adults. Vaccine was highly efficacious in preventing COVID-19 illness and showed a high level of efficacy for the variants of concern and variants of interest that circulated during our Phase 3 Study.

Vaccine also completely prevented moderate and severe COVID-19 in the study. Before I describe our clinical data, I'd like to briefly summarize our non-clinical results. We conducted a number of non-clinical studies during the development of the vaccine. In immunogenicity studies, the vaccine induced high levels of functional antibodies and induced a strong

TH1 virus and cellular immune response. In animal challenge studies, the vaccine effectively suppressed viral replication in both the upper and lower airways. And this was an important milestone because it suggests that the vaccine could be highly protective in human's.

In addition, reassuringly, there was no evidence of enhanced disease in these studies. We performed a comprehensive toxicology program, and there were no adverse findings seen in these studies. There were also no adverse findings in our developmental and reproductive toxicity study. These results combined with the absence of the safety findings in all of the studies supported moving the vaccine into clinical development.

Turning next to the results from our U.S./Mexico 301 Study. The results are called PREVENT-19. This was a randomized, observer-blinded, placebo controlled study. We randomized participants in a 2 to 1 ratio to receive vaccine or placebo. And we did this so that we could gather additional safety data on the vaccine from a larger number of participants. The

study initially enrolled adults 18 years of age and older, but we then amended it to also include adolescents 12 through 17 years of age.

About four months after the initial vaccination period, participants remained blinded and were crossed over to the opposite treatment arm. And we did this so that all participants in the study could receive active vaccine. Participants are now being followed for up to two years following primary vaccination. The primary endpoint of the study was mild, moderate, or severe disease occurring seven days or more after the second dose of vaccine. The terms of the definition of success: in order to meet the primary endpoint for vaccine efficacy, the lower limit of the 95 percent confidence interval needed to be greater than 30 percent.

One of the main secondary endpoints we were interested in was how effective the vaccine would be in preventing the more concerning cases of moderate and severe COVID-19. As Dr. Dobovsky mentioned, a large number of variants of interest and variants of concern

circulated during the study. Sequenced data were available for 75 of the endpoint cases and 61 of these, or about 80 percent, were due to variants of concern or variants of interest, with the Alpha variant being the most common and isolated.

These strains are now classified as variants being monitored, but they aren't circulating to a large extent. However, efficacy for these variants remains relevant as some of them contain those (inaudible) mutations, like the L452R being the Omicron subvariant that could also be seen in future variants. Turning now to the results. Demographics and baseline characteristics were well-balanced between the two arms as shown. Thirteen percent of participants were 65 or older. It's important to note that enrollment of older adults was somewhat limited. This is because COVID-19 vaccines became authorized and recommended for those over 65 while we were enrolling.

Black or African American participants made up about 12 percent of the study population. Seven percent were American Indian, and 22 percent were

Hispanic or Latino, representative of the overall U.S. population. BMI was one of our study goals. About 95 percent of participants were considered at increased risk of COVID-19. Either due to underlying medical conditions, their occupations, or living conditions. About seven percent were seropositive at baseline, and we excluded these individuals from the immunogenicity and efficacy analyses.

In terms of immunogenicity, in Study 301 there was a robust neutralizing antibody response on day 35, 14 days after the second dose of vaccine. Now, as you can see, this was true for both younger and older adults. In fact, there was 123-fold increase for younger adults and an 87-fold increase in older adults from baseline. Turning to the efficacy results.

(Audio skipped)

DR. PRABHAKARA ATREYA: Dr. Raburn, we can't hear you.

DR. RABURN MALLORY: Sorry about that, I appear to have been muted. I'll start this slide again. Looking at the Kaplan-Meier curve, we can see

that cases began to diverge between the placebo and vaccine arms at around the time of the second dose, the day 21. And that there were very few cases in the vaccine arm through day 98. We achieved our primary efficacy endpoint in the study with 90 percent protection from mild, moderate, and severe disease. In fact, there were only 17 cases in the 17,000 or so vaccine recipients, compared to 79 cases in the 8,000 placebo recipients. And, as a reminder, we randomized participants 2 to 1 to receive vaccine. We also observed 100 percent protection against moderate or severe illness, a key secondary endpoint.

As I showed previously, a number of different variants of interest and variants of concern were circulating during the study. And were responsible for about 80 percent of the cases where sequence data are available. Our vaccine showed 93 percent efficacy against these PCR-confirmed variants of interest and variants of concern. Including the Alpha variant. All of our cases that did occur in the vaccine arm were mild in severity. Notably efficacy was 97 percent for

strains that would be considered more closely matched to the vaccine.

When we look at vaccine efficacy based on race, the vaccine provided a consistently high level of protection across all groups. The efficacy estimate for Hispanic or Latino participants was somewhat lower than that seen for the overall study. Though with broad confidence intervals. In order to evaluate this in more detail we looked to see if lower immune responses might have contributed to this finding. However, what we found was that ITG and neutralizing antibodies in Hispanic and Latino participants were actually slightly higher than those seen in non-Hispanic/Latino participants.

As a result, this efficacy estimate may reflect the (inaudible) finding. However, we will continue to gather additional information about the effectiveness of our vaccine in this subgroup in our planned, U.S. post-marketing effectiveness study. The vaccine also provided a very high level of protection against severe disease, and for individuals who had

baseline comorbidities that puts them at increased risk from COVID-19. As you can see, the number of cases in older adults was limited. As you may recall older adults made up 13 percent of the overall study enrollment, but they were clearly practicing social distancing measures during this time. But they only made up six percent of the cases in the study. The estimate for vaccine efficacy in older adults was 79 percent, so this was based on a total of six cases. And we believe that that's likely attributable to the very small number of cases that occurred.

On the next slide I'll provide some additional data on vaccine immunogenicity and efficacy by age that indicates the vaccine continues to be immunogenetic and efficacious in older adults. On this slide I'm showing the relationship between geometric mean neutralizing antibody titers, efficacy, and age. When we look at adults 18 to 64 years of age, they had a neutralizing antibody titer of approximately 1300. And this was associated with 91 percent efficacy. Within this group, we then evaluated whether vaccine efficacy might

be decreasing with age.

However, this did not appear to be the case because vaccine efficacy remained high at 91 percent for the 50 to 64-year-olds, even though their antibody titer was somewhat lower at 979. We also saw an efficacy estimate of 89 percent for adults 50 or older, with a corresponding neutralizing antibody titer of 922. Finally, for those 65 or older, the efficacy estimate was 79 percent, but with a broad confidence interval that overlaps with the primary efficacy endpoint.

When we looked at the neutralizing antibody titer for this group, which was 900, it is quite similar to and, in fact, non-inferior to the titers for the 50 to 64-year-olds and for those 50 or older that were associated with around 89 to 90 percent efficacy. These data, along with supportive efficacy data in older adults from a large Phase 3 Study conducted in the U.S. in the UK, not presented today, provided assurance the vaccine is efficacious in older adults. Supporting this indication in all countries in which

the vaccine has been approved to date.

So, to conclude, our vaccine was highly efficacious in preventing COVID-19 in a large Phase 3 Study. This efficacy was demonstrated against all the variants that circulated during the study. The vaccine also provided complete protection for moderate or severe COVID-19 in our pivotal study. Our vaccine also demonstrated consistently high efficacy across subgroups, including race, gender and in individuals with comorbidities. I'll now turn the presentation to my colleague, Dr. Kim, to present the safety results. Thank you.

SAFETY

DR. DENNY KIM: Thank you, Dr. Mallory. I'm the chief safety officer at Novavax. And it really is a pleasure for me to be able to present the safety results for our Novavax COVID-19 vaccine. While our presentation will focus on the U.S./Mexico Phase 3 Study 301, we will also take into consideration the

other studies from our clinical development when there are safety data that adds additional insights.

The total safety database includes nearly 50,000 people enrolled across four studies. More than 30,000 received our vaccine and more than 19,000 of these individuals received the vaccine in our Phase 3 U.S. and Mexico Study 301 in the pre-crossover portion of the study. This is a large data set that can provide us confidence that we have a well-characterized safety profile that supports positive benefit/risk and a favorable reactogenicity profile across the diverse populations that Dr. Mallory described.

Now, taking into account follow-up time, during the placebo controlled period of Study 301 we have more than 5,500 person-years of follow-up in the vaccine arm alone. The median follow-up was 89 to 92 days. Our study compliance was high, actually more than 96 percent of study participants received two doses. I'd like to briefly review now how our safety follow-up was conducted.

Beginning in the pre-crossover phase

participants received two doses 21 days apart at day zero and day 21. On the day of each vaccination in the pre-crossover phase participants recorded local and systemic reactions using an electronic diary for seven days. Unsolicited adverse events were collected through day 49. Approximately four months after initial vaccination, participants entered a blinded crossover and received two doses 21 days apart.

Local and systemic solicited reactions were not recorded post-crossover. However, unsolicited adverse events were collected through day 49. Participants were then followed by visits occurring at six month intervals in person or by phone until the end of study. In addition to the nasal swab that was collected prior to each vaccination, continued monitoring for COVID-19 was ongoing with active and passive surveillance, and prompt PCR testing when warranted.

This study includes long-term follow-up with SAEs and AEs of special interest collected through two years following initial vaccination. Let me begin with

a summary of our solicited adverse events collected through e-diary entries for seven days following each vaccinations. Shown here are the local reactogenicity events after the first dose. Participants 18 to 64 years of age are represented in the top panel. And those 65 and older in the bottom panel.

Within each of that column, on the left are vaccinated participants and placebo participants are on the right. Pain and tenderness were the most commonly reported events. And those 65 years of age and older experienced fewer local events compared to those 18 to 64 years of age. While many participants did not report reactogenicity events, those who did mostly reported events that were grade one or two, which is mild to moderate in severity, shown in blue. Grade three and higher, shown in yellow, occurred at low rates.

Overall, these events resolved quickly with a median duration of one to two days. As expected, events occurred more frequently following the second dose. And again, as expected, more participants in

the vaccine group experienced these symptoms. And most events remain grade one or two in severity with low numbers of grade three and higher events.

Now, I'd like to turn to systemic reactogenicity. On this slide are systemic events after the first dose. Malaise, fatigue, muscle pain, and headache were the most commonly reported. And as well for systemic events, we also see lower frequencies in those 65 years of age and older. Again, events were reported as grade one or two, and resolved quickly with a median duration of one to two days. Notably the rates of fever were quite low in less than one percent of participants.

Following the second dose, while higher overall, most systemic events remained mild to moderate in severity as grade one or two. Rates of grade three and higher events were low and occurred in relatively few participants. And even after the second dose, participants reporting fever continued to remain low. Moving to an overview of unsolicited adverse events. Overall the frequency of unsolicited adverse events was

comparable between vaccine and placebo groups. And severe adverse events are reported in few participants. Both pre- and post-crossover.

Medically attended adverse events as well as potential immune-mediated conditions were similar between groups. SAEs were also balanced across vaccine and placebo groups. And, as you can see in the last row, that's also occurred at similar rates between treatment arms. This figure shows pre-crossover unsolicited AEs by system organ class occurring at a frequency of at least one percent through day 49. This was our primary safety collection window through four weeks after receiving the second dose.

Frequency between treatment groups was similar and the overall percentage of participants reporting adverse events remained low. Here, we see more data on potential immune-mediated conditions. These all occurred with low frequency. Individual events occurred with less than one percent incidence and without any obvious patterns that would suggest associations with vaccination. There's a lot of data

on this slide, so let me give you a moment to review the table.

And, as you'll note, overall events were balanced between both vaccine and placebo arms. Shown here are pre-crossover serious adverse events by system organ class with frequency of at least 0.1 percent. SAEs by system organ class were infrequent and comparable between vaccine and placebo groups with the exception of the infection system organ class due to COVID-19 cases in the placebo arm.

When we looked at individual preferred terms there was a numerical imbalance driven by events reported as cholecystitis. And I'd like to provide you a little more of our analysis on this topic. Because we saw an imbalance in cholecystitis cases, we looked at the totality of the data, including a deep dive into individual cases. We do believe that the weight of evidence does not suggest a causal link. In Study 301, the overall frequency of cholecystitis in the vaccine group is low, 0.05 percent, which is consistent with the expected background rate.

In the UK Study 302, there was one additional event in the vaccine arm as well as another in the placebo arm. No events occurred in Studies 501 and 101. All these events occurred in participants with known risk factors for cholecystitis. And all participants had gallstones at the time of event onset. A broader look at related terms with a standard Medrol search did not reveal any additional findings. Importantly there was no clustering or temporal relation to treatment, and we have not received and post-authorization reports with more than 740,000 doses administered.

On this slide we've plotted time to onset of cholecystitis following vaccination. The Y axis is the patient's age, and the X axis represents the number of days from the first dose to when the event was reported. As you can see, we did not observe any temporal patterns and see a pretty random spread over a long period following vaccination.

Because of the importance of myocarditis/pericarditis we wanted to provide you a

complete summary of our clinical data. For this analysis we will be presenting from our entire pool of safety database for a little context. And, as Dr. Shimabukuro reviewed in detail, with the numerous investigations into the myocarditis findings of the past year with messenger RNA vaccines I think we've learned that we can expect to see natural background events of myocarditis in any sufficiently large database.

We've also learned that young males are at higher risk for both vaccine-induced myocarditis and other forms of myocarditis. Most often caused by non-specific infections. COVID infections can also cause myocarditis. It's important to note that our studies were largely conducted during this time of heightened awareness for myocarditis. And so, for our data, overall in our placebo-controlled phase of our clinical development program the rates of myocarditis were balanced between the vaccine and placebo arms at 0.007 percent for vaccine and 0.005 percent for placebo. No pericarditis was reported. In Study 301 one case

occurred in the active arm and one case in the placebo arm.

As a reminder, there was a 2 to 1 randomization in Study 301 in order to increase the sample size of vaccinees. And one case occurred in the active arm of Study 302. Of the two cases in vaccine recipients, one 67-year-old male also had a concurrent severe COVID infection after dose one. The other cases from Study 302 occurred in a 19-year-old male three days after the second dose of vaccine and was without a definitive alternative cause. In the post-crossover portion of Studies 301 and 302, where all participants had been exposed to our vaccine, events of myocarditis or pericarditis occurred within the expected background rates as determined by the EMA Access Study.

This study was specifically designed to determine background rates of interest for COVID vaccines. There were three reports of myocarditis or pericarditis, and all had plausible infectious alternative causes. One notable case occurred in a 16-year-old male two days after the second crossover dose

of vaccine with a viral diagnosis that was diagnosed by a healthcare provider. One 20-year-old male had strep throat preceding the events of pericarditis diagnosed by EKG findings and normal troponin levels.

While the cases in the two teenage males, one during the placebo-controlled phase and one post-crossover, have characteristics of vaccine-induced myocarditis we believe that the totality of the clinical evidence here is not enough to establish an overall causal relationship with the vaccine. I wanted to mention that we did not include here a case that the FDA has included in their briefing document of a 28-year-old male who had features of myocarditis but was diagnosed by a cardiologist with non-ST elevation myocardial infarction. We also, a few days ago, received a follow-up report of a cardiac MRI that did not show evidence of a recent episode of myocarditis.

Our latest monthly summary safety report with post-authorization data includes more than 740,000 doses administered and was submitted in May with a data cutoff of April 30th. We analyzed a cumulative 35

spontaneous reports of potential myocarditis or pericarditis received from passive surveillance systems. These reports often come with very limited information. Because of the general limitations of spontaneous reports, we carefully adjudicated these reports and applied the Brighton Collaboration case definition.

Out of the 35 potential reports none met a definitive case definition. One report was a probable case of myocarditis in a 47-year-old male with an unknown time to onset. There were 10 reports of probably pericarditis. Of these, seven were in males and three were females with a median age of 42 years. The time to onset was 2 to 14 days from vaccination. One of the 10 probable cases of pericarditis was in a participant with a history of messenger RNA vaccines and pericarditis.

Illustrating the limitations of this type of spontaneously reported data we just recently received confirmation by the Australian Health Authority that two pairs of pericarditis cases are duplicate reports

bringing the 10 reports of probable pericarditis down to 8. It's worth noting that as of April 30th all of the probable cases were reported from Australia despite the fact that the doses administered in Australia account for only 17 percent of global administration of the 744,000 doses administered worldwide. No reports of probable cases have been received from other regions, including the EU and South Korea, which also have robust surveillance systems. And those regions also account for the majority of doses administered.

We take all reports of adverse events seriously. As we examine the accumulating data and continue our collaborations and discussions with global regulators, we will get a better understanding of the nature of the cases and a more precise and stable estimate of the rates. We then expect to have more clarity on whether or not this important safety risk is related to the vaccine. We do consider myocarditis an important potential risk and we are very carefully monitoring our post-authorization data. Additionally, we attempt to follow-up each reported case with

targeted questionnaires and these data are being communicated in our analyses in our monthly summary safety reports.

Our close monitoring will also include safety studies which will cover large populations and administrative claims databases and electronic health records. For these other specific events of interest in our clinical development program there were no reports of anaphylactic reactions, or TTS, in our integrated safety data. While our integrated safety data from our EUA submission did not have any cases of Guillain-Barré, a recent update to an SAE of neuropathy from Study 302 has provided information that meets the Brighton Collaboration case definition for Guillain-Barré Syndrome.

We will of course continue to carefully monitor for these events in our post-authorization surveillance activities. Because pregnant women were excluded from all our studies there is limited information on pregnancy. For all women of childbearing potential a negative urine pregnancy test

was required at screening and prior to vaccination. But as it occurs for all large studies with long follow-up, we did have some reports of pregnancies. As of March 15, 2022, a total of 147 pregnancies were reported across the entire clinical program. Fifty-six of the pregnancies were still ongoing and 41 resulted in live birth. Twenty-five experienced miscarriages, 13 women elected to have voluntary terminations, and one had an ectopic pregnancy. There were no fetal deaths or stillbirths reported.

Because pregnancy data was systematically collected and there are inherent reporting and ascertainment biases, you can't make direct comparisons to background rates and draw definitive conclusions. But overall this data does not indicate a potential risk for the mother or fetus and there are no specific restrictions for pregnant women in our global labels. In order to continue safety surveillance for very rare events that may not have been seen in clinical development we also have plans and strategies in place to address potential safety concerns following

Emergency Use Authorization.

Our post-authorization pharmacovigilance investigates potential risks, such as vaccine associated enhanced disease and myocarditis. Novavax supplements our routine monitoring with monthly summary safety reports and targeted follow-up questionnaires. Qualitative and quantitative reviews using multiple data sources for signal detection are conducted on a daily, weekly, and monthly basis. Additionally, we plan to conduct five post-authorization studies. They include two effectiveness studies and two safety studies using administrative claims and electronic health record databases to robustly characterize the safety profile in the post-marketing setting.

And Study 405 is a global registry that will provide us with important data in pregnant women who receive our vaccine. So, in summary, the Novavax COVID vaccine safety data supports positive benefit/risk and a favorable reactogenicity profile. Our vaccine is well-characterized with exposure in more than 30,000 recipients across the entire clinical program in the

pre-crossover placebo-controlled portion of the studies. Local and systemic reactogenicity events were generally grade one to two in severity and resolved within one to two days. Grade three and higher events were infrequent.

Importantly, we saw low rates of fever post-vaccination and most AEs were mild to moderate in severity. When we look at our long-term post-crossover follow-up where more than 40,000 recipients received the vaccine rates of SAEs were low and comparable to placebo. And for the important potential risks we will continue to monitor for these events with our ongoing and future safety studies. Thank you. I'd like to invite now Dr. Greg Poland to share his clinical perspective on the Novavax COVID vaccine.

CLINICAL PERSPECTIVE

DR. GREG POLAND: Thank you. Good morning, everybody, I'm very pleased to be here to provide my clinical perspective on the Novavax vaccine. I've been

a practicing internist for 40 years and have served as a PI of over 40 vaccine clinical trials. And I'm the editor-in-chief of the *Journal Vaccine.* I've spoken to this Committee before about the need for COVID vaccines, and I'm here today to discuss why the Novavax vaccine is an important addition to what is already authorized.

As we are all well-aware two years into this pandemic the SARS-CoV-2 variants continue to challenge and re-challenge us. And a major reason for the continuing pandemic is that despite the availability of safe and effective COVID-19 vaccines and the constant efforts of our public health officials to increase vaccination rates, millions of Americans today are still unvaccinated, as we've heard.

While I expected some of the challenges, we're seeing today with this pandemic I am still surprised to see how this virus continues to unfold and what we're learning about the long-term and multidimensional impact the virus is having on individuals and the public health. There's no question that our ability to

quickly develop vaccines has been impressive, however, the complexity and dynamic nature of this virus emphasizes the need to have multiple vaccine platforms to fight it.

