FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
164th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN PUBLIC MEETING

Web-Conference
Silver Spring, Maryland 20993

February 26, 2021

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

ATTENDEES

COMMITTEE MEMBERS	
Paula Annunziato, M.D.	Merck
Archana Chatterjee, M.D., Ph.D.	Rosalind Franklin University
CAPT Amanda Cohn, M.D.	National Center for Immunizations and Respiratory Diseases Centers for Disease Control and Prevention
Hayley Gans, M.D.	Stanford University Medical Center
Michael Kurilla, M.D., Ph.D.	National Institutes of Health
H. Cody Meissner, M.D.	Tufts University School of Medicine
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Steven A. Pergam, M.D., M.P.H., FIDSA	Seattle Cancer Care Alliance
TEMPORARY VOTING MEMBERS	
Arnold Monto, M.D. (Acting Chair)	University of Michigan
A. Oveta Fuller, Ph.D.	University of Michigan
James Hildreth, Sr., Ph.D., M.D.	Meharry Medical College
David Kim, M.D., M.A.	U.S. Department of Health and Human Services
Jeannette Lee, Ph.D.	University of Arkansas for Medical Sciences
Ofer Levy, M.D., Ph.D.	Massachusetts Institute of Technology
Wayne A. Marasco, M.D., Ph.D.	Harvard Medical School
Pamela McInnes, D.D.S., M.Sc.	National Institutes of Health
Patrick Moore, M.D., M.P.H.	University of Pittsburgh Cancer Institute
Stanley Perlman, M.D., Ph.D.	University of Iowa
Jay Portnoy, M.D.	Children's Mercy Hospital

Eric Rubin, M.D., Ph.D.	Brigham and Women's Hospital
Mark Sawyer, M.D., F.A.A.P.	Rady Children's Hospital San Diego
Melinda Wharton, M.D, M.P.H.	Centers for Disease Control and Prevention
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Tom Shimabukuro, M.D., M.P.H., M.B.A.	Centers for Disease Control and Prevention
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Kathleen Hayes, M.P.H.	Food and Drug Administration
Monique Hill, M.H.A.	Food and Drug Administration
Michael Kawczynski	Food and Drug Administration

TABLE OF CONTENTS

OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning and welcome to the 164th meeting of Vaccines and Related Biological Products Advisory Committee meeting. I'm Mike Kawczynski, project manager with FDA, and I'll be today's meeting facilitator. This is a live virtual public meeting that is being broadcast in its entirety though C-SPAN, YorkCast, Facebook Live, YouTube, Twitter, and various other methods.

Today's event is also being recorded and will be posted on the FDA's VRBPAC webpage along with all relevant meeting materials. Throughout today's meeting, I will be reminding our speakers and presenters committee members and sponsors as to when it's closer to their allotted time and assisting them when needed.

Just a reminder to everyone that once called upon, please manage your mute and activate your webcams. Note to all members and participants, we are aware of the adverse weather conditions some of you -- and are having to take precautions, and, if we

encounter any issues, we will take it on a scheduled break. At this time, I'd like to now introduce Dr. Arnold Monto, the acting chair, who will now provide opening remarks.

Dr. Monto, please, activate your webcam and take it away.

DR. ARNOLD MONTO: Good morning. I'd like to open this meeting, the 164th meeting of the Vaccines and Related Biological Products Advisory Committee and to specifically tell us -- state the reason for our meeting, and this is to provide and discuss Emergency Use Authorization of the Janssen Biotech COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

I would also like to welcome to the meeting our voting members, our standing members, the other speakers, those representing the sponsor Janssen as well as the public. Your participation is very important because you will see an open meeting discussing scientific findings in action.

And now I'd like to turn over to the designated federal officer for this meeting, Prabha Atreya. Prabha.

ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICT OF INTEREST STATEMENT

DR. PRABHAKARA ATRAYA: Thank you, Dr. Monto. Good morning, everyone. This is Prabha Atraya, and it is my great honor to serve as the designated federal officer for today's 164th Vaccines and Related Biological Products Advisory Committee meeting.

On behalf of the FDA, the Center for Biologics Evaluation and Research, and the Committee, I would like to welcome everyone to this virtual meeting. The topic of the meeting, as Dr. Monto mentioned, is the Emergency Use Authorization of Janssen Biotech's COVID-19 vaccine for the active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years and older. Today's meeting and the topic were announced in the federal register notice that was

published on February 11, 2021.