For those individuals who are not fully vaccinated and waiting for another option, having a vaccine platform that multiple stakeholders, including regulators, physicians, and the public are familiar with, can help mitigate some of the challenges we're facing today. Indeed a recent Ocugen/Harris Poll found that 73 percent of Americans would like additional COVID-19 vaccines developed from a more traditional method.

Perhaps this is no surprise considering what we've witnessed during the pandemic when people become concerned about vaccine safety or tolerability. The latest CDC data reports that 89 percent of the U.S. population over the age of 18 have received one dose. And then we see the uptake of a second dose and booster shot fall precipitously. Only 77 percent have gotten a second dose, and only 50 percent the first booster.

There are many indications that decrease is linked in part to concerns people have about vaccine safety, reactogenicity, and efficacy. I certainly see that in my own practice. In the last year I've received innumerable requests from physicians asking how to treat patients who've had a reaction to one of the currently available COVID-19 vaccines. Reactogenicity is a real problem, and one that prevents a significant number of people from being fully vaccinated.

So what is the benefit of the Novavax vaccine platform? The data shows that combining the SARS-CoV-2 spike protein with an immune-enhancing adjuvant stimulates robust antigen-specific immune responses and provides high efficacy. Importantly, the vaccine is not highly reactogenic and compares favorably with other vaccines. We saw that borne out in the Sponsor's clinical trials, where most events were mild to moderate and resolved in just a day or two. And, as a reminder, the vaccine was able to deliver 90 percent efficacy with this favorable reactogenicity profile.

This well-defined recombinant protein platform demonstrated safety and efficacy in two large Phase 3 clinical trials against numerous variants. The combination of the immunogenicity data showing robust antibody responses across multiple variants with clinical efficacy data from the Phase 3 trials signals broad cross-protection. This will be vital as we head into an era where we simply don't know what the next variant will be. Simply put, it's important to have choices in vaccine platforms in a pandemic that is constantly evolving.

It's also important to make it as easy as possible to get vaccines to the people who need them. While many of us think of logistics in the cold chain and increased access is an issue in the developing world, there are also many healthcare providers in the United States who will find the ease of storage and administration of the Novavax vaccine to be a significant benefit over current vaccines. Every day we're learning more about just how important it is to remain vigilant about trying to control this pandemic

in the longer term for both the individual and the public health.

Someone who is unvaccinated has a four-fold greater chance of getting infected, is 23 times more likely to be hospitalized, and has a 20-fold higher chance of dying than a vaccinated person. The fact that we're still seeing more than 300 people die every day in American from COVID-19 is simply unfathomable to me. In fact, there are four more than the 100,000 new cases being reported each day. This is clearly an undercount due to the amount of home testing.

These cases are resulting in almost 3,000 new hospitalizations per day. And this represents a significant opportunity to protect health with vaccines. And this is just the impact from the immediate acute infection. One aspect of this pandemic that is just starting to be understood is the long-term impact. And this includes both the individual and our healthcare system. A study published in *Nature* this February showed that one year after recovery people with COVID, whether mild or not, had a substantially

higher risk of 20 different cardiovascular conditions than those who did not have COVID.

These conditions, like heart disease, vascular disease, and heart failure are likely to negatively affect the health and life expectancy of people for years, if not decades, to come. In addition to physical ailments the new research is also documenting the mental COVID is having on people. A study also published this February, this one in the *BMJ*, reported that people who had COVID and were hospitalized were more likely to experience anxiety, depression, suicidal thoughts, and to experience opioid disorders.

And these physical and mental health issues due to COVID are preventable if we get a handle on this pandemic and offer people choices that they may be more likely to use. Thereby encouraging them to get vaccinated. In summary, as a clinician, I believe the Novavax vaccine offers benefits to multiple stakeholders. Patients and providers will find the Novavax vaccine an easy and logical option based on its efficacy, safety, and tolerability, especially the

millions of Americans who say they are waiting for another option.

Pharmacies and distributors will find this an easy and logical option for logistical reasons because, as we've heard, it's easier to ship, store, and administer. Employers will find this an easy and logical option to encourage people to get vaccinated. And, finally, policymakers will find this an easy and logical option because it's a vaccine that's easy for people to access, easy to explain, and a choice that people want. One last note, while we're here today to discuss only the COVID vaccine, the clinician in me is also hopeful about the continued potential of this vaccine platform.

By design it's inherently amenable to combination vaccines, including influenza, RSV, and other respiratory illnesses. We've had remarkable success increasing vaccine compliance utilizing combination vaccines in children. And, ultimately, this can be true in adolescents and adults. As I conclude, I want you to understand that speaking to you

today is both personal and professional for me. I've dedicated my career to researching and fighting infectious diseases. I've taken care of patients for over 40 years, and I've seen firsthand the miracle of what vaccines can do.

We have an opportunity and a need to be proactive and continuously vigilant as the challenge and the fight against COVID is likely to continue for the foreseeable future. Authorizing an effective vaccine with a different mechanism of action is not only important for Americans but will have an impact on global health. Our goal should be to have the right vaccine for the right person for the right purpose at the right time. And having more vaccine options with different platforms is a key component of achieving just that. Thank you for your attention, I'll now turn the presentation over to Dr. Dubovsky to conclude.

SPONSOR PRESENTATION CONCLUSION

DR. FILIP DUBOVSKY: Thank you, Dr. Poland.

The results from our clinical development program strongly support Emergency Use Authorization for people 18 years of age and older. Our vaccine is based on the differentiated platform that is well-understood. Recombinant protein vaccines have been used globally for decades. Our adjuvant, Matrix-M, is a natural saponin product and saponin-based adjuvants are used globally.

Importantly, our vaccine achieved 90 percent efficacy in our Phase 3 Study in the U.S. and Mexico despite the majority of cases been attributed to variants. Our vaccine offers a favorable reactogenicity profile with most symptoms resolving after one or two days. And our safety data, that was collected in a diverse American population, supports a positive benefit/risk profile.

In summary, NVX2373 can be a useful tool in addressing the ongoing pandemic, providing a different option, and may be helpful in increasing the incomplete vaccination rates in the U.S. Thank you, and I'll turn it over to Dr. Monto.

DR. ARNOLD MONTO: Thank you. We have just a few minutes for some specific questions. I want to remind the Committee that we will have a much more, less time-constrained discussion after we hear the FDA presentation. And I want to remind you that yes, we do know there have been other variants, yes, we know there are booster shots being given, and there are mix and match strategies. But that's not what we're going to be talking about in the next few minutes of questions. We're going to be talking about the presentation of the data on the clinical trial that is being considered for our evaluation right now. Dr. Levy.

DR. OFER LEVY: Hello, thank you for that presentation which was very interesting. I had two quick questions. One is regarding the apparent lower vaccine efficacy, or VE, in Hispanic or Latino individuals. The presentation pointed out that this was puzzling because the immunogenicity appeared to be similar to other groups. And that maybe this was a chance observation. Another interpretation may be that we don't understand the correlative protection well

enough.

And that's what's being measured for the immune response doesn't capture what is protecting. So does Novavax have a comment on that? The other question regarding safety, are there any lessons to be learned from looking at safety data of other studies with other saponin-based adjuvants? Thank you.

DR. FILIP DUBOVSKY: Yeah, so as far as your first question goes, there's emerging data now from our Phase 3 Study, 301 Study, that was supported by the U.S. government. And there's a close-up protection analysis that's emerging now. And the best correlative that was in fact identified appears to be looking into neutralization (inaudible) antibodies. Now we looked at those patients, the Hispanic participants, very closely.

We were interested to know if they were from the U.S. or Mexico, in fact all the cases were in the U.S. And when we looked carefully at their other risk factors, we didn't identify anything specifically which seemed to have pointed to an increased risk. So right

now our best estimate is that may be a chance finding alone.

As far as other saponin-based vaccines, the largest database for our particular version of saponin is clearly the studies we presented today. We have data from multiple antigens that we've tested previously in pre-live interest studies. And that includes influenza, which we took through a Phase 3 Study. And the reactogenicity profile looks comparable. And certainly, we didn't see anything that looks like any of the events of concern that we talked about previously.

The other saponin-based vaccines are largely, well, they're distributed both in the U.S. as well as globally. And I'm not sure that there's anything specific we can learn from them because clearly, they are given with different antigens. So that leads to a different biological profile.

DR. ARNOLD MONTO: Thank you. Dr. Pergam.

DR. STEVEN PERGAM: Okay, I think I was unmuting, and somebody unmuted me, I apologize. I had

a question just about the incidence of COVID. It seemed as though the benefit was primarily after the second dose of the vaccine, which was around three weeks that second dose was given. Does the company have any data on antibody responses following the first dose knowing that the data that Dr. Poland presented? Not everyone does get a second dose of vaccine, and is there evidence, or do they have additional data on those who only received on dose of vaccine and the antibody responses in those?

DR. FILIP DUBOVSKY: Yeah, so the Kaplan-Meier that Dr. Mallory showed, showed the rates diverging on day 21, which was the day the second dose was administered. So, obviously it takes time for that second dose immune response to mature, so we would posit that some of that benefit we're seeing is really from the first dose. We have looked at efficacy following the first dose, and I think I'll need to bring that data to you after the lunch break. I don't seem have it readily available right now.

DR. ARNOLD MONTO: That's perfect.

DR. STEVEN PERGAM: Okay, thank you.

DR. ARNOLD MONTO: Looks go on to Dr. Berger.

MR. MICHAEL KAWCZYNSKI: You don't have to wait till your camera pops up to speak, go ahead, Dr. Berger.

DR. ARNOLD MONTO: We see you.

MR. MICHAEL KAWCZYNSKI: Dr. Berger, did you mute your phone? Yeah, did you mute your own phone? There you go, sir.

DR. ADAM BERGER: Okay, sorry. I just wanted to come back to the question around vaccine efficacy in Hispanic populations again. And just see if you've been able to conduct any sub-group analyses to look at the 18 to 64 range and the 65+ to evaluate vaccine efficacy in each of those sub-populations by themselves.

DR. FILIP DUBOVSKY: Yeah, there were very few number of cases, if you remember. There were a total of 27 cases. In the elderly there were really very few cases, as Dr. Mallory presented, there were only six cases total. So, I'm not sure that would be an

informative analysis to look at, but we can try to do a 2 by 2 table over the break.

DR. ARNOLD MONTO: Thank you. Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Monto. I have one comment which will lead into my question. That is there's an interesting editorial this week in the *New England Journal* about whether the world needs additional vaccines. And the article points out that there have been 11.5 billion doses of COVID vaccines that have been distributed, which sounds like a big number until you remember there are almost eight billion people on the planet that we need to vaccinate.

And the distribution obviously of those vaccines have been unequal between high income, middle income, and low income countries. Clearly there's a need for additional vaccines. And, furthermore, it may be that a protein platform vaccine such as the one you're using offers advantages over the messenger RNA vaccine, which is what leads to my question. And that is, Dr. Mallory mentioned that there was a reduction in upper airway viral numbers among people who had

received the vaccine.

Suggesting that there may be some mucosal impact from this vaccine, and it might have perhaps better effectiveness at reducing infection in addition to severe illness. Can you quantify that? Have you looked at IG, mucosal IGA or do you have a sense of how well this vaccine might protect against infection versus severe disease? Over.

DR. FILIP DUBOVSKY: Yeah, the data that Dr. Mallory referenced was primate work and there, what we demonstrated and is published now, is that the vaccines capable of generating sterile immunity in the upper and lower airway. We don't have IGA data from the studies to collect, and during the pandemic we weren't actually able to do that. What we do know is the vaccine is capable of preventing infection from our clinical studies. And we measured this by looking at zero conversion to N, at the N protein as well as being PCR positive.

Perhaps I'll be able to briefly share that data with you, but what we saw is that in the UK study,

we were able to prevent infection in 82 percent of the people who were vaccinated. And, obviously, if you don't get infected you can't transmit, you can't develop the emergence of variants, and you can't have long COVID because you're not infected.

DR. ARNOLD MONTO: Thank you. Finally, Dr. Marasco.

DR. WAYNE MARASCO: Yes, thank you, Dr. Mallory. So I have a -- Dr. Mallory's, I have a comment on Dr. Mallory's presentation and a question on Study 301. If I have the data right, you looked at neutralizing antibody responses 35 days after their second boost. And you followed the patients for roughly 50 days.

Is there a time dependence for breakthrough infection? Do you have enough data to know that? Because with your high neutralizing antibody titers that were measured at day 35, and then your follow-up period, is there a time dependent risk in acquiring infection?

DR. FILIP DUBOVSKY: Right. It's an excellent

question. As we described, for all of our studies we had to institute a crossover into the design, and that's because Emergency Use vaccines became available and to maintain integrity of the study, we had to provide everyone a vaccine. What that did is it took away our ability to have placebo-controlled data beyond the crossover period.

The issue with looking at the breakthrough cases for our specific vaccine in Study 301 is there were very, very few cases. So you could see from the Kaplan-Meier curve kind of where they fell out. And there wasn't a specific uptick as time went on, it was relatively flat, if you remember the data that Dr. Mallory showed.

DR. ARNOLD MONTO: Thank you. We're going to try to catch up by taking a break now. Why don't we stick with the 15 minutes we had before, so we will reconvene at 11:30 Eastern Time. And then we're going to shorten our lunch to half an hour so that we can fully catch up and start the oral public hearings on schedule. So, break until 11:30 Eastern, 15 minutes.

[BREAK]

FDA REVIEW OF EFFECTIVENESS AND SAFETY OF NOVAVAX COVID-19 VACCINE IN INDIVIDUALS 18 YEARS OF AGE AND OLDER

MR. MICHAEL KAWCZYNSKI: All right. Welcome back from that quick break. Just to keep us on time, I'm going to hand it over to our Chair. Dr. Monto, are you ready?

DR. ARNOLD MONTO: I am ready. We have one presentation before our lunch break from the FDA presenting the review of effectiveness and safety of Novavax COVID-19 vaccine in individuals 18 years of age and older. Dr. Lucia Lee will be our presenter. Dr. Lee.

DR. LUCIA LEE: Good morning. I'll now present the FDA review of clinical data submitted in the Novavax COVID-19 emergency use authorization request. I'll start with the regulatory background and

the overview of clinical studies followed by the design of Study 301, the main source of efficacy and safety data to support the EUA request, additional safety data from other studies, and then a summary of risks and benefits and the VRBPAC question.

The Novavax COVID-19 vaccine contains five micrograms of recombinant spike protein and 50 micrograms of Matrix-M adjuvant. The proposed primary series is two doses given three weeks apart. This slide presents an overview of clinical studies and the number of vaccine recipients in the safety population during the pre-crossover period.

The primary source of clinical data to support the EUA request is Study 301, which provides the safety and efficacy data in approximately 20,000 vaccine recipients who were initially randomized to receive the vaccine. Additional safety data from approximately 10,000 additional vaccine recipients were provided from three studies conducted with the vaccine produced by an earlier manufacturing process than the vaccine evaluated in Study 301.

In Study 301, an ongoing, randomized, observer-blind, placebo-controlled Phase 3 efficacy, safety, and immunogenicity study, a total of approximately 30,000 participants 18 years and older in the U.S. and Mexico included adults who, by virtue of age, race, ethnicity, or life circumstances, were considered at substantial risk for exposure to SARS-CoV-2.

These participants were stratified by age groups 18 to 54 and 65 years and older. During the course of the study, COVID-19 vaccines authorized for emergency use became available, and participants who ineligible for vaccination per national and local public health prioritization recommendations were offered the opportunity to cross over from the originally assigned study treatments to the other study treatment, the vaccine to placebo and placebo to vaccine.

The primary efficacy endpoint was assessed until the participant received the first blinded crossover vaccination or until the data cutoff of

September 27th, 2021, whichever came first. And there was also an assessment of humoral antibody responses assessed in a subset of participants.

The safety assessments concluded the following: the solicited, systemic, local and systemic adverse reactions during the seven days after each vaccination, unsolicited adverse events and medically-attended adverse events through 28 days following a second vaccination in both the pre-crossover and the post-crossover period, and through the duration of the study, medically-attended adverse events attributed to study vaccine, serious adverse events, and adverse events of clinical interest.

Efficacy was assessed through daily surveillance of symptoms suggestive of COVID-19 throughout the study follow up. Symptoms of COVID-19 experienced by participants during the post-vaccination follow up prompted an unscheduled illness visit in person. A nasopharyngeal swab was collected and sent to the central lab for processing.

Additionally, participants were also given a

kit to begin a daily self-nasal swabbing within three days of symptom onset and collected for a total of three days. The swabs were also sent to the central lab for processing. Molecular confirmation of SARS-CoV-2 infection by the central laboratory was required to meet primary and secondary efficacy endpoint case definitions.

The primary efficacy objective was to prevent PCR-confirmed symptomatic COVID-19 illness diagnosed seven or more days after completion of the primary series. Primary efficacy endpoint was the first episode of PCR-confirmed mild to moderate or severe COVID-19 assessed up until the blinded crossover period. The primary objective would be met if the point estimate of the vaccine efficacy was 50 percent or more and the lower bound of the 95 percent confidence interval was greater than 30 percent.

And below, some of the secondary and exploratory efficacy objectives are also shown on this slide. These are the case definitions for mild, moderate, and severe COVID-19 and the dataset to

support the EUA. The FDA conducted independent analyses of datasets with different cutoff and extraction dates. These included efficacy and safety data with the data cutoff of September 27th, 2021. These were cleaned datasets.

And then safety data was requested from FDA to review clinically important safety events with an extraction date of February 17th, 2022. And these were from datasets that were not fully cleaned. This slide presents disposition of all randomized participants as of the data cutoff, September 27th, 2021. A total of 29,945 participants were initially randomized in a two-to-one ratio with 19,963 vaccine participants and 9,882 placebo participants who received saline.

96.8 percent of the vaccine group and 95.7 percent of the placebo group completed the two-dose primary series. Then, 77.7 percent of participants who were initially randomized to the vaccine group and 64.8 percent in the placebo group elected to participate in the crossover portion of the study. This slide presents the efficacy analysis population.

Per protocol, population for efficacy was comprised of participants who received two doses of the vaccine or placebo at the pre-specified time points and had no major protocol deviations prior to the first COVID-19-positive episode, no confirmed SARS-CoV-2 infection during the surveillance period, or prior infection due to SARS-CoV-2 at baseline and were not censored prior to the start of the observational period.

Seventy-eight percent of vaccine participants, recipients and 73.1 percent of placebo recipients completed at least two months of follow up after Dose 2. And then the second per-protocol efficacy sets included all participants regardless of baseline SARS-CoV-2 status. Here's the pre-protocol efficacy population. They were balanced in terms of percentage of male and female. The median age was 47 years with 12 percent of participants 65 years and older.

In terms of race and ethnicity, 11 percent of participants were African American. Six percent were American Indian or Alaskan native. Four percent were

Asian, and 22 percent were Hispanic. The main comorbidities were obesity and chronic lung disease. The primary efficacy endpoint was assessed until the participant received the first blinded crossover vaccination or until the data cutoff of September 27th, 2021, whichever came first.

In the per-protocol efficacy set, during the pre-crossover period, 21.7 percent of participants who received the placebo were unblinded with the intention to receive a COVID-19 vaccine under EUA as compared to 13.2 percent of participants who received the vaccine. These participants were censored for the primary efficacy analyses at the time of unblinding.

For the results, the primary endpoint for 18 years and older as a whole was met. The vaccine efficacy for the first episode of PCR-confirmed mild, moderate, or severe COVID-19 was 90.4 percent. And of the 17 cases of COVID-19 in the vaccine group, all were mild in severity. In the placebo group, there were 66 cases which were mild, 9 which were moderate, and 4 cases that were severe.

There were no hospitalizations or deaths due to COVID-19 among the 96 primary endpoint cases. In the analysis of the primary efficacy endpoint provided for participants who were SARS-CoV-2 positive at baseline, among the 3,300 participants who were SARS-CoV-2 positive at baseline, there were no COVID-19 cases that occurred at least seven days after the second dose. So the vaccine efficacy, regardless of baseline SARS-CoV-2 status, was 89.8 percent.

And in the age group 65 years and older, the lowered limit of the 95 percent confidence interval for the vaccine efficacy estimate was negative 16.6. There were six cases, two in the vaccine group and four in the placebo group. And the 95 percent confidence interval for the estimate was wide. To provided supportive data for the effectiveness in adults 65 years and older, a post-hoc analysis of the vaccine efficacy among participants 50 to 64 years of age was conducted at FDA's request.

The neutralizing antibody titers in this age group was compared descriptively to those participants

65 years of age and older. The table on the left summarizes the results of the immunogenicity comparison between the two age groups. The GMT for the participants 65 years of age and older was a little lower than the GMT for the age group 50 to 64 years of age, but the GMT ratio was 0.91 with the lower bound of the 95 percent confidence interval that would've met FDA's usual success criterion for immunoprotein.

On the right, the vaccine efficacy estimate for age groups 50 to 64 years of age was 90.7 percent, which was comparable to the overall vaccine efficacy for ages 18 years and older, which was 90.4 percent, and for the age group 18 to 64 years of age, which was 90.1 percent. These are the results of the secondary and exploratory efficacy analysis. First, the efficacy against COVID-19 for variants.

Of the 96 cases in the primary efficacy analysis, 75 cases has sequencing data available, which were mainly the Alpha variant. These were classified in the sponsor's presentation according to the CDC classification during May 2021. Currently, as of June

2022, none of the variants identified in the primary efficacy analysis were considered variants of concern or variants of interest. The second analysis was vaccine efficacy against moderate to severe COVID-19.

There was a total of 13 cases in placebo arm and none in the vaccine group, resulting the vaccine efficacy estimate of 100 percent. Third, the vaccine efficacy by rase was comparable to the overall study population. And, as discussed previously, there was a lower vaccine efficacy estimate for participants of Hispanic ethnicity. The participants in the safety analysis, these participants were enrolled from a total of 119 sites in the U.S. and Mexico.

In the pre-crossover period, as of the cutoff date, September 27th, 2021, the median duration of follow up during the pre-crossover period was 2.5 months. In the safety analysis, that included 19,111 participants in the vaccine group and 9,416 participants in the placebo group. And 77.8 percent in the vaccine group and 72.8 percent of placebo recipients completed at least two months of safety

follow up after the second dose.

In the post-crossover period, the median duration of follow up after the fourth dose was 4.4 months, and 99 percent of participants in each study group were followed for at least 2 months after the second crossover dose. Third, the Sponsor provided, at FDA's request, additional safety data through the extraction date to February 17th, 2022, to assess clinically important adverse events.

And at the time of the extraction date, the median duration of follow up was 8.4 months after the completion of the crossover series. The demographics for the safety analysis population in the vaccine group and the placebo group were similar.

(technical difficulties 03:14:21)

MR. MICHAEL KAWCZYNSKI: Go ahead with your microphone.

DR. LEE: Thank you. Can you still hear me now?

MR. MICHAEL KAWCZYNSKI: Yep. I can here you now. Go ahead.

DR. LUCIA LEE: Okay. The safety analysis population -- okay. The demographic and baseline characteristics -- I think I'm hearing an echo.

MR. MICHAEL KAWCZYNSKI: Yeah. Go ahead and turn off your speaker -- turn down your speaker. Again, if you want to just reconnect your audio, ma'am. Right now you're on speaker but on your microphone on your computer. If you want dial back in, it's up to you. otherwise you can continue but just turn your volume down. I'll help you.

DR. LUCIA LEE: Okay.

MR. MICHAEL KAWCZYNSKI: Yeah. Ma'am, I'm going to dial you in a different way real quick. If you could, look at the chat pod. Just give us a quick momentary break, and I'm going to help our speaker here. Again, just give us a minute while we help out Dr. Lee. Dr. Lee, you with us?

DR. LUCIA LEE: Yes. Can you hear me now, Mike?

MR. MICHAEL KAWCZYNSKI: Yes, I can. Just go ahead and mute your speakers then continue, okay? On

the top of your screen, just go ahead and mute the speaker symbol, and you can continue. Okay, ma'am?

DR. LUCIA LEE: Okay.

MR. MICHAEL KAWCZYNSKI: All right. Take it away.

DR. LUCIA LEE: Okay. So the demographic baseline characteristics in the safety analysis population in the vaccine group and placebo group were similar in the pre-crossover period. Also, the pre-crossover period the demographic and baseline were similar to the post-crossover period and the safety analysis set was similar to the per-protocol efficacy set.

This slide shows the overall rates of reactogenicity.

(technical difficulties 03:19:51)

MR. MICHAEL KAWCZYNSKI: You still there, ma'am? Lucia, you still there? Ma'am, did you mute your own phone? Oh, you dialed back in. Here we go.

DR. LUCIA LEE: Okay?

MR. MICHAEL KAWCZYNSKI: There you go. There

you go, ma'am. Go ahead.

DR. LUCIA LEE: So the solicited adverse reaction were reported in higher proportion of the vaccine recipients than the placebo recipients and more frequent after vaccine Dose 2 than Dose 1. In the interest of time, I'm going to skip the details of this. In general, the local and systemic adverse reactions were mild to moderate and lasted about one to three days.

This slide shows unsolicited adverse events. The frequency of nonserious unsolicited adverse events occurring through 28 days after Dose 2 by time period are shown here. In the pre-crossover period, the percentages of participants reporting at least one nonserious unsolicited adverse events were comparable between the vaccine and placebo groups. In the post-crossover period, the percentage of participants reporting at least one unsolicited adverse events was lower than the pre-crossover period and slightly higher than the vaccine group and placebo group.

In terms of Grade 3 reactions and Grade 3

reactions considered by the investigator as related to the study product, all those percentages in both the vaccine group and the placebo group were low. The key findings in the pre-crossover period included that there were no adverse events by preferred term reported by more than one percent of participants in either study group.

There were imbalances in the system organ class of general disorders and administrative site conditions and blood and lymphatic system disorders, which were largely due to reactogenicity and lymphadenopathy, respectively. Lymphadenopathy was reported by a higher proportion of participants in the vaccine arm for Dose 1 and Dose 2, which was 0.06 percent and 0.2 percent, respectively, than in the placebo group.

The most commonly reported severe unsolicited adverse event in the vaccine group was fatigue. The percentage of participants reporting serious adverse events was similar in the placebo group and the vaccine group in both the pre-crossover and the post-crossover

period and range from one percent to 1.4 percent across study groups. The percentage of participants reporting SAEs related to study vaccination was 0.1 percent in both the vaccine group and the placebo group and in both time periods.

The percentage of deaths reported in the vaccine and placebo groups was less than 0.1 percent in both time periods. This slide shows the number and percentage of deaths reported in the pre- and post-crossover periods by study group and the causes of death. For participants with fatal cardiac arrest, there were five in the vaccine group during the pre-crossover period compared to three in the placebo group and one in the post-crossover period in the vaccine group.

For most of these participants, they had underlying factors and conditions which were risk factors for cardiac arrest. However, at this time, there is limited information available to assess the cause of death as some of the autopsy data were not available. Participants in this study were randomized

in a two-to-one ratio which could account for more events in the vaccine group. Additional data presented through the February 17th, 2022, extraction date: all of these deaths had a time onset of 140 days or more following the Dose 4 in the crossover period.

None of these deaths were considered by the investigator or FDA as related to vaccination. In the pre-crossover period, the most common serious adverse events that occurred at higher rates in the vaccine group than the placebo group were cerebrovascular accident, acute cholecystitis, atrial fibrillation, aspiration pneumonia, and spontaneous abortion.

In the post-crossover period, the most common SAEs occurring at higher rates in the vaccine group versus the placebo group were ischemic cardiac events, which included myocardial infarction, cholecystitis, both chronic and acute, and pneumonia. In terms of events of clinical interest, which included potentially immune-mediated medical conditions, there were numerical imbalances observed in the following categories of cardiac, neurovascular, embolic and

thrombotic, and biliary events.

In terms of cardiac events, there was an imbalance of events of cardiac failure and cardiomyopathy with 0.5 percent in the vaccine group and 0.02 percent in the placebo group. Almost all of these participants had underlying conditions that were risk factors, and the time to onset is comparable between the two groups. In the post-crossover period there was imbalance events consistent with myocardial infarction.

The time to onset was comparable between the two groups. In terms of neurovascular events, in the pre-crossover period there was an imbalance in events consistent with stroke, and three of the events occurred within 15 days of the most recent vaccine dose. And both events in the placebo group occurred within 15 days of the most recent placebo dose. Cumulatively through February 17th, 2022, there were a total of 19 neurovascular events consistent with stroke that were reported in the vaccine group in the pre-and post-crossover period.

The time to onset from last vaccine dose for 11 of the 19 cases occurred greater than 61 days after the last vaccination. In terms of thrombotic and embolic events, in the pre- and post-crossover period, the noncardiac non-neurovascular thrombotic and embolic events were balanced in the pre- and post-crossover periods. However, there were 8 participants in the vaccine group that experienced events within 21 days of the most recent vaccine does without plausible alternative etiologies.

And cumulatively through February 17th, 2022, there was an imbalance of pulmonary embolisms that occurred during the post-crossover period. However, most of the events in both study groups had an onset of greater than 90 days after the most recent dose, and the proportion of events with onset less than two weeks were comparable.

In terms of biliary events, in the pre- and post-crossover period, there was an imbalance in cholecystitis. And the 18 events in the vaccine recipients in both time periods, 6 of those had an

onset within 30 days of the vaccine dose. In terms of other events of clinical interest, those included Bell's palsy, and these were all in the pre-crossover period.

There was 1 case of Bell's palsy within 30 days of vaccination in each of the placebo and vaccine groups. In terms of uveitis, there were three participants in the vaccine group with new-onset uveitis within three weeks of vaccination, one of which recurred with rechallenge.

In the placebo group, there were two events of uveitis, one of which had onset within one week of placebo in a participant that had a history or uveitis. Lastly, there was one event of angioedema and urticaria that occurred two days after Dose 2 in the vaccine group, which was potentially related, but the participants also started an antibiotic concomitantly.

In review of the additional safety data from Studies 101, 301, and 501, which were conducted in Australia and the U.S., 302 was in the United Kingdom, and 501 was in South Africa, the FDA reviewed serious

adverse events and adverse events of clinical interest. These studies were conducted with a vaccine produced by an earlier manufacturing process than the vaccine evaluated in 301.

Out of the three studies, there was one event, Guillain-Barre syndrome, that was reported by a 65-year-old female in the vaccine group who experienced progressive neuropathy starting at 9 days after Dose 1. Other than this event, there were no new serious adverse events, adverse events of special interest, or potentially immune-mediated conditions in these studies that were considered at least possibly related by FDA that were not already previously identified in Study 301.

In a total clinical safety database of about 40,000 vaccine participants to date, 6 vaccine recipients reported myocarditis and/or pericarditis, including 5 events that occurred within 20 days after the Novavax vaccine. These are the cases, a little bit more detail. These cases were concerning for the following reasons. The temporal relationship for 5 of

the cases occurred within 20 days after vaccination.

And only one of the events among the vaccine group had a clearly identified alternative etiology associated with myocarditis. And the other events had only circumstantial evidence of potentially plausible alternative etiologies. Four of the events occurred in young men, which is a subject population known to be at high risk for mRNA COVID vaccine-associated myocarditis.

Now, I'm continuing to the Sponsor-submitted post-marketing safety data. As of April 30th, 2022, there are about 700,500 doses administered in Australia, Canada, the European Union, New Zealand, and South Korea. The Sponsor reported a potential safety signal for myocarditis and pericarditis listed here. The observed-to-expected rate ration for all doses was 4.95.

In summary, the known potential benefits include that the vaccine was efficacious with an estimate of 90.4 percent and the efficacy estimates from Study 301 were generally consistent among some

groups stratified by demographic variables and for the risk of severe COVID-19. The uncertainty in the benefits include vaccine effectiveness against currently circulating SARS-CoV-2 variants, long-term effects of COVID-19 disease, effectiveness in certain populations at higher risk of severe COVID-19, and the duration of protection.

The known and potential risks associated with vaccination include local and systemic reactogenicity, myocarditis and pericarditis and Guillain-Barre syndrome. And there are uncertainties in the risk in certain populations and for adverse reactions that are uncommon and that require longer follow up, which include biliary events, neurovascular events, cardiac events, and uveitis.

Sponsor submitted a pharmacovigilance plan to monitor safety concerns that could be associated with the Novavax COVID-19 vaccine. The FDA recommended adding myocarditis and pericarditis as an important identified risk. And the Sponsor considered as important potential risk vaccine-associated enhanced

respiratory disease, myocarditis and pericarditis and anaphylaxis. The Sponsor will conduct several post-marketing activities, which include active and passive surveillance activities, periodic aggregate safety review of safety data, and five planned surveillance studies.

So the pharmacovigilance activities include adverse event reporting, which come from vaccine recipients, vaccine providers, or the Sponsor themself. First, the vaccine participants will be notified that adverse events can be reported to VAERS through the vaccine for recipients and health care providers or from the V-SAFE program, and this reporting is voluntary.

For the vaccine provider and the Sponsor, these adverse event reporting is mandatory. For both the vaccine providers and the Sponsor, they report to VAERS the following information; serious adverse events irrespective of attribution to vaccination, cases of multisystem inflammatory syndrome in adults, and cases of COVID-19 that result in hospitalization or death.

In addition, the Sponsor will also conduct periodic aggregate safety review of safety data and report newly identified safety concerns. Both the FDA and CDC take a collaborative and complementary approach to reviewing adverse events. In the initial stage of post-authorization surveillance, FDA will individually review all serious adverse events on a daily basis.

FDA will also examine other sources of AE, such as in the literature, and perform data mining to determine if the adverse events are disproportionately reported for the candidate vaccine compared to other vaccines in VAERS. And other potential safety signals will also be investigated. In addition to passive surveillance, FDA will also perform active surveillance studies for safety outcomes.

These studies will be conducted using the Biologics Effectiveness and Safety System which obtains safety outcomes from various health care settings. Active surveillance will also be performed using data from the centers for Medicare and Medicaid services. The Sponsor also proposed five post-authorization

surveillance studies.

The first is a Pregnancy Exposure Registry, and the second and third are two active follow-up safety studies, one in the U.S. and one in the U.K. And the last two are real-world effectiveness studies, one in the U.S. and one in Europe. Lastly, the Sponsor was requested to include certain safety outcomes in active surveillance studies, which includes the basement of cardiac, neurovascular, embolic and thrombotic, and biliary events.

The Sponsor will also perform enhanced pharmacovigilance activities for safety outcomes of GBS and uveitis. This concludes my presentation.

DR. ARNOLD MONTO: Thank you, Dr. Lee, and apologies for the interruption. You did very well considering. We do have a few minutes for questions now before the lunch break. I don't see any hands raised. Is that the system's fault?

MR. MICHAEL KAWCZYNSKI: No, no. There's no hands raised at the moment. I was looking too.

DR. ARNOLD MONTO: No hands raised? I can't

believe it.

MR. MICHAEL KAWCZYNSKI: No. Oh, wait. Here we go. We got out first one.

DR. ARNOLD MONTO: There we go. Okay, Dr. Gellin.

DR. LUCIA LEE: I also wanted to mention that Dr. Brandon Day will answer questions pertaining to the pharmacovigilance plan.

DR. ARNOLD MONTO: Thank you. Dr. Gellin.

DR. BRUCE GELLIN: Okay. Thanks. Maybe we're going to get into later. Thank you for that great presentation. It's a lot of detail, and you had to deal with the system. None of that is easy, so thanks for that. Are we going to get into sort of the real-world part of this? We heard the study data is through the end of September. A lot has happened since then. I'm guessing study participants have had real lives and done other things, like gotten other vaccines from whomever, maybe had other experiences. Is that going to come into play at some point?

DR. LUCIA LEE: Dr. Day, do you want to take

that question?

MR. MICHAEL KAWCZYNSKI: Who did you want to take that question again?

DR. LUCIA LEE: Brandon Day.

MR. MICHAEL KAWCZYNSKI: Brandon go ahead and unmute yourself.

DR. ARNOLD MONTO: Or anybody else who wants to answer that question.

MR. MICHAEL KAWCZYNSKI: I don't see Brandon in here right now. I'll call Brandon back in just to be safe. Go ahead. Let's go to the next question real quickly.

DR. ARNOLD MONTO: I don't see another question. Can't believe this.

MR. MICHAEL KAWCZYNSKI: If you give us a moment, we'll bring Mr. Day back in here.

DR. ARNOLD MONTO: Or anybody else who can answer that question. It might Dr. Fink or Dr. Marks.

MR. MICHAEL KAWCZYNSKI: Here we go. There's Brandon. Brandon, are you there? Brandon, go ahead and answer that question.

DR. BRANDON DAY: I'm reconnected. Can you restate the questions?

MR. MICHAEL KAWCZYNSKI: Hi. We hear you. Go ahead.

DR. BRUCE GELLIN: Want me to go again?

DR. ARNOLD MONTO: Bruce, why don't you go again.

DR. BRUCE GELLIN: All right. Thank you.

DR. ARNOLD MONTO: Dr. Fink's here as well.

DR. LUCIA LEE: I also wanted to mention that we did review the safety data through February 2022.

DR. BRUCE GELLIN: So that's the good news, that somebody's continued to follow these patients, as you said, for safety past the end of the study. The questions is what else are we going to lean about the trial participants since the study, durability, other vaccines that they may have received. Did they get boosters of Novavax as well? This is entering into the real world of other vaccines.

While it's not our purview to figure how they're going to be used if and when they're available,

that's going to be an important consideration. So any data about that and including any data about Omicron, which is missing from this discussion because it wasn't present in September, but it's quite present now. And hopefully people are still being followed in an Omicron environment. Thank you.

DR. LUCIA LEE: The study was conducted quite a while ago, and so the cases that accrued were not during the time that Omicron was circulating. We tried to focus mainly on the primary series, which is the topic of this VRBPAC. We were not prepared to further discuss the topics of participants who got boosters and those related topics.

DR. ARNOLD MONTO: Dr. Fink, are you in the position to straighten things out?

DR. DORAN FINK: I will try. Although I have to admit, I'm having a lot of problems on my end with the system figuring out --

DR. ARNOLD MONTO: We hear you.

DR. DORAN FINK: -- on or not. Can you hear me?

DR. ARNOLD MONTO: Yes, we hear you.

DR. DORAN FINK: Yes. Okay. Great. I think that the main points, as Dr. Lee summarized, are that we do have rather long-term safety follow up that we were able to review in detail for all of these study participants. There has been some use of the vaccine worldwide in post-authorization settings. Although, we really don't have much data to report on that beyond what is summarized in the slides.

If this vaccine is authorized for use in the U.S., clearly we will need to have the same intense level of post-authorization safety surveillance as we have had for the other COVID-19 vaccines that have been authorized, some of which have gone on to be approved and fully licensed. Again, I just have to reiterate. I know that there is intense interest in the potential for using this vaccine as a booster dose in individuals who might have received a primary vaccination with some other COVID-19 vaccine.

We don't have the capacity to discuss that potential use today or data related to that use. If

this vaccine were to be authorized for use as a primary series, we could take an approach similar to what we have for the other authorized COVID vaccines who are considering use as a booster dose, and we would evaluate study data to inform the safety and effectiveness as a booster dose as it comes to us.

DR. ARNOLD MONTO: Thank you.

MR. MICHAEL KAWCZYNSKI: We have Brandon Day (phonetic) also on as well. Brandon, did you have anything to add?

DR. BRANDON DAY: No. I think they covered it. Thanks.

DR. ARNOLD MONTO: Okay. This will be a persistent item of discussion as we go through the rest of the day is my humbled prediction. Dr. Lee.

DR. JEANETTE LEE: Yes. Thank you for that presentation. I think one of the questions that I have -- and I don't know if you're exactly the person to ask. This actually was designed as a crossover so that individuals were randomized to either receive the vaccine first followed by placebo and then placebo

followed by vaccine. So far, obviously, the primary endpoint was based on the original randomization of vaccine versus placebo before the crossover, although we have seen some safety data after the crossover period.

Is there any plan to analyze -- typically in a crossover, you have a wash out period, and then you do the second comparison. The reason I ask that is it would seem as though those that have started with a vaccine and then went to placebo -- that there might actually be a carry-over effect that might actually give us some indication as to waning immunity or not. I didn't know if there were any plans for that analysis to be done to separate the pre- and post-crossover in terms of efficacy not just safety.

DR. LUCIA LEE: I think the Sponsor can add. But since the study is still ongoing, there are provisions to collect samples to look at the duration of protection.

DR. JEANNETTE LEE: Okay. All right. Thank you.

DR. ARNOLD MONTO: Why don't we park that question, Dr. Lee, and this is something we can come back to when we have a broader discussion with the Sponsor online as well after lunch?

DR. JEANNETTE LEE: Okay. Thanks.

DR. ARNOLD MONTO: Dr. Meissner.

DR. CODY MEISSNER: Dr. Lee, thank you for the presentation. I would like to ask you about the FDA's experience with baculovirus, insect cell protein expression systems. I don't think it's been used very often. Do you have any other specific issues regarding safety with that eukaryotic protein expression system that the FDA worries about?

DR. LUCIA LEE: I'd have to defer this question to Dr. Fink or others from the FDA.

DR. DORAN FINK: Hi. So we do have an example of a recombinant protein-based seasonal influenza vaccine, Flublok, that has been approved and is manufactured using a similar expression system. We don't have any safety concerns attached to that vaccine specific to that manufacturing platform.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Not seeing any further hands raised to my amazement. We will be able to start lunch a few minutes early. Thank you, Dr. Lee for your carful presentation and handling the technical issues in the middle. Back for the open public hearing at 1:00.

DR. LUCIA LEE: Thank you.