I would like to introduce and acknowledge the excellent contributions of the staff in my division and the great support team we have in preparing for this meeting.

Ms. Kathleen Hayes is my backup and co-DFO providing excellent support in all aspects of preparing for and conducting this meeting. The other staff are Ms. Monique Hill, Dr. Jeannette Devine, and Christina Vert, who provided excellent administrative support. Thank you, DSAC team, for your support.

I would like to express CBER's sincere appreciation to Mike Kawczynski for facilitating the meeting for today and also a big shout out to many FDA staff working hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one like the previous three VRBPAC meetings on the COVID topic.

Please direct any press or media questions for today's meeting to the FDA's Office of Media Affairs or FDAOMA -- one word -- @fda.hhs.gov. The

transcriptionist for today's meeting is Ms. Linda Giles.

We will begin today's meeting by taking a formal role call for the Committee members and temporary members. When it is your turn, please turn on your camera, unmute your phone, and then state your first and last name, and, 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, can we start with you, please?

DR. ARNOLD MONTO: Good morning, again, and welcome to all.

DR. PRABHAKARA ATRAYA: I think, Dr. Monto, your volume is a little bit low. If you can improve it, that would be great. Thank you. Dr. Amanda Cohn.

DR. AMANDA COHN: Good morning. Dr. Amanda Cohn, Chief Medical Officer at the National Center for Immunization and Respiratory Diseases.

DR. PRABHAKARA ATRAYA: Thank you. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Good morning. My name is Archana Chatterjee. I am the dean of Chicago Medical School and Vice President for Medical Affairs as Rosalind Franklin University of Medicine and Science. I'm a pediatric infectious diseases specialist with a background in research in vaccines. Thank you.

DR. PRABHAKARA ATRAYA: Great. Dr. Cody Meissner.

DR. CODY MEISSNER: Good morning. My name is Cody Meissner. I'm a professor of pediatrics at Tufts University School of Medicine and head of the Infectious Disease Service at Tufts Children's Hospital in Boston. Thank you.

DR. PRABHAKARA ATRAYA: Great. Next slide, please. Dr. Gans.

DR. HAYLEY GANS: Good morning. I'm Dr. Hayley Gans. I'm the professor of pediatrics and pediatric infectious disease at Stanford University and I currently do research on the immune response of different infectious disease pathogens in children and

special hosts including vaccines. Thank you.

DR. PRABHAKARA ATRAYA: Next to Dr. Kurilla.

DR. MICHAEL KURILLA: Mike Kurilla. I'm a pathologist by training, currently director of the Division of Clinical Innovation at the National Center for Advancing Translational Sciences within the National Institutes of Health.

DR. PRABHAKARA ATRAYA: Dr. Offit.

DR. PAUL OFFIT: Yeah. Good morning. I'm Paul Offit, a professor of pediatrics at the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine.

DR. PRABHAKARA ATRAYA: Okay. Dr. Annunziato. Paula. We can't hear you. You need to unmute your phone.

DR. PAULA ANNUNZIATO: Good morning. My name is Paula Annunziato. I'm Vice President and Therapeutic Area Head of Vaccine Clinical Development at Merck, and I'm the nonvoting industry representative this morning.

DR. PRABHAKARA ATRAYA: Thank you. Dr.

Pergam.

DR. STEVE PERGAM: Hi. I'm Steve Pergam. I'm an associate professor at the Fred Hutchinson Cancer Research Center and University of Washington.

DR. PRABHAKARA ATRAYA: Great. Next slide, please. Dr. Fuller.

DR. OVETA FULLER: Good morning. I'm Oveta Fuller. I'm an associate professor in microbiology at the University of Michigan and a member of the STEM Initiative in the African Studies Center, and I'm a virologist by training.

DR. PRABHAKARA ATRAYA: Dr. Kim. You are muted. Dr. Kim, you need to unmute your phone.

DR. DAVID KIM: I'll check. Is this working better?

DR. PRABHAKARA ATRAYA: Yes. Yes. Can you start again? Thank you.

DR. DAVID KIM: This is David Kim, Director of the Division of Vaccines and the Office of Infectious Disease and HIV/AIDS Policy in the HHS Office of Assistant Secretary for Health.

DR. PRABHAKARA ATRAYA: Thank you. Dr. Rubin. You have to unmute yourself, Dr. Rubin.

DR. ERIC RUBIN: Wrong button. Hi. I'm Eric Rubin. I'm at the Harvard TH Chan School of Public Health, the Brigham and Women's Hospital, and the *New England Journal of Medicine*.