MR. MICHAEL KAWCZYNSKI: All right. So everyone, just give us a moment as we pull up the lunch. Nobody log off and take break yet.

[LUNCH BREAK]

MR. MICHAEL KAWCZYNSKI: Welcome back to the 173 meeting for Vaccines and Related Biological Products Advisory Committee meeting. I will now hand the meeting over to our chair, Dr. Monto, and our DFO, Dr. Prabhakara Atreya. Take it away.

OPEN PUBLIC HEARING

DR. ARNOLD MONTO: Thanks, Mike. Welcome everybody 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 such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the Sponsor, the product, and, if known, its direct competitors. For example, this information may include the Sponsor's payment of expenses in connection with your presentation 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 the issues of financial relationships at the beginning of your statement, it will not preclude you from speaking. Prabha, over to you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Monto. Before I begin calling on the registered speakers, I would like to add the following FDA guidance. FDA encourages participation from all public stakeholders in its decision-making process. Every Advisory Committee meeting includes an open public hearing session, during which interested persons may present relevant information of use.

Participants during the open session are not FDA employees or members of this Advisory Committee. FDA recognizes that the speakers may represent a range of viewpoints. The statements made during this open public hearing can reflect the viewpoints of the individual speakers and of their organizations only, and they're not meant to indicate Agency's agreement with the statement made.

With this guidance provided, I'm going to call on the first registered speaker, Mr. Benjamin Newton. You have five minutes to speak. Thank you.

MR. BENJAMIN NEWTON: Thanks so much for your time. I really appreciate it. The question we have here -- and it is always the question -- is how can we save the most lives. This is the question that constantly chases this Committee and all of the FDA. The question before VRBPAC today is easy to answer: authorize Novavax's vaccine. It's highly effective. It's something we knew more than a year ago. Plus, it hurts less than the mRNA vaccines.

It appears, from the limited data that the FDA has shared, the myocarditis issues are likely a result of data mining errors, but we will only know with more data. From my view, there's a clear benefit to a vaccine that hurts less. For example, I have an acquaintance who recently got sick with COVID because he didn't want to get boosted because the mRNA vaccines hurt too much. All of this is really an aside to the rest of my presentation.

Next slide. Really the thrust here is about how we can better protect people, right? the question we have to ask ourselves as a regulatory body is how best can we serve the people of this nation? Should we provide people with options, or should we stand in the way of people protecting themselves? Today, children under five still have no access to vaccines nearly a year after the American Academy of Pediatrics recommended approval using sero-bridging data.

Today, Omicron-specific boosters have not yet been approved six months after we knew that they were required. Today, we all suspect that antibody half-life long term would be about 90 days. So we will need boosters about every six months. However, it is very challenging for people to get access to needed boosters. The question we are trying to answer is not if these vaccines are safe, but rather are they safer than the alternative. They are clearly safer than COVID. Next slide.

So why was Novavax delayed? Novavax's vaccine demonstrated efficacy superior to J&J's vaccine before

J&J was approved. Instead of approving Novavax in January of 2021, the FDA required a second Phase 3 trial for one of the best vaccines, delaying approval. At this point, Novavax's vaccine has been authorized for use in more than 100 countries, courtesy of the WHO. Like all approved vaccines, this could've been approved sooner.

What went wrong at the FDA? What can we do better next time? These are questions that only the FDA can answer. Next slide. The FDA prevents access to life-saving medicines. Why? In fact, that is the entire point of the FDA: block access to drugs to prevent dangerous drugs from entering the marketplace. This is a constant balancing act, one that is impossible to get right but that the FDA must constantly work to improve.

Some reasons for delayed approval are likely to be incentives. No one gets fired for being conservative with drug approval. FDA Committee members derive revenue from illness and/or clinical trials. This is to be expected as it's populated by doctors.

You are all likely familiar with the trolley problem. People feel differently about having agency in an outcome versus just letting people die by preventing access to medicines.

The FDA does not quantify the mortality and morbidity associated with both action and inaction. We count the people injured taking bad medicines. We don't count the people injured by lack of access to good medicines. Diversity matters, and it's highly important for effective decision making. There is almost no diversity on VRBPAC, partially by design. Someone is not on mute.

We know that there are problems; it would be surprising if there were not. So what can the FDA do to improve? You can set clear guidelines for approval of vaccines for all known pathogens today. You can create data standards and automated data feeds for clinical trials. You can publish this data in real time, redacted of personal and identifiable information, allowing for real-time analysis. You can quantify and assess the risks of both action as well as

the cost of inaction.

You can increase diversity on FDA committees. You can create a process to authorize vaccines in 30 days for all ages, then name a pathogen and let the FDA and the industry practice. We are going to have another pandemic; it's only a matter of time. And this group is the group that can best prepare us for that eventuality. Next slide. On slide six, our future is bright. So this may have seemed like all doom and gloom, but it's not.

We have this bright future. There are a few hundred viruses that cause disease in humans. It's a trackable problem. What is nice is that vaccine development is actually very cheap, less than a million dollars per vaccine. Unfortunately, clinical trials cost hundreds of millions of dollars, with most of the cost occurring during phase three. With modern statistics and a highly effective vaccine, phase three trials are a measure of how effective and safe a vaccine is, not if it is safe and effective.

This allows regulators the ability to

streamline and standardize trials and dataflows, reducing cost, increasing the speed of innovation. If we want people to stop getting sick and dying from viruses, the safest course of action today is vaccination, a process impeded by a current regulatory environment. I really thank you for your time and attention to this matter. You've done so much work over the last couple of years getting these vaccines approved. Thank you.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Ms. Cathy Keaveney.

MS. CATHY KEAVENEY: My name is Cathy Keaveney. Thank you for the opportunity to speak. (Inaudible) Japan, Australia, New Zealand, India, Switzerland, Thailand, Indonesia, the Philippines, The United Arab Emirates, 4 countries of the United Kingdom, 27 countries of the European Union, Canada, and the World Health Organization have all approved the Novavax vaccine, a vaccine developed by a company in Maryland, funded with $1.8 billion of United States citizens' hard-earned taxpayer money.

And yet, it has still not been approved for the American citizens who paid for it. Why not? Why, in the United States, bastion of freedom of personal choice, are Americans served up only one type of vaccine option, mRNA, while the rest of the world gets choice? When Operation Warp Speed was initiated, (inaudible) companies. Practically speaking, we are now down to two, Moderna and Pfizer, and both are mRNA platforms.

The FDA's response to (inaudible) delay in approving Novavax has seemingly been two issues: the amount of trial data to be reviewed and the need to inspect Novavax's manufacturing. I question both. Your (inaudible) and review boards across the world have managed to review Novavax's (inaudible) data and expeditiously approved this vaccine. What is it about this data that is somehow more onerous for the FDA to interpret?

A *Wall Street Journal* article attributed the delay to manufacturing inspections, quoting a source as saying, "Pandemic safety protocols made it more

difficult for FDA inspectors to get to Novavax's overseas manufacturing sites." I fail to see why, in the midst of a global pandemic with millions dying, the FDA couldn't put on a mask, get on a military plane, and fly to India to inspect Novavax's one manufacturing site.

Certainly, many inspectors from other countries did. Throughout the last two years, I've learned a great deal about why others want Novavax. I've learned that there are American citizens who, after two years, still haven't left their homes because they have medical reasons that won't allow them to take mRNA vaccines. I've learned that many Americans have been fired or quit their jobs rather than be forced to take the one type of vaccine that their employers mandate.

I've learned that many have had adverse reactions to the mRNA vaccines. At this same meeting two months ago, this very Committee heard from American citizens, many in tears, who described their adverse reactions to mRNA and pleaded with you to help. I've

learned that Americans with dual citizenship have resorted to going to other countries in hopes of receiving the Novavax vaccine where it has been approved.

Americans paying to go to other countries to get a vaccine that's headquartered 20 minutes from your office. I've learned that, while we deny our own citizens the Novavax vaccine, we allow citizens from other counties who have been vaccinated with Novavax there to freely travel here. I've learned that Americans who want Novavax choice are not vaccine-hesitant or anti-vax or afraid or whatever other terms the media likes to use to marginalize us.

We are simply informed Americans who believe that this is a better, safer vaccine, and we want what our $1.8 billion paid for. And where is America's leadership on this? Full disclosure, I voted for President Biden, but I don't understand how a country can evoke the Defense Production Act to manufacture and import baby formula, yet, in a time when millions are dying, can't figure out how to get Novavax from India

or, better yet, help them produce it in the United States.

I year ago, President Biden was quoted as saying, "The problem right now is that we have to make sure we have other vaccines like Novavax and others coming on." Also a year ago, Ashish Jha, Biden's COVID czar, had this to say about Novavax: "I realize that the Novavax vaccine results won't get the same attention that we heard from Moderna, Pfizer, and Johnson & Johnson. But, for vaccinating the world, this is huge, very, very good news. Novavax is essential to vaccinating the globe. The fact that Novavax has 90 percent efficacy is awesome."

And yet, still nothing. Awesome news for the globe, just not for the United States. An emergency use authorization based on today's meeting will certainly be a step in the right direction, but it would be largely meaningless if you do not follow quickly behind that with a EUA to allow people to choose Novavax as a booster to the Moderna and Pfizer mRNA vaccine they have already received.

A week from now, on June 14th and 15th, the same Committee will review Moderna and Pfizer's applications for immunizing six months to four-year-old children. For some Byzantine reason, Novavax can't advertise in any other countries where it's already been approved until it's approved by the FDA. Without advertising or marketing or media coverage or governmental promotions, parents aren't informed.

Many don't know that out there in the world vaccine choice exists, and it should exist for they and their children. Parents don't have the time or energy to sit around and read up (inaudible). Instead, they will rely on your recommendations. Because they are scared and wanting to protect their kids, they will rush to vaccinate our most vulnerable with the only option you've allowed them.

(Inaudible) on them but you should until they're given a choice. Parents should be able to make informed decisions about their children's health, and you should inform them. Which brings me to the media; you are complicit. I'm a mother, not an investigative

reporter and have eight-grade math homework to focus on. Do your job. Ask questions. Quit regurgitating what you were fed.

I challenge you to verify or discount every detail of what I've said here today. You have one week until this Committee meets again to determine approval in mRNA in infants and toddlers. Again, parents should be informed; you should inform them. Members of this Committee, you were charged with evaluating the benefits of this vaccine. But you also have the awesome responsibility of ensuring American citizens continue to have freedom of choice. Thank you for allowing this mom for Novavax to speak.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Mr. Mitchell Goldstein.

DR. MITCHELL GOLDSTEIN: Yes. I'm Dr. Mitchell Goldstein. I'm a professor of pediatrics at Loma Linda University Children's Hospital. The emergency use authorization request by Novavax for a vaccine to prevent COVID-19 in individuals 18 years of age and older should be granted. As reported by Dunkel

et al. in the *New England Journal of Medicine*, data from two separate studies involving over 30,000 participants demonstrated a composite efficacy of approximately 90 percent in preventing significant infection.

Although this data was collected prior to the presence of Omicron and other subvariants, this vaccine product is the first traditional protein-based vaccine to achieve this level of protection. The vaccine has been authorized for emergency use by the World Health Organization and can be used in over 170 countries worldwide. Current mainstream United States immunization regimens for COVID-19 involve the use of mRNA technologies.

These immunizations have resulted in decreased morbidity and mortality when measured against the demographic considerations of an unprotected population. However, the frequent need for boosters and the broad public perception of these technologies as untested, and thus untrusted, demonstrates the need for a traditional protein-based technology that mirrors

those of the more trusted traditional vaccine products currently on the market for other viral diseases.

Further, the need to provide effective protection to pregnant women and their particular concerns regarding the use of mRNA immunizations and potential consequences to their unborn babies, as described by Hageman and Goldstein in *Neonatology Today*, provides further corroboration of the need for an effective, traditional, protein-based vaccine product.

Please make this vaccine available to provide additional protection for those most at-risk groups. Thank you.

DR. PRABHAKARA ATREYA: Thank you for your comment. The next speaker is David Charles.

MR. MICHAEL KAWCZYNSKI: David, you're unmuted. Make sure your own phone isn't muted.

DR. DAVID CHARLES: Thank you and good afternoon. Thank you for allowing me to address today's Food and Drug Administration Vaccines and Related Biologics Product Advisory Committee. My name

is David Charles. I'm a practicing physician in Tennessee, and I'm here today on behalf of my role as founding member and chief medical officer of the Alliance for Patient Access.

The Alliance for Patient Access is a national network of policy-minded health care providers who advocate for patient-centric care. The Alliance is supported through associate memberships, grants, and donations from a diverse group of organizations, including Novavax and other vaccine manufacturers. The Alliance supports health policies that reinforce clinical decision making, promote personalized care, and protect the physician-patient relationship.

Motivated by these principles, Alliance members participate in clinical working groups, advocacy initiatives, stakeholder coalitions, and the creation of educational materials. On behalf of the Alliance for Patient Access, we would like to commend the FDA and the Advisory Committee on the important work that you have done in ensuring safety and the efficacy of COVID-19 vaccines throughout the pandemic.

As we know, access to FDA-approved vaccines has slowed the spread of COVID and undoubtably saved the lives of untold numbers of Americans. However, despite the work that the FDA and the emergency use authorization process has done in approving COVID-19 vaccines, there continues to be vaccine hesitancy among the American population. The World Health Organization has listed vaccine hesitancy as one of the top threats to global health.

They further noted that the reasons some are choosing not to vaccinate are complex, but a lack of confidence in the vaccine is a concern. This lack of confidence can stem from a lack of understanding about the newer or unknown vaccine designs and technologies. While the mRNA and viral-vector vaccine designs are available, they're still not well known to the general population, which makes additional vaccine options valuable.

Having another vaccine design introduced, such as a recombinant-based design, may encourage those who are vaccine hesitant to finally become vaccinated.

There continues to be many unknowns about the virus, variants, and long-term effects of contracting COVID-19. It is imperative that Americans have access to a variety of safe and effective vaccines to ensure greater uptake and to protect individuals and the public.

As the virus evolves, additional vaccine options are important to meet the needs in keeping the Americans safe. The benefits of more COVID-19 vaccine availability, especially with those who are vaccine hesitant, greatly outweighs the risk of declining to authorize the use of safe and effective vaccines. We're asking the Committee to strongly consider emergency use authorization of safe and effective COVID-19 vaccine applicants that use different, historically well understood vaccine designs.

It is to the benefit of every American to have additional vaccine options other than mRNA, including protein-based vaccines if available. Thank you very much for allowing me to participate.

DR. PRABHAKARA ATREYA: Thank you for your

comments. The next speaker is Chad Rittle.

MR. CHAD RITTLE: Okay. Thank you very much. My name is Chad Rittle. I am a professor of nursing at Chatham University in Pittsburgh and have been promoting public health and universal vaccination of adults for many years. Thank you for this opportunity to address the Vaccines Related Biological Products Advisory Committee meeting today to discuss the issue in emergency use authorization request for the Novavax vaccine to prevent COVID-19 infection in individuals 18 years of age and over.

I would like to put forward three reasons to support this EUA. First, there are currently approximately 258 million Americans who have received at least one dose of vaccine and two-thirds of the population can be considered fully vaccinated. That's 221 million. Accepting these statistics, that approximately one-third of the population is still skeptical of the COVID-19 vaccine, how can we persuade those reluctant Americans to get vaccinated?

The Novavax vaccine produces an exact replica

of a spike protein of the COVID-19 virus that prompts our immune system to produce antibodies against the virus. This may help those who are hesitant, who are not supportive of the messenger-RNA technology that comprised the first two vaccines currently under EUA. This vaccine does not involve utilizing any of the genetic functions in the human cell.

Specifically, there is no production of messenger-RNA to make new proteins within the cell. The vaccine uses proven technology by presenting antigens to the immune system resulting in production of antibodies. Additionally, the Novavax COVID-19 vaccine includes a special adjuvant, Matrix-M1, bonded to the particles in the vaccine. This Matrix very strongly boosts immune responses similar to the adjuvant used in the SHINGRIX Zoster vaccine.

With this boost, even people over 80 years of age who typically have weak immune responses to vaccines can respond. Secondly, I have been actively working to promote vaccines to enhance public health in America for close to 20 years. My first publication

promoted universal vaccination against pertussis -- was the result of my doctoral research project addressing an outbreak within a school district that resulted in over 70 cases in multiple age groups.

The paper was published in 2010. Vaccines have been proven to help to prevent disease in all age groups. And the meta-analysis describes the effectiveness of pertussis vaccines, showing that patients were more than twice as likely to contract pertussis if vaccine doses containing pertussis antigen were missed or administered late.

Third, during the past two years, I have been closely monitoring the COVID-19 pandemic while attending ACIP meetings as the ANA liaison representative and conducting research doing an academic sabbatical in fall of 2021. One result of that study was publication of an article titled "COVID-19 Vaccine Hesitancy and How to Address it," published early this year.

Points discussed included, vaccine hesitancy described an unwillingness of citizens to accept

vaccines that are accessible and available. Currently, one-third of the population has not received any dose of vaccine and are at risk for significant disease, hospitalization, and death. We need another tool in the arsenal to address the concerns of this significant segment of the population. Secondly, not all health care workers are acceptant of COVID-19 vaccine.

A *Relias Media* report documents that 20 percent of nurses refused the initial vaccines due to questions about safety and efficacy. A proportion of the population, a third point, are grouped as in-betweeners, those adults who have taken a wait-and-see attitude. This group typically includes women, younger adults, and an ethnic minority background with less education.

Common concerns include vaccine safety and skepticism about the risk of COVID-19, belief they are already immunized from prior exposure, and reservations about efficacy. There are many approaches to educating this hesitant population. It is key that we make another effective vaccine available, that they'd be

more acceptable to this broad and complex population -- as you can see crosses many boundaries between gender, ethnic group, and socioeconomic classification.

Let's not forget the social determinants of health can also influence vaccine acceptance. Some of those factors include political belief, education, low trust in scientists, where they live, where they work, where they get their news information, and how they evaluate health risk. Just because someone in the family had COVID would not necessarily influence acceptance of the vaccine.

I strongly urge the Vaccines and Related Biological Products Advisory Committee to approve this emergency use authorization to make another vaccine tool available to help achieve universal vaccination against COVID. With another choice available to doctors and nurses, we will have a better change of convincing adult citizens to accept COVID-19 vaccine more readily.

The Novavax COVID-19 vaccine could help break down some of those barriers of which many of us are

aware and help achieve the World Health Organization's goal of 70 percent coverage with COVID-19 vaccines throughout the world. Thank you very much.

DR. PRABHAKARA ATREYA: Thank you. Thank you for your comments. The next speaker is Ms. Sophia Phillips.

MS. SOPHIA PHILLIPS: Hello. Thank you for the opportunity to speak today on behalf of the National Center for Health Research. My name is Sophia Phillips, and I am a fellow at the center. We analyze scientific data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from drug or medical device companies, so I have not conflicts of interest.

Today, the panelists were asked to evaluate if the benefits of the Novavax COVID-19 vaccine outweigh its risks for youths and individuals 18 years of age and older. While this vaccine demonstrates similar levels of efficacy as compared to vaccines approved for COVID-19, the data suggests additional safety risks. As was stated in the FDA materials, there was an

elevated risk of myocarditis and pericarditis demonstrated in Study 301.

Further, this risk could be higher in the Novavax vaccine compared with mRNA COVID-19 vaccines. There were six cases identified pre-authorization of Novavax, while no cases were identified before the authorization of mRNA COVID-19 vaccines. Although these serious complications were also identified for mRNA vaccines, that was only when the much larger numbers of people were vaccinated, not the original mRNA study participants.

Data from passive surveillance in other countries where the Novavax vaccine is authorized also indicate a higher-than-expected rate of myocarditis and pericarditis associated with the vaccine. As a result, the FDA requested that the Sponsor change myocarditis and pericarditis to important identified risk on the pharmacovigilance plan.

The design of Study 301, which is the basis for today's discussion, initially resembled that of the three COVID-19 vaccines granted in EUA. They were

similarly Phase 3, randomized placebo-controlled trials with a similar number of vaccinated participants. However, when the study design transitioned to a blinded crossover due to the availability of EUA vaccines for certain populations, it weakened the value of the data.

Efficacy of the drug compared to placebo could only be determined in the pre-crossover period after Dose 2 for approximately two months before the opposite treatment was given to each participant. Therefore, it is not possible to assess sustained efficacy over a longer period of time. It remains unclear how long protection lasts. While the FDA remains hopeful that Novavax will provide some meaningful protection against Omicron, that is also uncertain since the vaccine was primarily studied on the Alpha variants.

Additionally, very few of study participants were immunocompromised, pregnant or lactating, or at risk of severe COVID because of cardiovascular, chronic renal, and chronic liver disease. That made it impossible to meaningfully evaluate the vaccine's

efficacy for those populations. Few cases of PCR-confirmed COVID-19 were analyzed for participants over 65 years of age, limiting the value of the efficacy data for that age subgroup.

For those that were studied, there was a 12.5 percent dip in vaccine efficacy for individuals 65 or older, which is also typical for the mRNA COVID-19 vaccines. What would be the value of this vaccine compared to the three COVID vaccines that have already been approved? If it is less safe than the other three vaccines, it does not provide additional benefit to make up for that.

Even if it not proven to be less effective than the other COVID vaccines, it lacks long-term, placebo-controlled efficacy data. And there is very little safety or efficacy data for the most at risk patients. When we already have vaccines on the market that are FDA approved and based on much better data, why would the FDA authorize this vaccine? Wouldn't it just add to the controversy surrounding COVID-19 vaccines? Thank you.

DR. PRABHAKARA ATREYA: Thank you for your comments. The next speaker is Martha Dawson. Ms. Dawson.

MS. MARTHA DAWSON: Good afternoon, everyone. Thank you so much for allowing me to speak today. I'm here today to support another technology to fight COVID-19 and the many growing variants. When one is at war, many different approaches are used by land, air, and water. Although the public is exhausted and ready for this pandemic to end, there really is no light at the end of the tunnel.

As a nurse for 45 years and the current president and CEO of the National Black Nursing Association, representing over 500,000 registered nurses, licensed, practical, and vocational nurses, and nursing students nationwide, I am also fatigued from educating, testing, vaccinating, and addressing other health and social determinants that place black and brown population at risk during this pandemic. And we know that more of them have died.

In addition, NBNA nurses have been on the

frontline. We have been serving every day from March the 20th, when the first variant of COVID hit our nation. Therefore, I encourage the FDA to give us another, more traditional medical innovation in this fight and approve this vaccine. African Americans and black nurses that I represent and give voice to are on the frontline of this pandemic, and they continue to watch more of our population die.

They have lost colleagues, spouses, partners, parents, children, and other relatives and friends. Let us be very clear, COVID-19 is a public health crisis. However, it has been politicized with mis- and disinformation. Therefore, some people will never become vaccinated, putting others at risk. Unfortunately, people are not following public health policies and best practices.

It appears that the world is just tired of wearing masks and washing their hands, isolating and being social distanced. However, through the lens of public health, this is exactly what is still needed today. But, again, since the majority of the

population is not leaning in that preventive and health-promotion direction, we have to look for other measures.

I do believe that having another vaccine will give people options. Maybe some of those that are still sitting on the sideline saying, "Well, let's just wait until a few more are vaccinated." But that put us at risk, and it brings to mind of me talking to a close friend this week, I mean just this week, with another under-40-year-old relative ended up with COVID pneumonia.

How many of our young people are we going to allow to die or who we're going to allow to become sick? Again, it's unfortunate that people are not following public health policies and best practices, so we have to look for other options and give people more options. Many believe that these measures did not work and are not going to work. However, we see cases still increasing. Yes, again, we have a breather. It's now summertime; we can be out.

We can have more fresh air. But make no

mistake, within another eight to ten weeks, we're going to move back into our kids going into the school system. And we will probably see another spike if we don't do something. As I stated, I represent nurses and nursing students, and the future workforce for this profession is not good. It is projected that over one million nurses will be needed in the United States and over six million will be needed worldwide by 2030.

My colleagues, it takes three to four years just to educate one nurse. So, if we continue to lose nurses because they are fatigued and they're tired and they just can't see one more patient expire from this COVID pandemic, then we're going to continue to have them leave the occupation and look for other things to do. So I want to just say let's think about this because, yes, I know nurses and physicians and others in the health care space; they are also refusing to be vaccinated.

But we need to continue to provide option to reduce excuses and as many excuses as we possibly can. This is why I strongly support and encourage the FDA to

approve the Novavax vaccine. I would like to close with this; in the art of humanity and public safety, since we as a country have not been able to lean in and accept that this a public health crisis and that we should not only protect ourselves but those around us, then we need to have other options.

So let's look at this and say is it going to do more harm, or do we lean that pendulum towards it? It could be the next thing that saves your life or your loved one's life. Thank you.

DR. PRABHAKARA ATREYA: Thank you for your comments. Last but not least, Mr. Kermit Kubitz.

MR. KERMIT KUBITZ: Hello, can you hear me?

DR. PRABHAKARA ATREYA: Yes, we can. Go ahead please.

MR. KERMIT KUBITZ: Okay. Thank you. I'm a graduated of Caltech, Harvard Law School, and the Harvard Business School. I have participated in VRBPAC and ACIP meetings, including the October 22nd, 2020, VRBPAC meeting on developing and licensing vaccines, the December 20th Pfizer EUA meeting, and the September

17th, 2021, VRB meeting on boosters.

And I have no conflicts and no fiscal interest in the company being considered. The question to the ACIP is do the benefits outweigh the risk of a two-dose series of vaccination for persons 18 years and older for NVX-CoV2373. I look at this and the evidence in the form of a structured benefit-risk table of the form previously adopted by the FDA: one, the condition to be treated, two, available alternative therapies, three, the benefits of the proposed drug, including uncertainties, four, the risks of the proposed drug, including uncertainty, and five, the summary conclusion in view of all available evidence, including uncertainty, about the benefit-risk, and is it positive?

Point five is similar to the question presented to the ACIP meeting. In my analysis, the condition to be treated is prevention of COVID-19 mild, moderate, or severe, including hospitalization and death. The alternatives are other vaccines, Moderna, Pfizer, as well as Jansen and AstraZeneca, and

treatments such as Paxlovid. As one of the initial questioners on this panel asked, why EUA if there are other available vaccines?

As other speakers before me have discussed, vaccine hesitancy is a serious problem. Some people may not be able to take mRNA vaccines, and we need as many tools as we can get to control and eliminate this pandemic. The benefit of the Novavax vaccine is elimination in the treatment arm of 17,000 patients of moderate to severe COVID-19.

The risks of the Novavax vaccine are significant adverse events of about one percent for Novavax and one percent for placebo. The Novavax vaccine versus the placebo showed about no moderate or severe cases versus 11 percent moderate cases and 5 percent severe, or about 16 percent severe or moderate COVID-19 cases which were not occurring with the Novavax vaccine.

This demonstrates significant efficacy. In addition, the Novavax vaccine has now been administered to hundreds of thousands of patients outside the U.S.,

so there is available data on its effectiveness. See the study published in *Cell* (phonetic) by the La Jolla Institution of Immunology professor, Daniela Weiskopf and Shane Crotty, who found antibodies after six months were highest with the Moderna, Pfizer, and Novavax vaccine.

All participants retained a similar percentage of memory CD4+ helper T cells. It's important to have multiple vaccines ready and approved to fight COVID-19 to provide initial protection, to provide protection against variants, and to provide protection against boosters. As the CDC has noted, heterologous booster vaccinations may provide significant benefits even if mixing and matching vaccines.

Finally, I'd like to thank the ACIP and the FDA. You have saved a million lives by you providing vaccinations through all the vaccines despite all the time its cost you to attend these meetings. Thank you very much.

DR. PRABHAKARA ATREYA: Thank you for your comments and the presentations. This concludes the

open public hearing session. We're going to be moving onto the next items of the agenda as we are finished with the public comment speakers. Thank you, and I hand over the meeting to Dr. Monto. Monto, take it away please.

DR. ARNOLD MONTO: Thank you, Prabha.

ADDITIONAL Q & A REGARDING SPONSOR AND FDA PRESENTATIONS

DR. ARNOLD MONTO: Thank you, Prabha. Question is, do we -- we have a break scheduled and reconvening at ten minutes past 2:00. Is it possible to begin the meeting at 2:00 instead? Prabha? Dr. Marks? Or should we go to 2:10 as we are scheduled?

DR. PETER MARKS: Let me just check with our technical people. But as long as they say we can move ahead; we will move ahead.

MR. MICHAEL KAWCZYNSKI: Yep, we're ready. We can move ahead if you'd like to.

DR. PETER MARKS: I believe then that would be

wise to do. Thank you, Dr. Monto. Go ahead and proceed.

DR. ARNOLD MONTO: Okay. Well, we're moving ahead now to the additional question and answer session, which is regards of both the presentations of the sponsor and the FDA. And, Dr. Marks, would you like to say a few comments before we go ahead with this session?

DR. PETER MARKS: Yes, thank you. Thanks very much. So, there have been some questions about how the Novavax vaccine will fit into the other vaccines. And I think what we need to say here is that we are here to consider the authorization for the primary series right now, and that means that this is the initial step. There will be additional submissions, I am sure, and additional consideration by FDA of both booster doses, additional populations, as well as potentially the activity of this vaccine or variant vaccines using this technology that will be submitted or considered in the coming weeks to months.

So I think we need to, just so the Advisory

Committee members think about this, there will obviously be some evolution of this. I believe it's fair to say that and you can certainly feel free to ask the company that question as well over the coming weeks to months to essentially make it consistent with the vaccine paradigms that we are using now.

Dr. Monto, is that helpful to the Committee?

DR. ARNOLD MONTO: That's very helpful, and perhaps I could start the discussion by asking the sponsor if there is anything further that they would like to tell us which might help in our deliberations given the fact that all the testing was done in the era of Alpha, and we're now preparing to launch a vaccine in the era of various Omicrons. So, does the sponsor want to give us any additional information that might be valuable to us?

DR. FILIP DUBOVSKY: Sure. And, Dr. Monto, should I start off with that topic, or do you want me to cover some of the questions that we deferred from previously today?

DR. ARNOLD MONTO: It's up to you. We have

more time than I anticipated, so we can an in-depth discussion. This is very helpful.

DR. PETER MARKS: Can I make a suggestion? Why don't we stick to that? Since I just mentioned that, maybe it'd be good -- if you don't mind -- just to address that question now so we take care of that issue before moving on.

DR. ARNOLD MONTO: Okay.

DR. FILIP DUBOVSKY: Okay, sounds good. So, let me parse it apart. So, a couple things we talked about. One of them was expanding our indication beyond adults greater than 18 years of age and as we've already talked about, we've completed studies in adolescents 12 to 17 years of age, and those studies have been the basis of approvals in other territories. And certainly, as soon as we reach the EUA in the U.S., our intent is to file that and to seek regulatory approval to expand that indication.

We also have data on boosting, both homologous and heterologous boosting, and once again that's the sort of data which we are going to bring to the FDA to

seek approval for the booster indication as well.

So, it's true that the efficacy studies we conducted were conducted in the era before Omicron emerged. What we do know is the data that we've shown you is the vaccine works well against the variants that have circulated during the conduct of the study, and there were a broad number of variants. And this is a feature we think of our technology.

So, the recombinant proteins are made in six cells, which give benefit to antigenic spread along with the adjuvant system and this is proved to be true in our influenza vaccine where which the immune responses were shown to recognize a broad array of H3N2 drift as well as ancestral strains. And it's true in efficacy data we showed you that showed that the vaccine worked well against the variants that circulated.

We additionally have data, immunologic data, from our studies which look at how they respond to the Omicron variant, and perhaps we can show some of that now. This is data from the U.S. Adolescent Study, and

I bring this up because we don't have the comparable data for the adult data. What you can see is the immune response against the original prototype on the left-hand side and the immune responses against the various variants that circulated, including Omicron on the far right-hand side, and this is the VA1 version.

Now, what we can also look at is data from our previous study, our 101 Study. Once again, what this is looking at is immune responses IgG after two doses and after three doses: two doses in dark blue, three doses is in light blue. And you can see we've got a nice boost against all those variants with a third dose.

Importantly, if you look at Omicron and look at the values achieved after three doses, it's really comparable to what we saw for two doses to the original. And those were the kinds of immune responses that were comparable with 90 percent protection in our efficacy study. This is binding. We'll have our neutralization responses.

Here what I'm showing is a comparable graph:

original on the left-hand side, Omicron on the right. And you can see there's a good boost once again between two doses and three doses. But importantly between Omicron after two doses, there's only a 3.6-fold difference than from the original. And this is data generated by the Matt Frieman lab at the University of Maryland, and so we have good confidence that not only are we sharing binding antibody, but at least in this assay, induction of neutralizing responses.

So, overall, it's factual that we don't have efficacy data against Omicron, but what we do have is the technology that we think generates a broad immune response demonstrated against a broad array of variants.

DR. ARNOLD MONTO: Thank you. And now that we've had that question answered, you had some other information that you wanted to give us. So let's go onto that, and then we've got hands raised. We've got questions from the members.

DR. FILIP DUBOVSKY: Okay. So, there was a question asked by Dr. Meissner about IgA responses.

And what I'm showing you here now is data from rhesus macaques, and what we're looking at is IgA titers in the vaccine group versus placebo group. And on the left-hand side of the panel, we're looking at upper airway, so these are nasal IgA. And on the right-hand side, lower airway, so bronchial airway lavage. And you can see that the vaccine does in fact induce IgA in both the upper and lower airway, and this was associated with sterilizing protection in this animal model in both the upper and lower airway system.

Now, I mentioned some data earlier about the ability that we have to stop infection, whether it be symptomatic or asymptomatic infection, and I wanted to bring complete a read of that. What I'm showing you here is the 302 data from the U.K. on the left-hand side, I mentioned, and comparable data in the U.S. on the 301 study. So, this is the ability for the vaccine to block all infection, whether it be symptomatic or asymptomatic, and the only difference between the 302 and the 301 study is the time. The meeting time of surveillance in the U.K. study was longer; it was a

hundred days versus 60 days in the U.S. study.

And the point, once again, being is the sterilizing protection and the IgA that we saw in the animal models may be a signal this is what we're seeing as far as the ability for the vaccine to protect against all infection. I'd like to mention that, obviously, we stopped infection by the ability to prevent long COVID and transmission.

There was a question asked by Dr. Pergam about efficacy after Dose 1. And what I'm showing here is data from the U.S. study -- the 301 study -- and you can see that after Dose 1, the totality of 133 cases in the vaccine group and 156 in the placebo group, two to one amortization, and that gave an efficacy of almost 59 percent. And after Dose 2, it was 86 percent in this analysis. And this is an FAS analysis, so it's like an ITT analysis, so it doesn't take into account the observation window which starts seven days after post-Dose 2 in seronegative alone.

Now, the efficacy that you see at 58 percent, that includes the timeframe after Dose 2, so a lot of

that efficacy is attributed to the time period after the second dose is administered.

There was a third question asked about the Latinos and the proportion that was in those greater than 65 years of age. In fact, there were no cases in the Latino group in those that were greater than 65 years of age.

And I think that's what -- I did think perhaps you'd be interested in the immune responses we talked about during the main presentation. On the left-hand side, you see the Day 0 values; on the right-hand side, you see the Day 35 values. In dark blue are the Hispanic/Latino participants, and in light blue are the non-Hispanics. And you can see the Hispanic population, in fact, had a slightly higher IgG titer than those in the non-Hispanics. And when we look at neutralizing responses, we see a very similar pattern, once again, a slight increase in the dark blue representing the Hispanic population at the peak immune response at Day 35.

So, I think those tidy up the questions that

were asked prior to the break.

DR. ARNOLD MONTO: All right, and now we're going to be moving into the discussion, and I want to remind the members that not only is the sponsor here to answer questions but also the FDA representatives. So, Dr. Offit, you're up next.

DR. PAUL OFFIT: Yeah, thank you, Arnold. This is directed, I guess, to both the FDA and CDC presenters. I agree with the FDA's assessment that that handful of cases of myocarditis that occurred within three or four days of receiving the second dose of vaccine in young men is consistent with what was seen with the mRNA-induced myocarditis. So, I think that is likely a causal and not coincidental association.

It's also interesting in the document that the FDA handed us, or handed out to us, that they referred to a 2020 paper where there was suspected molecular mimicry between SARS-CoV-2 spike protein and the heavy chain of (audio skip) on cardiac muscle cells.

If that's true, then you would argue that

really all COVID vaccines, as well as COVID itself should cause myocarditis, but that may well not be true. And this gets to Dr. Rubin's question, we really need to know whether or not this is true for the vectored virus vaccines like J&J or AstraZeneca. We really may need to know whether this is true for a whole and activated viral vaccine-like (inaudible) vaccine which has now been administered to millions of people, or whether it's true -- I think is most interesting -- for the Covovax vaccine which is a receptor-binding domain vaccine. In other words, a truncated protein vaccine that's been given out to many people in India.

I think it's incumbent upon us to know this, to know whether it's about the protein itself or whether it's about the way the protein is being processed, so that we can use that knowledge to make safer vaccines for a disease that is going to be with us for decades, if not longer.

So, I think that this is a real opportunity to learn something. I hope that it's not lost. We need

to get the data -- the kind of data that Dr. Rubin was referring to earlier. Thank you.

DR. ARNOLD MONTO: Who's up to answer this rather critical question? I think the FDA, I think in the briefing document you raised the issue of mimicry, though it's -- why don't you try to answer it first?

MR. MICHAEL KAWCZYNSKI: I'm sorry, who are you calling upon, Andrew? I mean, Arnold?

DR. ARNOLD MONTO: I'm calling on FDA, since it was in the briefing document, the reference to the issue of mimicry.

MR. MICHAEL KAWCZYNSKI: There's Doran. Doran, I'll unmute you. There you go.

DR. DORAN FINK: Okay, thank you. Yeah. So, Dr. Offit, I couldn't agree with you more that this is a critical question to understand whether vaccine-associated myocarditis is a class effect related to S-protein antigen and if so whether there are other features of specific vaccine platforms that mitigate either positively or negatively toward a risk of vaccine-associated myocarditis.

I think the situation is clear for mRNA vaccines. We have some preliminary evidence from the clinical trials of this vaccine from Novavax that raises this concern. Although I think we need more data from post-authorization use in larger numbers of individuals to really get at what the rate of myocarditis associated with this vaccine is and what exactly the risk is.

As you heard earlier from Tom Shimabukuro from CDC, as we accumulate more experience with the Janssen vaccine which has been used to a much lesser extent than the mRNA vaccines here, as well as outside the U.S., we are continuing to evaluate the occurrence of myocarditis after that vaccine, and, of course, there's the AstraZeneca vaccine and other platforms that you mentioned as well. I couldn't agree with you more that we really need to look closely at these events and also to do the work necessary to understand what the mechanism might be.

And so, I guess here from an FDA perspective, we would endorse that viewpoint strongly and, of

course, are here to assist vaccine manufacturers in the research community in addressing this very important issue.

DR. ARNOLD MONTO: Any further comments from CDC on this or from the sponsor? Dr. Filip Dubovsky.

DR. FILIP DUBOVSKY: Yeah. A couple points to what Dr. Offit said. I mean, it's curious in the data we saw. There's the third boosting dose. There wasn't as big an increased risk after Dose 2, and that makes me wonder if there are other mechanisms at play that wasn't proposed. And we also know about other vaccine-associated myocarditis from the smallpox/monkeypox, and they don't even have the spiked antigen.

So, I think the story's incompletely written here, and we do need to more fully understand what's going on before we can think about a class.

DR. ARNOLD MONTO: Thank you.

DR. TOM SHIMABUKURO: Hi, this is Dr. Shimabukuro from CDC. Can you hear me?

DR. ARNOLD MONTO: We can.

DR. TOM SHIMABUKURO: Dr. Offit, I would just

reinforce what Dr. Fink said about the importance of getting the data that you mentioned, and I'm not so familiar with some of the other vaccines that are used outside of the United States. But I'm not aware of a similar association observed with the AstraZeneca vaccine which was widely used in Europe similar association as seen with the mRNA vaccines.

And with respect to disease, my understanding is that isolated myocarditis following COVID disease is pretty rare and the adverse cardiac outcomes that you see after disease are often in association with MIS which may be a different mechanism altogether.

But with respect to disease and just pure myocarditis or isolated myocarditis, it's a fairly rare occurrence after COVID.

DR. ARNOLD MONTO: Thank you. And thank you all for a discussion of an important topic that we need more information about. Dr. Levy.

DR. OFER LEVY: Yes, I wanted to thank the sponsor for showing the additional data a few moments ago with some slides about antibody responses. And I

wanted to note, those data were elegant, they were helpful, and yet, without knowing what level or concentration of antibody correlates with protection, it's a little hard to draw any conclusions as to whether this vaccine -- how it would perform against Omicron.

I mean, it seems like there were lower responses -- lower binding and neutralization of Omicron than the other variants, yet there were some. But without -- maybe I'm stating the obvious -- without a correlate of protection, it's hard to draw a conclusion one way or another.

The sponsor made some comments about their impression of the correlate of protection earlier in the day, and I'm wondering if they can make some further comments in terms of where they would see the correlate of protection to be on those graphs and does Omicron reach up. I realize there's an element of speculation here, but it is the elephant in the room, I think.

DR. FILIP DUBOVSKY: Yeah.

DR. ARNOLD MONTO: Dr. Dubovsky, do you care to speculate?