DR. PRABHAKARA ATRAYA: Thank you. Dr. Hildreth. Dr. Hildreth?

DR. JAMES HILDRETH: Good morning. I'm here. I'm here. Good morning. I'm James Hildreth. I'm president of Meharry Medical College and professor of internal Medicine. I'm a viral immunologist, and I study the way that the body responds and clears viruses from our system. Thank you.

DR. PRABHAKARA ATRAYA: Thank you. Dr. Portnoy.

DR. JAY PORTNOY: Good morning. I'm Dr. Jay Portnoy. I'm a professor of pediatrics at the University of Missouri, Kansas City School of Medicine in the Division of Allergy, Immunology at Children's Mercy Hospital in Kansas City, Missouri. And today,

I'm serving as a consumer representative.

DR. PRABHAKARA ATRAYA: Okay. Thank you. Dr. Lee.

DR. JEANNETTE LEE: Good morning. My name is Jeannette Lee. I'm a professor of biostatistics at the University of Arkansas for Medical Sciences. Thank you.

DR. PRABHAKARA ATRAYA: Thank you. Dr. Mark Sawyer. You have to unmute yourself, Dr. Sawyer. Still can't hear you.

MR. MICHAEL KAWCZYNSKI: There we go. We unmuted you, Dr. Sawyer.

DR. PRABHAKARA ATRAYA: So now.

DR. MARK SAWYER: Try again. Sorry. Mark Sawyer, Professor of Pediatric Infectious Disease at the University of California San Diego and Rady Children's Hospital San Diego.

DR. PRABHAKARA ATRAYA: Thank you, Dr. Sawyer. Dr. Wharton.

DR. MELINDA WHARTON: Good morning. I'm Melinda Wharton. I'm Director of the Immunization

Services Division at the Centers for Disease Control and Prevention, and I'm an adult infectious disease physician by training.

DR. PRABHAKARA ATRAYA: Thank you. Dr. Ofer Levy.

DR. OFER LEVY: Good morning. My name is Ofer Levy, and I'm Director of the Precision Vaccines Program and an attending physician in the Division of Infectious Diseases at Boston Children's Hospital and a professor of pediatrics at Harvard Medical School.

DR. PRABHAKARA ATRAYA: Thank you. Next slide, please. Dr. McInnes.

DR. PAMELA MCINNES: Good morning. My name is Pamela McInnes, recently retired deputy director of the National Center for Advancing Translational Sciences, a component of the National Institutes of Health. Thank you.

DR. PRABHAKARA ATRAYA: Thank you, Pam. Dr. Moore.

DR. PATRICK MOORE: Good morning. I'm Patrick Moore. I'm at the University of Pittsburgh Cancer

Virology Program, and I study cancer viruses, two viruses that we've covered here.

DR. PRABHAKARA ATRAYA: Thank you. Dr. Perlman.

DR. STANLEY PERLMAN: Good morning. I'm Dr. Stanley Perlman, the University of Iowa at the Department of Microbiology and Immunology. I'm a long-term coronavirus researcher, and I'm also a pediatric infectious disease (audio cut out 00:13:19).

DR. PRABHAKARA ATRAYA: Thank you, Dr. Perlman. Dr. Marasco. Wayne?

MR. MICHAEL KAWCZYNSKI: I don't think Dr. Marasco has his audio connected at the moment.

DR. PRABHAKARA ATRAYA: Okay. So we will move on then in the interest of time. When he comes maybe later, we can introduce him.

So next, thank you all. Next, I would like to introduce the FDA staff. Dr. Marion Gruber, Director of the Office of the Vaccines who will say a few welcome remarks. Dr. Gruber, please turn on your camera and unmute your phone, please. We can't hear

you, Marion. You have to unmute yourself.

DR. MARION GRUBER: Yeah, I know. Okay. Sorry. Yeah, good morning to everybody. My name is Marion Gruber. I'm the director of the Office of Vaccines Research and Review at the Center for Biologics, FDA.

And, on behalf of my colleagues in the Office of Vaccines, I would like to welcome this morning the Committee, Janssen, as well as the public to this discussion. And again, once again, I really would like to express my appreciation for the Committee to take time out of their busy schedule to come together and lend their perspective advice and recommendation regarding the topic at hand today. I would like to really hear from them, you know, whether the totality of the evidence and the data that are presented today by Janssen and the FDA will support, also, authorization of their COVID vaccines under an EUA. So I look forward to today's discussions. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Gruber. I would also like to acknowledge the presence

of Dr. Celia Witten, Deputy Director of CBER, and Dr. Philip Krause, Deputy Director of Office of Vaccines at this meeting. They may chime in later as needed. Dr. Peter Marks, our Center director, will join us after I complete the reading of the Conflict of Interest statement to make his remarks.