DR. FILIP DUBOVSKY: I will always speculate, but I agree that, without definitive data, we won't know. Listen, we think that -- we simply don't know if an Omicron-based vaccine is required, right. Those studies are ongoing. They're ongoing, and we sponsored a study in Australia, but we're looking both at an Omicron vaccine as well as the bivalent form. I have to see if that offers any advantage.

What we do know is what we've showed you as this technology, in general, does a good job with antigenic spread and having a broad response, and we do know that the binding and immune responses we see are relatively favorable. The best I can do to compare -- and I understand this is very, very fraught with potential error -- is to try to compare back to the levels we saw after Dose 2 to prototype, and as you saw for prototype in U.S. study, we had 97 percent protection.

So where is the cutoff isn't clear. The

signals we're getting right now is, in our view, favorable, but we'll know for sure when the study reads out in Australia.

DR. ARNOLD MONTO: Thank you. Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Arnold. I had a question about the adjuvant in particular. I know that the adjuvant comes from a particular tree; I believe it's in South America. My understanding is that's a highly regulated supply chain. Do you guys have any comments about the ability to get this on a regular basis to make the vaccine available because I know that is an issue?

DR. FILIP DUBOVSKY: So, we took steps early on to secure the supply chain. There is zero supply problem with the adjuvant.

DR. STEVEN PERGAM: Okay, thanks.

DR. ARNOLD MONTO: Thank you. Dr. Lee.

DR. JEANNETTE LEE: So, thank you for that presentation. I think one of the questions I had earlier -- and I think this is really for the sponsor -- had to do with the current design is that protocol

which was actually a crossover. Most of the data we're seeing for efficacy is obviously related to the first random -- the first part with the randomized obviously with the vaccine and placebo. And I do understand the study is ongoing so the crossover part from vaccine to placebo and placebo to vaccine.

And I think the comparison of the second part after the crossover would be very illustrative in terms of what kind of carry-over effect it might have from those that started with a vaccine and then were getting placebo. Do you have that data, or when do you anticipate we would be able to see that?

DR. FILIP DUBOVSKY: Yeah, so you're right; the crossover complicated, or eliminated, our ability to look at placebo control data at this crossover time. Furthermore, we've taken the opportunity to boost those participants with both Dose 3, and some with Dose 4, which complicates the story even more.

DR. JEANNETTE LEE: Yeah.

DR. FILIP DUBOVSKY: Now without a good comparator and with new variants emerging and the

different course of infections across time, it becomes extremely difficult to do anything but make model-based assumptions.

Now that work is ongoing, and we'll have that available in due course. I'm not sure how trustworthy it is because I'm convinced we know how to guess the efficacy against the variants until we get real data on that.

DR. JEANNETTE LEE: Okay, thank you.

DR. ARNOLD MONTO: Thank you. Dr. Gellin.

DR. BRUCE GELLIN: Thanks. So, thanks for all this. I want to start by thanking the public who commented, and then the many, many more of the public who commented in writing that didn't get a chance to speak. This is an important part of these conversations.

Filip mentioned a couple times something that doesn't always get mentioned about sterilizing immunity, so I'd like to hear some more about that. He showed us a little bit of data about it but the grade of which you believe this vaccine can lead to

sterilizing immunity and any data that you have from anywhere that might have insights about its limited or its ability to dampen transmission.

And then finally, we hear a lot about its authorization in other countries. It'd be interesting to know, A, to know about how much it's being used in other countries and what other data you might have that's relevant to these discussions today from other country experiences.

DR. ARNOLD MONTO: A very broad question.

DR. FILIP DUBOVSKY: I think I got these, so we'll see. So, as far as the sterilizing protection data, it's a broad leaf feature we've seen in animal models we've tested, and our best data for what we saw in humans is the data I showed you. So, there's no direct measurement that we have in hand of a transmission. You need to make that leap of faith of logic that, if you don't get infected, you can transmit.

The durability of that period where you're protected from infection is also variable. In any case

study, like I mentioned, that was measured across -- those cases were accrued over six months with a median of about 101 days observation in those groups. So, I think it's speculative, frankly, but we're hopeful.

As far as real-world evidence from the doses that are administered, it's still early days for us. We're shipping doses; they're being used. Right now, you heard from Dr. Kim from the pharmacovigilant side, we have good line of sight to about 770,000 doses having been administered. We have imperfect visibility into this. Our customer is the governments; the governments deploy those. So we to a certain degree rely on the governments to feed that data back to us, so we understand how many are used.

For us to get into real-world effectiveness, which we want to do, and we will do -- we're committed to doing it -- we need to get the vaccine usage up enough in certain areas where we can do a test study or a controlled design. Without adequate doses being deployed, we can't do those studies.

DR. ARNOLD MONTO: Does that answer all your

questions, Bruce?

DR. BRUCE GELLIN: It did. Thank you.

DR. ARNOLD MONTO: Okay, I just wanted to interject a question of my own for Dr. Dubovsky, and that is we've heard that there are differences in the vaccines that are being authorized for use in other countries versus the vaccine that we're now considering for the United States. Would you speak about that and how different are they would suggest the question of where they were manufactured? What's the story there?

DR. FILIP DUBOVSKY: Right. So, all vaccines are being distributed globally/commercially, are being made in a single facility in bio partners in (inaudible). That includes the vaccines which are being deployed around the world as well as the ones that'll be initially deployed in the U.S.

As far as the previous studies that were done, all the clinical and commercial lots were released after being tested to assure they met a set of critical quality attributes. This includes the lots that were used in the early studies in Australia, U.S., U.K.,

South Africa, as well as in the U.S./Mexico study.

And it's normal for these specifications to tighten as experience is gained with the manufacturing process. Now we've completed a comparability program that we believe demonstrates the comparability between the early lots and the lots used in Study 301 and the commercial lots. And we acknowledge the FDA has a perspective on this that's different from ours, but the quality of that material and the results of all those studies are really the basis of our global licensure. So, I think that's where we stand.

But importantly, all the vaccine which is being deployed commercially comes from a single facility.

DR. ARNOLD MONTO: Thank you. Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Monto, and thank you, Dr. Dubovsky. I feel like you're carrying a heavy load here. You're facing all of these questions. But let me -- I have a question about the adjuvant -- two questions about the adjuvant. The first one, and it may be you simply don't know, but what happens if a

person gets at the same visit or the same day two saponin-containing adjuvants? For example, if someone were to get the shingles vaccine that contains AS01 on the same day that your vaccine is administered, are you worried about an increased risk of adverse events that might occur?

And then secondly, a little bit -- one of your earlier studies with respiratory syncytial virus that I thought was very interesting because you really broke new ground with that publication and -- but during the study with the same platform I think using RSV fusion glycoprotein, used a different adjuvant. You used an absorbed aluminum adjuvant, and I think that was because there was some concern about using the saponin-based adjuvant during pregnancy -- in a person who might be pregnant -- and so I'm assuming you no longer feel that's a concern and that's why you haven't expressed any reservation in that setting. Over.

DR. FILIP DUBOVSKY: Yeah, so the RSV maternal program, which was a study done before my time, was also a study done before the company had the Matrix-M

adjuvant in its portfolio. The immune responses induced by alum were probably quite good at that time. We don't have any specific concern with saponin; the reproductive tox studies have been clean, and certainly in the data that Dr. Kim presented, we didn't see anything that looked concerning to us. I'll remind you that the amounts of -- just back to your previous question -- the amounts of adjuvant we were deploying were very low, at 50 micrograms.

We've previously tested doses that are higher, up to 75 micrograms for a quadrivalent influenza vaccine program. We know that there are a small number of people who received Shingrix in our study -- less than ten -- those probably weren't co-administered, those were just given close by, but certainly we didn't see any concerns with that.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Perlman.

DR. STANLEY PERLMAN: Yes, so I just have two questions. One, what will it take for this to obtain a full licensure as opposed to an EUA because we keep

hearing about why it should be an EUA instead of a full licensure? But what more would be needed to obtain full licensure? The other thing is what's the adjuvant? I know you looked for things related to autoimmune disease, but was there any hints of exacerbation of preexisting autoimmune disease with this adjuvant?

DR. FILIP DUBOVSKY: Okay, I'll handle the first question, and perhaps I'll turn it to Dr. Kim to talk about the second question. The long pull in the tent, the thing that takes the longest to get a BLA is through a lot-to-lot consistency study, and this is a requirement that's unique in the U.S. And to do that study, we need to generate lots which are deemed to be comparable and appropriate for such a study by the FDA before we do the study.

So that's really the thing which is going to take the longest. We have some additional data requirements for length of follow-up, and those we'll come to terms with, in discussions with the FDA before we bring it to them for the full BLA. Dr. Kim, do you

have a perspective on enhancement of autoimmune disease?

DR. DENNY KIM: Yes, can you hear me?

MR. MICHAEL KAWCZYNSKI: Yes, we can.

DR. ARNOLD MONTO: Yes.

DR. DENNY KIM: It seems like my camera's not on.

MR. MICHAEL KAWCZYNSKI: There you go. I'll turn it on for you sir. I'll turn it on for you sir. There you go.

DR. DENNY KIM: All right. Thank you. Yeah, so we've seen very low frequencies of potential immune-mediated conditions, and so whether it's new onset or potentiation of existing comorbidities that some participants had in our study population, we didn't really see any patterns that suggested a worsening of conditions.

DR. STANLEY PERLMAN: Thank you.

DR. ARNOLD MONTO: Dr. Sawyer?

DR. MARK SAWYER: The point has been made that one of the main audiences for this being are vaccine-

hesitant people who, by now, many of whom have been infected with natural disease because of their reluctance to get vaccinated. And we've also discussed the fact that this vaccine has been used in other countries for quite some time.

Perhaps I missed it in the presentation, but I don't think we heard much data about vaccine reaction in people who had prior exposure to the natural virus. I think the 301 study specifically was in seronegative individuals. So, I'm wondering if you could either remind me, or share, any information that we have about the experience with the vaccine in people who've already had infection.

DR. ARNOLD MONTO: You might as well stay on, Dr. Dubovsky. I think that you're in the hot seat. Please, go ahead.

DR. FILIP DUBOVSKY: I mean, you remember correctly that seven percent of the people in Study 301 were positive in baseline. And while they were excluded from the efficacy analysis, we do have data both immunologic as well as safety data on what the

vaccine does. Let me see if I can get that data pulled up. But in general, if I were to summarize, what we see is we see really quite a nice boost of the immune response in people who are previously vaccinated.

Let me start with a slide that shows you what the neutralizing responses were by age group in those that were seronegative. And you can see overall in those that were greater than 18 is the value of about a thousand, and those greater than -- the younger group, 18 to 64, it was 1,200. When you compare it to the values that we see in those that were seropositive, what you see is an increase of roughly three to four-fold. So, they're getting a nice priming response from a natural infection, those vaccines boost through it quite well.

From a safety perspective, we didn't really see any difference in the reactogenicity of the vaccine when it was delivered in the seropositives versus the seronegatives.

DR. ARNOLD MONTO: Thank you. Doctor --

DR. MARK SAWYER: Sorry. Could you quickly

tell us how many people -- I know it was seven percent, but what was that total that you had experience with?

DR. FILIP DUBOVSKY: So, in this particular study, it was 7 percent in both groups so 7 percent of 30,000. So, I've got to do that math.

DR. MARK SAWYER: Thank you.

DR. ARNOLD MONTO: Dr. Fuller, did you have your hand raised?

DR. FILIP DUBOVSKY: We have additional exposure data in people who were seropositive in our other studies. That attack rate was very, very high in South Africa, for instance, where a much larger portion were seropositive, and we see the same pattern. We don't see increased safety signals, but we do see an increased immune response.

DR. ARNOLD MONTO: Thank you. Dr. Fuller, did you have your hand raised? I thought you did.

DR. JAY PORTNOY: Hi there. So, I have two questions. Can you hear me? Okay.

DR. ARNOLD MONTO: Yep.

DR. JAY PORTNOY: I have two questions. As an

allergist, I would be remiss if I didn't ask whether you observed any allergic reactions to the vaccine? After all, it was a protein-based vaccine rather than mRNA, so the risk of having an allergic reaction might be higher. I guess you can answer that one first, and then I have one more question.

DR. FILIP DUBOVSKY: Yeah, I'll give a scientific spin to it, and then I'll pass it off to Dr. Kim, actually. So, our adjuvant is the Th1-biased, so in a sense, it's tightly antiallergic as far as that goes, so I think that plays in our favor. Dr. Kim, do you want to review the hypersensitivity? And there's no anaphylaxis as has been mentioned in the pre-licensure database. Dr. Kim?

DR. DENNY KIM: Yes. So, as to confirmed anaphylaxis, we had no cases of anaphylaxis in our clinical development program pre-crossover or post-crossover. Certainly, we do a broad search to look for any type of allergic-type reactions or hypersensitivity-type reactions, and I can show you some of that data here.

And so, as you can see, the pre-crossover -- and we use a standard metric query, and that's a very broad search and so, any sort of events that could possibly be related to allergic-type reactions. And we saw a minor imbalance and numerical imbalance. And so, you can see a 0.77 percent in the active arm compared to 0.57 percent in the placebo arm.

And the most frequent preferred terms or events were rash, as you can see there, and we had that in exposure-adjusted incidents. So, 0.93 events per hundred person-years versus 0.90 events per hundred person-years. That's fairly balanced, and the reason we did that is because there's differential follow-up oftentimes, especially when you consider post-crossover between placebo and active arms or those who'd receive vaccines because everyone will eventually receive -- will have received vaccine.

That small numerical difference is mostly driven by urticaria and dermatitis. And so, we didn't see clinically significant sort of patterns and associations here.

DR. JAY PORTNOY: So presumably all the patients would be advised to do the standard 15-minute wait after the vaccine and not a prolonged wait or anything like that. My other question is you're playing for emergency use authorization -- this is kind of a continuation of Dr. Perlman's question -- and yet we already have two vaccines available that are highly effective and relatively safe.

I haven't seen -- your vaccine seems to be comparably effective and comparably safe to the other ones, but you didn't show that it was superior in any particular way. And, since so many people in the United States have already been vaccinated, I assume that the large -- it's going to be promoted largely to the vaccine-hesitant individuals who might adopt a more conventional vaccine that's protein-based rather than these other technologies.

Do you have any information from vaccine-hesitant individuals suggesting that they might be more willing to consider getting this vaccine as opposed to one of the other vaccines? Have you talked to vaccine-

hesitant people or have any sense of whether they would be willing or more interested in using this vaccine than one of the others?

DR. FILIP DUBOVSKY: Yeah, so I'm going to ask Dr. Poland to step in and give his perspective. But I have to say one in ten Americans has yet to be vaccinated, and we haven't given up on them. We heard in the open public comment period that there seems to be a desire to use this product, and that's why -- that's what we want to bring to the U.S. population is another option, a choice.

Now whether the proportion that choose to be vaccinated from a primary series? That isn't clear; we'll find out. We do know that, in countries where the vaccine is being deployed, it is being used both as a primary series as well as a booster and are the choices that people are making in those countries -- to choose our vaccine.

Dr. Poland, do you have any other perspective?

MR. MICHAEL KAWCZYNSKI: Arnold?

DR. ARNOLD MONTO: Hello.

MR. MICHAEL KAWCZYNSKI: Yeah. Are we waiting on somebody?

DR. ARNOLD MONTO: We're waiting on Dr. Poland who was called on.

MR. MICHAEL KAWCZYNSKI: Oh, there we go.

DR. FILIP DUBOVSKY: No, I don't know that if he's even coming on, so maybe we'll take that as the sponsor's answer for the time being.

DR. ARNOLD MONTO: Okay, I see Dr. Reingold. He's not on my regular list. He's up among the presenters, so I don't know how long he's been waiting.

DR. ARTHUR REINGOLD: Hi, can you hear me?

DR. ARNOLD MONTO: We can.

DR. ARTHUR REINGOLD: Good. So, that's one of the problems with coming late is lots of questions that have been answered; particularly, the ones Dr. Sawyer asked. But I do have one other question building on what Dr. Meissner mentioned. It will be fall soon; we'll be giving a lot of flu vaccine to people. And I don't know about other people, but I got my flu shot and my booster dose of COVID in different arms on the

same day. I'm just curious what you know about the administration of this vaccine at the same time people get a flu shot.

DR. FILIP DUBOVSKY: Yep, I'd say a question that we have also been very curious about. In the U.K. study, we actually included a cohort of participants who received the first dose -- a dose of licensed influenza vaccine -- and what we saw there is that it didn't negatively impact the hemagglutinin responses. However, what we did see is a decrease in the anti-spike responses in that cohort. We still maintain efficacy. Efficacy was maintained at pretty much exactly the same rate as the overall population, but it did drive the anti-spike response.

This isn't unique to our platform. There are publications that show that, with other platforms when you give flu vaccine, it tends to drop those responses, including against mRNA vaccines. We've furthermore conducted a combination study with our flu vaccine and our COVID vaccine, and this was made public a few months ago. We capitulated the same finding. We do,

in fact, impact the anti-spike response, but we can overcome this response by minimally decreasing the hemagglutinin while increasing the spike antigen. And that's a combination product that we're taking forward as well.

DR. ARNOLD MONTO: Thank you. Dr. Marasco.

DR. WAYNE MARASCO: This is a question for Dr. Dubovsky. So, I wanted to follow up on a question I've asked before in a different way, and it has to do with your comments about antigenic spread.

So, your titers look pretty reasonable going across the lineages, but there is some drop-off. So, my question -- it's really two questions. One, do you know that the vaccine is not -- just because you're adjuvanted, and that's going to have some impact on this. Do you know that you're not getting epitope shift? I mean some of the more conserved regions of the spike are in the S2 domain, for example. So do you know that the reason you're getting less of a particular drop-off is because there's a difference in the antibody response that you're eliciting?

And relating to that, the other -- when you look at the studies that have been published on immune serum from people that have been vaccinated with the Wuhan strain versus hybrid immunity, it's pretty clear that it's both your -- and Dr. Marks comment on this -- it's both your peak response, your breadth of response, and the sort of rate of decay. So, do you know, for example, that the rate of decay is not lower because you're adjuvanting?

I mean, this would be a very important point for the public who recognizes now that the vaccine responses wane, and my real question is, because this is adjuvanted, do you know anything more about your rate of decay? I mean, it would really take you three time points to know that, or antigenic shifts in terms of subdomains of the spike that you may be eliciting the antibodies to.

DR. FILIP DUBOVSKY: Yep, so, let me show you the data we have on decay, and, since it takes time to develop those studies, they are from our earlier studies, although this is data that we're developing in

the 301 study as well. What I'm showing here is IgG responses in the first instance. We see that they peak at Day 35, they decay in the subsequent six months, and then they take a nice boost up to four or five-fold higher with the boost.

So, when I look at the comparable data, I'm not seeing there's any specific advantage in the length of decay. The IgG seems to be dropping at about the same rate. Just as far as the boosting, what we do know is that those titers that were achieved are quite high.

So what I'm showing you here is that same IgG with the third dose and showing you that the levels we achieve are much higher that's achieved in the two Phase 3 studies, and that gives us some assurance that a third dose boost is going to be quite efficacious. And, if you prefer neuts, although our neuts in IgG correlate extremely well, once again you can see a 5.5-to-5.6-fold increase in neuts with a third dose compared to the levels achieved in the two Phase 3 studies. So that's as far as decay and boosting.

I, as far as your question about what parts of the antigen we see or don't see. So, we know we recognize parts of this by domain that are distant from the RVD, right. We've mapped that out, and some of the common epitopes, including the original SARS epitope, are found by this vaccine and are utilized. The extent of that and how they've matured is something we're working on right now.

And maybe I'll stop there, and, if there are further questions, I'll need to call into my bench and perhaps I'll call on my colleagues if you have further questions.

DR. WAYNE MARASCO: No, that's good. Thank you.

MR. MICHAEL KAWCZYNSKI: Who would you like to call on?

DR. ARNOLD MONTO: Dr. Bernstein.

MR. MICHAEL KAWCZYNSKI: There we go.

DR. HENRY BERNSTEIN: Thank you, Arnold. So, I just had two questions. One is, can you remind me of Novavax study plans in the pediatric population and

specifically what experience do you have with the use of the adjuvant in the pediatric population in younger age groups? That's that the first question.

DR. FILIP DUBOVSKY: So, we've concluded the study in adolescents 12 to 17 years of age and that was in 3,000 adolescents in the U.S., and that's the basis of the licensure we're going to be requesting from the FDA subsequent to our EUA. Our further plans -- we have further plans to study this vaccine in first school-age children and then age deescalating down to children as young as six months of age in the first study.

Our colleagues in serum have done this study down to two years of age, taking the same adult vaccine dose, and what they've found in that study is that the reactogenicity profiles stayed very solid. The only small uptick they saw was in fevers, but less than one percent were a Grade 3 fever, and the immune responses were favorable. They were much higher than was seen in adults.

This adjuvant is in a Phase 3 study being

studied in West Africa for Malaria. And, in that study, the doses have been taken down to children as young as five months of age and, once again, they're not seeing a safety problem, although it is a different antigen, obviously, since it's against malaria. But overall, this appears to be quite favorable, and we'll know more as we develop more data.

DR. HENRY BERNSTEIN: Thank you and my second --

DR. FILIP DUBOVSKY: And I should say we have agreed upon a pediatric investigational plan and a specific study planned with the FDA, as well as the E.U.

DR. HENRY BERNSTEIN: Thank you. My second question is --

DR. ARNOLD MONTO: Thank you.

DR. HENRY BERNSTEIN: -- and I may have missed this, but can you explain -- you published the U.K. data in September of 2021 and the U.S./Mexico data in February of 2022. Is there a reason that we're talking about this in June of 2022 as opposed to earlier

request for EUA?

DR. FILIP DUBOVSKY: Yeah, so our first approval was in December of last year, but, when the pandemic started, this company didn't have a manufacturing base, so we had to build it from scratch and build a manufacturing network from ground up. What really took the longest time, however, wasn't the manufacturing of the product; it was the generation of the assays to demonstrate that we could make the product over and over again the same way and to deploy those assays against the multiple lots. All of them need to achieve those critical quality attributes.

So, our approach then was to settle on a single facility in India because they're the world's largest vaccine manufacturer by dose and that's the single process we've taken forward and that's the one that's the basis of licensure globally as well as a EUA request here in the U.S.

DR. HENRY BERNSTEIN: And do you have a concern about having a single manufacturing plant?

DR. FILIP DUBOVSKY: There's always a risk

there and we have a network and the subsequent sites are being brought on now. They're going to be variations, so first, you need to be approved with one -- in the instance, with serum -- and we're bringing on our sites one that we own in Europe and then one of our partners in South Korea. Those are being now applied for in various locations globally.

DR. HENRY BERNSTEIN: Thank you.

DR. FILIP DUBOVSKY: I would say that also Takeda and SK are licenses of ours, and they have a different relationship. They're not manufacturing for us; they're manufacturing for themselves, and they're licensed in Korea and Japan, respectively.

DR. HENRY BERNSTEIN: Thank you.

DR. ARNOLD MONTO: Thank you. That helps in some of our considerations. Dr. Fuller.

DR. OVETA FULLER: Yes. Thank you. Yes, so a question that I think the public will ask and trying to ask it in a way that the public will understand. For those who have not been vaccinated, as well as those who may want to use this in some other way, this

baculovirus-expressed protein in an adjuvant, we get asked all the time with other vaccines. Well, how long does it stay in my system? Could you just share in sort of general language for people who may be listening, how long this -- they can expect this particular baculovirus with adjuvant of the S protein to be in the system to get the response that we want from the immune system?

And secondly, if they get this, how long will it take you to make something else, if indeed something else is going to be needed later as far as a strain of SARS virus. Just some practical questions in a way people can understand.

DR. FILIP DUBOVSKY: Right. And just to be clear, even though we use baculovirus virus in the manufacturing process, the vaccine contains no virus whatsoever. In fact, the process has been specifically designed to eliminate all virus from a final product we generate. All that it's in there is the viral spike protein. Now, what we've talked about is that the adjuvant effect seems to peak right about 72 hours

locally with a longer protracted effect in the lymph nodes later on. What we saw from our immunogenicity data is it generally kind of peaks at two weeks and then goes lower after that.

I guess as far as the variants question, we're manufacturing Omicron right now. It isn't clear to us it'll be needed. It isn't clear to us what the public health agencies and the customers and the people will want; we just want to be ready to have that vaccine in hand should it be needed. I know there's a VRBPAC coming up later this month to decide or help decide on what kinds of vaccines we should be asking for in the fall.

DR. OVETA FULLER: So, in general with the side effects, the 72 hours expression -- or not expression, but presence of the vaccine -- does that prolong the time of side effects that people see or the appearance of the time of those side effects? You had data on that, but could you just restate that, please?

DR. FILIP DUBOVSKY: Yeah. No, it's an excellent question. So, the major side effects, you

know we follow very, very closely for the first seven days, and the vast majority were either mild or moderate. Actually, many people had no side effects whatsoever, and the side effects that did occur will resolve after one or two days. Those are both the local ones, things like pain and tenderness, as well as the broader ones like fatigue.

DR. OVETA FULLER: Okay, so those side effects that can be seen in many vaccines --

DR. FILIP DUBOVSKY: Two days.

DR. OVETA FULLER: -- yeah. They're from the actual injection versus from the 72 long-term hours of antigen being present?

DR. FILIP DUBOVSKY: What it is, it's they're likely to be caused by the immune response against the vaccine. Right, so now the act of the vaccine being delivered into your arm versus the immune response of inflammation which comes along with the body reacting to the vaccine and generating the protective immune response.

DR. OVETA FULLER: All right. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Nelson.

DR. MICHAEL NELSON: Thank you very much for a very thorough presentation and lineup this morning. I wanted to follow up a little bit on the durability question. I'm intrigued by the possibility that it may last longer.

To date, the data that has been shown has been with respect to clinical efficacy, as well as the humoral immune response. So, what I haven't seen is whether you're generating any cellular immune response data with respect to generation of memory B-cells and others; it might also provide an explanation. And is there anything unique about your vaccine that is inducing a different cellular response that may impact durability and memory response?

DR. FILIP DUBOVSKY: Yeah, let's talk about a slow immune response for a bit. Although, I don't have kinetic data on that, so I think I'll disappoint you in being able to look at it over time. But this is -- oops, that's not what I wanted. Let's try this one. This is data that we published in the *New England*

Journal by P. Chid Aoh (phonetic), and what it's looking at is the intracellular cytokine profile after vaccination on Day 28. On the left-hand side, we stained against Th1 cytokines, and, in this case, IL2 TNF alpha and interferon-gamma, and what you can see is we got a really nice bump at Day 28.

On the right-hand side, you can see the Th2 profiles. We look at IL5 and IL13 which is a lesser bump. Importantly -- at least we think importantly -- when we looked at those that were polyfunctional to those that either stained for two Th1 cytokines or three Th1 cytokines comparing to those that stained for two Th2 cytokines, we saw this polyfunctionality. And we think that's important as far as effective memory cells go. Although we don't have the kinetic data to demonstrate that fully.

DR. MICHAEL NELSON: Is that being required? And certainly, does -- Th1 skewing may impact on the observation of lower immediate systemic effects with respect to anaphylaxis and other immediate type of responses, which is favorable with your platform.

DR. FILIP DUBOVSKY: Right.

DR. MICHAEL NELSON: My second question is related to the distinction between your Hispanic and Latinx efficacy response. I thought I heard this morning that certainly it's been acknowledged that the difference -- no obvious explanation to date. I wondered if you wanted to clarify a little bit more as to what your plans are to tease out whether those differences were indeed due to chance versus something else.

DR. FILIP DUBOVSKY: Yeah. So, we've obviously been very interested in understanding what this data is trying to tell us, and what's even more interesting is when we looked at the racial profile of the Hispanics, they were all identified as Caucasian and not black Hispanics. So, there is something quirky happening in the data.

Well really, our best chance to understand this data is in our effectiveness studies. Those are planned for the U.S. where we'll obviously have the ability to probe that in the Hispanic population to

understand if it was a real difference over this chance finding. I'm a believer in immune responses, and the immune responses in the Hispanic population give me a lot of comfort that it's going to be a chance finding. I have to say in all the moderate and severe cases, there weren't any. So even in that population, all the cases were mild.

DR. MICHAEL NELSON: Acknowledged. Thank you very much.

DR. ARNOLD MONTO: Thank you. Dr. McInnes.

DR. PAMELA MCINNES: Hello.

MR. MICHAEL KAWCZYNSKI: Yep, we can hear you. Take it away.

DR. PAMELA MCINNES: Hi. Okay. I have a very simple question. It's for Filip. Hi, I searched these briefing documents, but I can't seem to find out what the placebo was, and it's important to me because I'm measuring a delta between that and the activation. Can you tell me what the placebo is?

DR. FILIP DUBOVSKY: Sure, it's normal saline.

DR. PAMELA MCINNES: Could you hear me?

DR. FILIP DUBOVSKY: Yep. Normal saline.

DR. PAMELA MCINNES: Normal saline. Okay, thank you.

DR. ARNOLD MONTO: Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Monto. And again, thanks for your persistence because I appreciate it. The question I have is you hadn't -- there was an earlier study, and I might've missed this this morning during some of the clinical trials, but it was done in South Africa, and it included HIV-positive subjects. And I think the vaccine efficacy was reported as 50 percent -- or something around that -- in the HIV-positive population, which seems pretty good in view of their degree of immunocompromise, I guess, depending on their reconstitution.

But can you provide any further data regarding that group and how this vaccine might work in individuals who are immunocompromised for other reasons?

DR. FILIP DUBOVSKY: Yeah, and maybe if I could have the immune responses in people with HIV in

Study 301, please? We can start there. Yeah, here we go. So, what I'm showing you here is IgG responses, and, on the left-hand side, you see those that are seronegative. So, meaning seronegative, meaning baseline seronegative against SARS, and you can see the HIV levels are higher than those that were living with HIV, although broadly the confidence intervals overlap.

Now in the U.S., these are people who are well controlled (inaudible), and they were immunologically reconstituted. We had a small number of individuals, that I'm showing on the right-hand side, who came in previously exposed, and you can see they boosted extremely well with the vaccine, so they achieved titers many-fold higher than was associated with protection in the HIV negative group.

Now our data so far on various levels of immunocompromised individuals is somewhat limited, and we're going to be gathering that data in due course. We've completed enrolling a study in South Africa where we looked at giving three doses and giving doses on different schedules to see if we can get an advantage -

- an immunologic advantage -- by delivering it in that manner.

Now, as far as the results in South Africa, Dr. Mallory, do you want to give a crack at reviewing the South African results for what our findings were?

MR. MICHAEL KAWCZYNSKI: Sorry, who would you like to call on?

DR. FILIP DUBOVSKY: Dr. Mallory.

DR. RABURN MALLORY: Can you hear me?

MR. MICHAEL KAWCZYNSKI: Yes, we can. Take it away.

DR. ARNOLD MONTO: We can. Yes, go ahead.

DR. RABURN MALLORY: I just wanted to clarify, Dr. Meissner, that I'm showing the results of the South Africa study here, and we did show a notable efficacy of around 50 percent. Remember, this study was conducted when the beta antigenic escape mutation was circulating. The efficacy in individuals without HIV was 55 percent. However, we had a very small number of individuals involved in this study who were living with HIV, and, in that group, we were not able to

demonstrate efficacy, but it was not powered for it.

So, I think maybe there's some miscommunication. The 55 percent is in individuals who were HIV negative in that study.

DR. CODY MEISSNER: Oh. Thank you.

DR. RABURN MALLORY: In all cases, again, there were no severe cases in this study, so the vaccine protected all participants enrolled from severe disease in that study.

DR. CODY MEISSNER: Okay. Thank you for that clarification.

DR. ARNOLD MONTO: Yes, thank you.

COMMITTEE DISCUSSION AND VOTING

DR. ARNOLD MONTO: Seeing no further hands raised, we're able to move to our next phase of our discussion, and that is the Committee looking at the question that we are going to have to vote on shortly. And that is whether we recommend emergency use authorization for the Novavax vaccine, and there is the

voting question. I'm going to be officially reading it later on, but just to remind you this is for the two-dose series, and it's based on whether the risks outweigh the benefits.

So, any of you who would like to start the discussion please raise your hands. We don't have to fill the full two hours in if a lot of our questions have already been answered. Dr. Rubin.

DR. ERIC RUBIN: I don't want to fill the two hours.

DR. ARNOLD MONTO: You don't have to.

DR. ERIC RUBIN: Very simply then, I think that the data that were presented looks very similar to the data that were presented for the mRNA vaccines that we approved a long time ago and, in fact, that's in part because those trials were done at the same time. But I think that the efficacy is quite similar --

DR. ARNOLD MONTO: I had the same feeling, Dr. Rubin. It was déjà vu.

DR. ERIC RUBIN: And if we're going to use the same criteria that we did then, I think that it's not

that difficult a decision now. It is disappointing -- and we've discussed this already -- that we don't have more updated information because we're looking at the efficacy against strains that don't exist any longer. Nevertheless, I think that the argument made earlier by Dr. Marks, and for EUA, if there really is a population of patients who are willing to take this and not willing to take existing vaccines, I think it's pretty compelling.

DR. ARNOLD MONTO: Thank you. I'm amazed. I see no hands raised. Anybody who doesn't feel that this is compelling? Dr. Sawyer.

MR. MICHAEL KAWCZYNSKI: Go ahead, Mark.

DR. MARK SAWYER: Yeah, I'd just like to sort of reiterate the previous comment. It is quite disappointing that we don't have any data in the Omicron era. Clearly, such data could have been presented, but I will follow what I understand is the FDA guidance which is we're supposed to evaluate this vaccine based on the data presented to date and leave it up to them whether they actually issue the EUA given

the lack of data about Omicron effectiveness, at least as presented on the Committee.

So, I do agree with the previous conclusion that the data that was presented is quite similar to what we've approved in the past with other vaccines.

DR. ARNOLD MONTO: Thank you. Dr. Reingold.

DR. ARTHUR REINGOLD: So, I agree with both of those statements. I certainly will support recommending FDA that they approve this vaccine.

I'm a little skeptical about how many of the vaccine hesitant are just waiting for this vaccine and are going to be convinced that this is better for them than the vaccines that are currently available, so obviously they're individuals who've testified to that. But at a population level, I'm hoping to be proven wrong that the large numbers of people who sign up for this vaccine, who wouldn't take an mRNA vaccine, but count me as skeptical about that.

And I do think that it remains to be seen just what the risk of myocarditis is, but we know that that certainly has dissuaded some individuals from getting

the mRNA vaccines, and it looks like it's likely to be the case that we'll see at least comparable levels following this vaccine.

DR. ARNOLD MONTO: Thank you. Dr. Gellin.

DR. BRUCE GELLIN: Thanks. So, having been in these discussions before, I know the FDA selects their words pretty carefully. Could you put it back on the screen because I think the question about the totality of the data available, we've only seen a subset of the totality of the available data? And there's a lot of other data that would help to inform this decision in use currently and going forward that we haven't seen. So maybe they want to talk about totality of evidence available.

DR. ARNOLD MONTO: I can tell you, Dr. Gellin, that that is the wording that's in the -- has been used before, and I think is taken from the regulations, but I'll let the FDA respond. Please.

DR. DORAN FINK: So, we would consider the totality of data available to consist of the data that had been presented and discussed at the meeting today,

and then primarily the data that have been reviewed and independently verified by FDA as outlined in our briefing document. I think it's important to make sure that the Committee members and the public understand that in response to some questions by Committee members, Novavax has presented some additional data that FDA has not covered in our briefing document, and the reasons for this are several.

First of all, it has been mentioned several times before, we view that there are important manufacturing differences between the product that was studied in the U.S./Mexico trial and the product that was studied in previous trials in our assessments due to inherent limitations in the product characterization for this platform. We just cannot conclude comparability of those products that would allow us to consider those data.

That being said, I think we have laid out a case in our briefing document to support why we think that the available data from the U.S./Mexico trial could meet the statutory criteria of -- may be

effective that is required to support emergency use authorization. And that rests primarily on the efficacy observed in Clinical Trial 301 that was conducted in the U.S. and Mexico and considering those data in the broader context of what we know about other COVID-19 vaccines that were evaluated at the same time and how they have performed in real-world use, including against currently circulating variants.

There are additional immunogenicity data that Novavax has presented as well that we did not review or discuss. Some of these relate to binding assays, IgG binding assays, that we have not used as the basis for regulatory decision-making for any of our EUA decision, and also come from clinical trials outside of the data that we are really considering in support of this two-dose series for use in adults 18 years of age and older. And I see that with Dr. Marks has also turned on his camera, and he might want to add some additional context.

DR. PETER MARKS: I think that this issue of why we're seeing a limited amount of the whole picture

presented is because we needed to feel comfortable that the process that was used to make the product that was studied was one that we were comfortable with and that it was one where we felt that going forward, what you would authorize as a committee would be what we would expect to see. Now, granted, it will be in a different era, perhaps, but what you're seeing is the product that you're getting and that is the reason for focusing on the manufacturing process that came from the facility that is producing the product currently.

We take manufacturing very seriously. I think it's very important for the public to understand that we don't benchmark ourselves against other countries when it comes to manufacturing. We consider that we have a very high standard, and it's why we're often considered a gold standard for our manufacturing. And particularly in the area of vaccines, we owe it to the American public to make sure that we have the highest quality of vaccines. And that means that, whether it be in any aspect of this including whether we will allow release of lots of vaccines to be used, we will

need to see the data that supports that before that can actually happen for any vaccine here in the United States.

So, I think it's important to understand that I fully respect the sovereignty of other countries to release vaccines based on what they see as their benefit/risk, but we have certain standards in the United States that we hold to because that is the expectation of the American public. Thanks.

DR. ARNOLD MONTO: Thank you. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thank you, Dr. Monto. My question actually is for our FDA colleagues. With regard to any kind of cautionary language that would be included for this vaccine to be authorized with regard to the risk for myocarditis, pericarditis, cholecystitis, these quite rare but serious adverse events that seem to be associated with this vaccine.

DR. DORAN FINK: Yes, thank you for that question. So that is a question that we are discussing as we have been reviewing the proposed EUA fact sheet for this vaccine. So what I think you might be hinting

at is, do we include something along the lines of a warning statement similar to what we have in the currently authorized development of mRNA vaccines? And so, the regulatory criteria for including a warning statement is to have reasonable evidence of a causal relationship.

Now, certainly, I think we can all agree that the extent of evidence for myocarditis being causally related to this vaccine is not at the same level as for mRNA vaccines where we have many more cases described among much more extensive use of the vaccine.

But I would actually like to get the perspective of Committee members to weigh in. What do you think based on the data that you've seen presented of these myocarditis cases? Is your impression about the likelihood of a causal relationship and whether you would see a warning statement being appropriate in the situation?

DR. ARCHANA CHATTERJEE: I actually would.

DR. ARNOLD MONTO: Dr. Chatterjee, if you're there. Please answer.

DR. ARCHANA CHATTERJEE: Yes, yes. And you're absolutely correct, Dr. Fink, that is what I was alluding to. If we go back and recall the data that were presented initially for authorization, we did not have this concern. It really became evident after the mRNA vaccines began to be used much more extensively, so that often happens as we know with vaccines.

And so, in this instance, we have an indication that there is a potential for these adverse events to occur more as this vaccine gets utilized. So I would be in favor of that type of language being included so that the public is clear. Vaccine providers are clear about the risk and can speak to them with their patients.

DR. ARNOLD MONTO: And since my picture is up there right now I will say that I agree as well. I think there's question and there will be answers, but we must be aware. Dr. Dubovsky.

DR. FILIP DUBOVSKY: Yeah, I just thought to hear our perspective, honestly. It's important to convey accurate level of risk for the available data.

We believe there's insufficient evidence to establish a causal relationship, but we're not really that far from where the FDA is. And, as we enter the final label negotiations, I'm sure we're going to come to closure on this. These regulatory agency reviews are clinical in our post-marking data and come to their own conclusions, and that's what informs their labels, so we completely respect the approach that the FDA is taking.

DR. ARNOLD MONTO: Any other questions? I see a number of hands raised. I'd like to settle this question at least in terms of the Committee's opinion about the myocarditis issue. Dr. Levy, is that what you're going to be talking about? You had your hand raised before.

DR. OFER LEVY: Hello, can you hear me?

DR. ARNOLD MONTO: We can.

DR. OFER LEVY: Okay. I had a question for FDA regarding the placement of this vaccine in the broader context of the (inaudible).

DR. ARNOLD MONTO: Dr. Levy, we wanted to

settle the Committee's views of the -- okay, did you have anything to say about that because then I'll come back to you?

DR. CODY MEISSNER: Can I make a comment?

DR. ARNOLD MONTO: Yes, please. Go ahead.

DR. CODY MEISSNER: Yes, on this risk, I have such a hard time with this problem as we all do, and there's been such variation in reports of the rates of myocarditis following administration of these vaccines that I think it's very hard to say that it occurs more frequent. It would be, at this stage, difficult to say that it occurs more frequently with one vaccine platform than with another.

I mean, I think if because if you look at the Israeli data, it's pretty high. It's higher than the numbers we're seeing here, and they may have better capture of rates of myocarditis to the messenger RNA vaccine.

So, I don't think we can have enough confidence in the rates because there's such a range, and I think that any statement regarding the risk of

myocarditis should be standard between all of the COVID-19 vaccine platforms. I think there is clearly an association, but, to try and make a gradation as to where the one platform is more likely to result in myocarditis than another, I don't think we have the numbers to make that statement. Over.

DR. ARNOLD MONTO: Thank you, Dr. Meissner.