Now, I will now proceed with the reading the Conflict of Interest statement for the record. Okay. The FDA Conflicts of Interest disclosure statement read for the public record by Dr. Prabhakara Atreya, Director of the Division of Scientific Advisors and Consultants and the designated federal officer for today's meeting.

The Food and Drug Administration, FDA, is convening virtually today, February 26, 2021, the 164th 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, the committee will meet in open session

to discuss the Emergency Use Authorization of the Janssen Biotech Incorporation's COVID-19 vaccine for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years and older. This topic is determined to be of particular matter involving specific parties.

With the exception of industry representative members, all standing and temporary voting members of the Committee are appointed special government employees or regular government employees 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 federal Ethics and Conflict of Interest laws including, but not limited to, 18 United States 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, regular government employees, and special government employee consultants of this Committee have been screened for potential financial conflicts of

interest of their own; as well as those imputed to them including those of their spouse or minor children; and, for the purposes of 18 U.S. Code 208, their employers.

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

FDA has determined that all members of this Advisory Committee, both regular members and temporary members, are in compliance with the Federal Ethics and Conflict of Interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts of interest when it is determined that the Agency's need for a special government employee's support service outweighs the potential for a conflict of interest created by the financial interest involved, or in the case of regular government employees from other agencies when the interest of regular government

employees is not so substantial as to be deemed likely to affect the integrity of services which the government may expect from the employee.

Based on today's agenda and all financial interests reported by the Committee members and consultants, there have been one Conflict of Interest waiver issued under the U.S. Code 208 in connection with this meeting.

As you have seen before, we have the following consultants serving as temporary voting members: Dr. Oveta Fuller, Dr. James Hildreth, Captain David Kim, Dr. Jeannette Lee, Dr. Ofer Levy, Dr. Wayne Marasco, Dr. Pamela McInnes, Dr. Patrick Moore, Dr. Stanley Perlman, Dr. Eric Rubin, Dr. Mark Sawyer, and Dr. Melinda Wharton.

Among all these consultants, Dr. James Hildreth, a special government employee, has been issued a waiver for his participation in today's meeting. The waiver was posted on the FDA website for public disclosure.

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. They also act on the behalf of all the regulated industry and bring general industry perspective to the Committee. Industry representative on this Committee is not screened, does not participate in any closed sessions we have, and does not have voting privileges.

Dr. Jay Portnoy is serving as the acting 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.

Disclosures of Conflict 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, its product, and, if known, its direct competitors.

We would like to remind the standing and temporary voting members 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 such involvement, and their exclusion will be noted for the record.

This concludes my reading of the Conflict of Interest statement for the public record. At this time, I would like to welcome our Center director Dr. Peter Marks to address the Committee. Dr. Marks, go ahead please.

DR. PETER MARKS: Good morning. I'm Peter Marks, Director for the Center for Biologics Evaluation and Research. On behalf of the FDA, I want to welcome everyone to this 164th meeting of the Vaccines and Related Biological Products Advisory Committee meeting. Thanks to the Committee members, the sponsor, the FDA

staff, and other presenters, and to all other interested parties for participating in this meeting today.

We look forward to a very productive day as we consider the third Emergency Use Authorization submission for a COVID-19 vaccine, this one from Janssen. We greatly appreciate everyone's participation, and we also appreciate your patience. We know that the AV can have issues, and, after our seventh or eighth or ninth Emergency Use Authorization for a vaccine, we'll probably get it perfect. But for today, thanks for bearing with us, and we really look forward to a very productive day. I'll turn this back over to Prabha and the Chair.

DR. PRABHAKARA ATREYA: Okay. Dr. Marks, thank you so much. Now I will hand over the meeting to our chair, Dr. Arnold Monto. Dr. Monto, the meeting is yours. Please take it away. Thank you.

DR. ARNOLD MONTO: Thank you very much. Thank you very much, Prabha. I'd like to invite first Maria Allende, Branch Chief, Clinical Review Branch of the

Office of Vaccines Research and Review of CBER to present a view of the FDA's Emergency Use Authorization. Dr. Allende, the floor is yours.