DR. DORAN FINK: Thank you, Dr. Meissner. Yes, I agree with you that at this point we don't have enough information to really describe relative risk of this event between different vaccines, but that's not a requirement or a necessity to have a warning statement. A warning statement is justified by -- and I'm going to clarify what I said earlier here. A warning statement is justified by reasonable evidence of a causal association, and there does not need to be definitive evidence of a causal relationship. It's reasonable evidence of a causal association, and so that really is the question that we're looking for input here. Based on the information that you've heard today, do you consider there to be reasonable evidence of a causal

association?

And, of course, it would be ideal if we could describe the magnitude of the risk for each vaccine and compare to the others, but we don't have the ability to do that. At least not for this vaccine just yet.

DR. CODY MEISSNER: Thank you for that comment, Dr. Fink, and I completely agree with what you've said. But I think my point is, I think there may be --

DR. ARNOLD MONTO: Is there anyone on the Committee that does not agree with that comment? Dr. Gellin, you have your hand raised. Do you disagree?

DR. BRUCE GELLIN: Well, my hand was up before you changed the question, so I'm just going to give you the answer from before.

DR. ARNOLD MONTO: You have to be nimble on this Committee.

DR. BRUCE GELLIN: I got it. On this topic, though, I want to support what Cody raised and what Dr. Fink supported. But I think we also have to put this in context that we talked about earlier about

myocarditis that comes from natural infection as well, so people can look at that and weigh those as well. And then most importantly what Paul Offit raised earlier that this is a priority question to answer mechanistically. Over.

DR. ARNOLD MONTO: Okay, I think you've got the message, Dr. Fink, that there is a concern that the topic be further investigated, and it's in your hands in negotiations with the sponsor exactly how that is to be done. But we do agree that there is a concern here.

DR. DORAN FINK: Thank you.

DR. CODY MEISSNER: Can I ask --

DR. ARNOLD MONTO: Okay. Do you think --

DR. CODY MEISSNER: Dr. Fink, don't you agree that the likely association between the messenger RNA vaccine and the Novavax vaccine -- and shouldn't it be a standard statement?

DR. DORAN FINK: Well, what we say in product labeling, including EUA fact sheets, needs to be supported by available data and the level of evidence is going to be different for different vaccines. I

think we're in a different place and can say more for the mRNA vaccines at this point in time than what we can say for this vaccine.

DR. CODY MEISSNER: Okay, thank you.

DR. ARNOLD MONTO: Okay. Moving on. Dr. Levy, I interrupted you when you were ready to make another point.

DR. OFER LEVY: Yeah, my question here -- can you hear me?

DR. ARNOLD MONTO: We can.

DR. OFER LEVY: Yeah. My question here is to FDA. In my view, we've seen great presentations today establishing reasonable safety, demonstrating efficacy at least against the variants that were circulating at the time this vaccine was evaluated. Now, as we vote to potentially recommend authorization of this vaccine, where does the whole topic of how we place the vaccine in a public health (audio skip) play into this? In other words, it's a very different landscape now than it was half a year or year ago. There are the well-established mRNA vaccines, some of which are not just

authorized, but approved as this Committee knows very well.

So, is there going to be a pecking order in (audio skip) the mRNA vaccines where there's much more data about the level of vaccine efficacy against Omicron? Are those going to be the preferred first-tier vaccines to use with the Novavax if and when it's authorized being that we've heard a lot of talk about people who might not want to trust or partake in the mRNA platform; they might want to try a different platform.

So, don't get me wrong, I'm a fan of this vaccine. It has a lot of attractive features. It doesn't require freezing. The adjuvant is intriguing. We might get more bang for our buck with that. But where does this get placed in the armamentarium? Because in isolation, this vote would almost imply that it just takes an equal spot on the shelf. But we know that it's more complicated than that.

So, Peter, where does that stand, and does FDA speak to that, or is that just a CDC matter?

DR. PETER MARKS: So I think we speak to making available another option for those who might not otherwise take a vaccine because, right now, any vaccine, even one that may need to be updated for the variants, right now getting that into someone's arm who has no vaccine is probably going to prevent them from having serious outcomes such as hospitalization and death from COVID-19, even from Omicron, we hope at least for a period of time. So, it's having additional choice.

That said, my guess is that CDC will have some discussion here around this as well about how they might position this, and I can't say how they'll come on this from ACIP.

DR. OFER LEVY: Of course.

DR. PETER MARKS: But from our perspective, it's making available another option to hopefully get some additional people vaccinated.

DR. OFER LEVY: Yes, it makes sense, but, in the past, the committee has been asked to take votes on very specifically worded for certain age groups, for

certain scenarios. This is a pretty broad statement. You're not crafting a vote question that says, for individuals who are reluctant to take mRNA. It's a broader statement. That might be fine, but I'm wondering, did you consider to phrase the question more narrowly or you want this broad phrasing?

DR. ARNOLD MONTO: This is a question that we voted on originally back in a year and a half ago.

DR. PETER MARKS: Yeah. I think the issue is there were no data for us to suggest that there was a reason to narrow this further at this point in time in terms of adverse safety concerns that might want to make one narrow this, and I certainly invite Dr. Fink if he wants to add anything to that to add it. But I think that, in the absence of data suggesting that a narrowing was necessary, we have asked the broader question here.

DR. DORAN FINK: Yeah, I'll just echo what Dr. Marks said. The more restricted authorization for the Janssen vaccine was participated by specific safety concern related to thrombosis with thrombocytopenia

syndrome. Here we have a package of data to support broad use in the general population of adults 18 years of age and older. We did not identify a specific safety concern that would cause us to think about a more restricted use of this vaccine, and so that's why the voted question was constructed, of course.

DR. OFER LEVY: No, I got that. (Audio skip) true that all other things being equal, we know more about the efficacy against Omicron of the mRNA than this vaccine. I'm a supporter of this vaccine; I'm just saying in terms of messaging, it's tricky, isn't it?

DR. ARNOLD MONTO: We all agree that it's tricky. Dr. Perlman, thank you.

DR. STANLEY PERLMAN: Yeah, I just have a question about something we actually didn't talk about much. So, this vaccine doesn't for the most part induce CD8 T-cell response; it's mostly CD4 and antibody and that's what was discussed. How does the FDA take that laboratory information? Does it consider that? The vaccine clearly works, so maybe it doesn't

matter, but I'm just curious how the FDA puts that into its equation in going forward.

DR. PETER MARKS: I'm not sure there's really a lot to say there. I mean, I think it's something we're aware of, but, given the clinical data, that's what we're hanging more of the hats on here. Doran, I'll pass it over to you.

DR. DORAN FINK: Yeah, I think we really have to look at the clinical data here. It's interesting to see and discuss this data on cellular remediated immunity to the extent that it is available. We don't have a sufficient enough understanding of those data to use it as the primary basis for making regulatory decisions. And so really, I would ask the Committee to focus on the clinical efficacy data that has been presented.

DR. STANLEY PERLMAN: Right.

DR. ARNOLD MONTO: Thank you. Seeing no further hands raised, I would like to turn the meeting over to Christina Vert who will start the voting process.

I'd like to remind the Committee that, after the votes are completed and reread, we will allow time for those who wish to explain their vote to do so. You don't have to explain your vote if it's clear to you and to the group, but that time will be made available afterwards. So, we move to voting.

MS. CHRISTINA VERT: Thank you, Dr. Monto. Can you hear me, okay?

DR. ARNOLD MONTO: We can.

MS. CHRISTINA VERT: Okay, great. Only our 10 regular members and 12 temporary voting members, a total of 22, will be voting in today's meeting. With regards to the voting process, Dr. Monto 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 which include yes, no, or abstain.

You will 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 has

closed, all votes will be considered final. Once all of the votes have been placed, we will broadcast the results and read the individual votes out loud for the public record. Also wait until I say, start the vote.

Does anyone have any questions relating to the voting process before I begin, and also do you feel you need more than one minute to cast your vote? If you need more time, or if I need more time to check things, we will continue to keep the vote open for the two minutes. Okay.

DR. ARNOLD MONTO: Okay, I'll read the question. I'm sure that you will see everybody voting within the minute and you'll know.

MS. CHRISTINA VERT: Yes, Dr. Monto, please read the voting question.

DR. ARNOLD MONTO: "Based on the totality of scientific evidence available, do the benefits of the Novavax COVID-19 vaccine, when administered as a two-dose series, outweigh its risks for use in individuals 18 years of age and older?" So, there is the pod. Begin.

MS. CHRISTINA VERT: Please start voting at this time. And set the timer. Yeah. Okay, I'm just checking the votes. Okay, it looks like all the votes are in. We can please end the vote, and then we can broadcast the results. Okay. We'll close. Okay. What is viewing? Okay, all right.

The majority -- so there's 22 total voting members, again, today and we have 20 -- let's see here. Oh, okay. We have 21 that have voted yes, zero have voted no, and one has abstained. So, the majority have voted yes, and I will read the voting responses of each voting member for the record.

Okay. Dr. Fuller, yes; Dr. Berger, yes; Dr. Cohn, yes. Okay. Dr. Chatterjee, yes; Dr. Monto, yes; Dr. Reingold, yes; Dr. Gellin, abstain; Dr. Meissner, yes; Dr. Kim, yes; Dr. Rubin, yes; Dr. Bernstein, yes; Dr. Portnoy, yes; Dr. Lee, yes; Dr. Sawyer, yes; Dr. Wharton, yes; Dr. Nelson, yes; Dr. Levy, yes; Dr. McInnes, yes; Dr. Offit, yes; Dr. Perlman, yes; Dr. Pergam, yes; Dr. Marasco, yes.

And that is everybody. Yes. Okay. That

concludes the voting portion of today's meeting, and I will now hand the meeting over to Dr. Monto for asking the Committee for their voting explanation. Thank you.

DR. ARNOLD MONTO: So, anybody who would like to explain their vote please raise your hand now. I do not see any hands raised.

DR. BRUCE GELLIN: Can you hear me?

DR. ARNOLD MONTO: Am I missing any?

DR. BRUCE GELLIN: I'm sorry. I got kicked out of the -- can you hear me now?

DR. ARNOLD MONTO: I can hear you; I can't see you.

DR. BRUCE GELLIN: I don't know -- something. I got kicked out of the meeting, but you can still hear me. I'm trying to get back in, but do you want me to explain mine or how do you want to proceed?

DR. ARNOLD MONTO: I want to -- it's up to you, if you want to explain your vote, please.

DR. BRUCE GELLIN: Yeah. Oh, I'd love to. Let me just say that this is a conditional yes, and I'll explain that. But conditional yes wasn't an

option.

I will say that this is a case study of perseverance by the company, and there's nothing about vaccine development that's easy. And the vaccine race is inspired by COVID, and it was reported by Warp Speed -- and I had nothing to do with that -- has brought us vaccines that we didn't think we would have to have an impact. That has been impressive.

And while global inequity remains, for which additional platforms and more user-friendly presentations will be welcomed, like this vaccine, that's not why we're here. The data that we've heard today and seen today has been impressive and support the original vision for this vaccine from its beginning. That it would provide safety and efficacy in a presentation that didn't require extraordinary logistics. With attribution to the novel adjuvant, the lower amount of protein appears to make it even less reactogenic.

With a focus on safety as we've discussed, myocarditis is a signal that many are paying attention

to, and attention to this by the company and government is critically important. As I said before, highlighting Dr. Offit's intervention, that we need to understand the mechanism here because this infection and the vaccines against this are going to be with us for the foreseeable future.

The question that we're asked is based on the totality of the scientific evidence available. We've already heard me ask about the availability word. And as Dr. Marks reinforced, in looking at the totality of the evidence presented, we can clearly say that it was, in general, safe, including the long-term safety follow-up in the study and because of its effectiveness to prevent serious consequences of the viral infection. But we don't know whether that attribute continues to be relevant today.

Dr. Levy's important question about the potential of cross-protecting immunity and the limited data that we've seen in response to that are certainly encouraging. But again, we don't really know whether it's likely to be effective going forward and what the

duration of that protection might be.

In the flu world, we're always challenged by mismatch; is the vaccine that's being made and distributed likely to be a good match for the flu virus that's likely to circulate? That's essentially the question here. This vaccine has incredible potential, and a lot has been learned about it that we didn't hear about that's likely to inform the durability of protection, transmission, the impact of boosting, adjustments to the dosage interval, the impact of mix and match, and its importantly impact against circulating variants.

So therefore, I want to be clear that I'm not voting against this vaccine because I did worry that such a vote would be misinterpreted and hence this conditional vote for it but as an extension. But as this is a real product that, if authorized, would be used, it would be important to evaluate whatever data's available but can give us insights into its performance, not just voting on the science that tells us about its promise.

So, recognizing we're an advisory committee and we're advising FDA and we know that FDA, as we heard from Dr. Marks and others, will continue to work with the company on some of the manufacturing issues, then our discussions today are just part of what they'll consider going forward in their decisions on authorization.

So, my conditional vote, yes, is based on my expectation that the FDA will review the totality of the data that will be available to them, including the data that we didn't see today to inform their authorization decision. Thanks.

DR. ARNOLD MONTO: Thank you, Dr. Gellin. Dr. Nelson.

DR. MICHAEL NELSON: Thank you, Dr. Monto. And certainly, with the question posed before is, do the benefits outweigh the risk? I'm entirely supportive of a yes there. It does come with a little bit of caveats because included in that question was specific reference to the two-dose primary vaccines.

I think this group was in full recognition

that this is probably a three-dose series and that they'll need to accumulate data supporting the need for booster doses and subsequent doses to probably make it a three-dose vaccine. But to address the question of the table, certainly, the benefits outweigh the risk for a primary series.

I also want to make reference to use Dr. Marks' words from this morning that this vaccine does, indeed, fill some unmet needs. So, he didn't ask us specifically how to apply these to the EUA criteria, but I'll offer my humble opinion, and that I do feel that it does offer something for fulfilling unmet needs, including those populations who have hesitancy with regards to the messenger RNA vaccines.

As an allergist, it offers me an additional tool for individuals who have hypersensitivity responses to initial doses of the messenger RNA vaccines, and there are other advantages that have been referred to today including storage. Who knows, even with supply chain challenges down the road, it will be nice to have these options going forward.

I'll offer one additional word with respect to myopericarditis. I've done some work in the Department of Defense, and we'll be publishing our work on long-term outcomes of myopericarditis with the smallpox vaccine shortly. This is an important question and should not be ignored. And I will say, Dr. Fink, with utmost confidence, that it would be a travesty if we didn't mention it in the EUA documentation for the public to show the concern that we have.

Is there evidence that it's a true causal link at a significantly higher relative risk? I have my own doubts there, as we've heard from the sponsor as well, but to be silent on the matter I think would be a travesty. I also think we should be focusing on the mechanism as has been discussed but also to put more effort into identifying what happens with subclinical appearance of myopericarditis. Our signals are those who get admitted to the emergency room in the hospital. I'm quite convinced that there are others who are experiencing cardiac events of a lesser severity that are worthy of being studied, both from a mechanistic

and outcome standpoint.

So, we have a lot of work to do, and I hope this Committee and the focus of the FDA, and the NIH remain on myopericarditis on all vaccine platforms, and I appreciate the opportunity to express this opinion, Dr. Monto.

DR. ARNOLD MONTO: Thank you, Dr. Nelson. Dr. Portnoy.

DR. JAY PORTNOY: Thank you. Yeah, I was a little bit torn when I first started the Committee this morning. I was a little bit skeptical about the need for an emergency use authorization of this vaccine since we have two other vaccines that are highly effective and relatively safe. So I was very skeptical about that. We've had those vaccines for a year and a half. If this vaccine had come up for discussion a year and a half ago, there would've been no problem at all getting it approved. I'm pretty sure that the Committee would've just voted enthusiastically yes, but now we've got these other vaccines. Is there really a need for an additional vaccine?

So that's what I was torn about, but I realize that this is a different technology; it's a more traditional protein-based vaccine. I'm very skeptical that vaccine-hesitant people will select to get this vaccine because of that. I'm good friends with a number of vaccine-hesitant people, and their hesitancy is more ideological than technological. So I really doubt that this vaccine is going to crack that nut, but perhaps some individuals would get this when they wouldn't get the other ones.

I see this as an opportunity to widely vaccinate people with the protein vaccine and to compare it with mRNA vaccines which are relatively new technologies because we know how protein-based vaccines work; we don't know how mRNA vaccines work. This is an opportunity to find out how they compare to each other over the long term when large numbers of people get vaccinated. So, I see this as an opportunity.

I agree that the benefits definitely outweigh the risks. Whether it meets the needs for emergency use, I'm not totally convinced, but I feel that at

least it was worth voting yes in this case because the vaccine deserves the opportunity to be given and studied and used by individuals who wish to use this vaccine.

Thank you for having such a transparent and open meeting, and I do want to thank the organizers of this meeting for holding it the way that you do. You do an excellent job, so thank you.

DR. ARNOLD MONTO: Thank you. Dr. Meissner.

DR. CODY MEISSNER: Thank you, Dr. Monto. I just want to note that the messenger RNA vaccines are truly remarkable. I mean, they are a great gift to humanity, and they were the first to cross the finish line. But whether or not they will turn out being the optimal vaccine for these viruses is not clear, and I think it's -- I also want to recognize the perseverance from the people at Novavax for developing this vaccine with a novel platform because I think it's -- we still need new vaccines.

I don't think we want to rest on just what we have at this point because there's always an

opportunity to improve on a vaccine, and we've talked about several of those issues such as sterilizing immunity and the duration of the immune response and the breadth of the immune response. And so I certainly think we want to continue to encourage the development of new vaccines despite the wonderful spot that we find ourselves in today with the two messenger RNA vaccines.

And I would also, just in response to Dr. Nelson's comment, again, just want to reiterate, I agree there does appear to be a causal association with the Novavax vaccine, but there's a causal association with the messenger RNA vaccines also. So, my point is I don't want to stigmatize this vaccine inappropriately relative to the messenger RNA vaccines. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Meissner. Dr. Marasco.

DR. WAYNE MARASCO: Yes, so I think to the question posed today, I think that the benefits certainly outweigh the risks. I voted yes because I feel that that's really the question that we will pose. I remain somewhat concerned about the timing of the

roll-out of this.

I know many of you have to be similar to me. The public knows that there is talk amongst the FDA about reformulating the vaccines in the fall to be more Omicron-centric, if you will. And the real question is, for the people that are vaccine-hesitant, are they going to say, great, we finally have a protein-based vaccine like we're familiar with? Or is the question going to be, but should we do it now with an ancestral strain or wait until the fall when the company itself has said they're investigating it?

So, I think on balance, we need to get these new vaccine platforms out there. I think there's some certain advantages to the adjuvanted vaccine that I'd like to see more about as we get more data, but it is a concern that I have in my mind about we're rolling this out, we're having a discussion two weeks before we're having another discussion about formulations for the fall. And although no decisions have been made, it'll be an active topic of discussion.

So overall, I applaud the company for having

the perseverance to getting this platform and the vaccine out, but there are some questions I think remain in my mind.

DR. ARNOLD MONTO: Thank you, Dr. Marasco. That's the last explanation of vote we have. I would like to turn the meeting over to Prabha who will ask Dr. Marks to give some closing remarks and thank you all for a very vigorous and productive meeting. So, over to you. I think you're muted.

MEETING ADJOURNED

MR. MICHAEL KAWCZYNSKI: Yep, Prabha, you're double muted.

DR. PRABHAKARA ATREYA: Yes, I'm sorry. Thank you, Dr. Monto. Dr. Marks, do you want to address the Committee and make some closing remarks? And then we can adjourn the meeting.

DR. PETER MARKS: Yeah, no, thank you very much. First of all, I want to thank the Committee members for a very good discussion today. Also want to

thank the sponsor, the open public hearing speakers. Again, they all contribute to what is an important open process -- transparent process here -- really appreciate that, and we will do our best to continue to work towards keeping technical glitches down to a minimum. Thank you for your patience with those.

I also want to thank Dr. Atreya and the Advisory Committee staff; they did a wonderful job preparing things for this meeting. And then the entire clinical team and the others that were involved from the various offices in the Center preparing for this advisory committee which took a lot of work. And as you're aware, there are some coming attractions of additional ones, so there's been a lot of work going on. Thank you to everyone for that.

Thank you to those who have tuned in today, we very much appreciate that. We will, again, look forward to working through what's been said today and moving forward and just appreciate everyone's input today. Prabha, I can turn it back over to you. Thank you, again, to everyone.

DR. PRABHAKARA ATREYA: Okay, thank you, Dr. Marks. And I would also like to extend my thanks to Dr. Arnold Monto for conducting the meeting very smoothly, and then also all the members who have been patiently working so that the (inaudible) such a productive meeting; thank you so much. And I also thank Michael Kawczynski for facilitating this meeting, and Christina Vert for doing the voting process very effectively. So, thank you and this meeting is adjourned now and have a good evening.

[MEETING ADJOURNED]