FDA PRESENTATION ON EMERGENCY USE AUTHORIZATION

MR. MICHAEL KAWCZYNSKI: Dr. Allende, let's make sure you unmute yourself.

DR. MARIA ALLENDE: Okay.

MR. MICHAEL KAWCZYNSKI: There you go. Perfect.

DR. MARIA ALLENDE: Okay. Good morning, everybody. My name is Dr. Maria Allende. I'm chief of the Clinical Review Branch 1 of the Division of Vaccines and Related Products Applications in the Office of Vaccines Research and Review at the Center for Biologics Evaluation and Research of the FDA. I will provide an overview of the regulatory basis for Emergency Use Authorization and considerations for COVID-19 vaccines.

As a way of introduction, this slide

summarizes the current status of the COVID-19 pandemic according to the latest data published online by the CDC.

More than 28 million cases have been reported, and deaths have surpassed five hundred thousand in the U.S. as of this week. Even though there is a decreasing trend in the last five weeks, there are more than four hundred thousand new cases and more than two thousand deaths reported during this past week ending on February 24th.

On December 11th, 2020, FDA issued an Emergency Use Authorization for the Pfizer-BioNTech COVID-19 vaccine for prevention of COVID-19 disease due to SARS-CoV-2 in individuals 16 years of age and older. A week later, on December 18th, 2020, an EUA was issued for the Moderna COVID-19 vaccine for prevention of COVID-19 disease in individuals 18 years of age and older.

MR. MICHAEL KAWCZYNSKI: Dr. Allende.

DR. MARIA ALLENDE: Yes.

MR. MICHAEL KAWCZYNSKI: Dr. Allende, hold on

one second. Just hold on one second, and this is to the public too. Since Janssen is oversees, we do have overseas callers dialing in all the time, so give us one second while we pause. Whoever is our 2302 number, please stop interrupting. Sorry about that. So, Dr. Allende, take it away.

DR. MARIA ALLENDE: Okay. Should I press anything?

MR. MICHAEL KAWCZYNSKI: No. You're good. Go ahead.

DR. MARIA ALLENDE: Okay. So I will restart. On December 11th, 2020, FDA issued an Emergency Use Authorization for the Pfizer-BioNTech COVID-19 vaccine for prevention of COVID-19 disease due to SARS-CoV-2 in individuals 16 years of age and older. A week later, on December 18th, 2020, an EUA was issued for the Moderna COVID-19 vaccine for prevention of COVID-19 disease in individuals 18 years of age and older. Both of these COVID-19 vaccines remain unapproved products and are not available in sufficient quantities to address current public health needs; thus, there is no

adequate, approved, and available alternative in the U.S. for prevention of COVID-19.

Janssen's EUA request was submitted on February 4th, 2021 for its adenovirus vector vaccine, known as Ad26.COV2.S, administered as a one-dose regimen. The proposed indication is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The information submitted in support for this request includes safety and efficacy data from more than 43 thousand randomized participants in their multinational, blinded, placebo-controlled Phase 3 trial COV3001, known also as ENSEMBLE.

Participants were enrolled from eight countries: the United States, Argentina, Brazil, Chile, Colombia, Mexico, Peru, and South Africa. And we will be hearing details about this trial, and the data from it is going to be discussed during the afternoon session.

FDA has been conducting a comprehensive review of the Janssen COVID-19 vaccine EUA submission received

on February 4th, 2021, and this in addition to several months of completed review work done on materials and information submitted previously in support and preparation for the EUA request.

Our review of the EUA includes verification of clinical data integrity and Janssen's analyses and additional FDA analyses from datasets provided in the submission; ongoing review of manufacturing, non-clinical and clinical assay information; review and revision of prescribing information and fact sheets to inform and instruct vaccine recipients and healthcare providers along with Janssen in this task. Multiple information requests have been sent to Janssen, and we have been exchanging daily communications to address questions and clarifications on the data submitted. Last but not least also, we have been preparing for today's VRBPAC meeting.

Today's VRBPAC meeting in which the Committee will advise the FDA with its own independent assessment of the data continues FDA's commitment to an expedited review process that is transparent, scientifically

sound, and data driven.

This slide is presented for your reference describing the legal basis for issuing an EUA and was presented in the two previous advisory committee meetings last December. As a reminder, the Health and Human Services Secretary issued a declaration on March 27th, 2020, justifying the EUA of drugs and biological products to address the COVID-19 pandemic. An EUA for diagnostic assays have been issued prior to that in January 2020.

The criteria for FDA issuance of an EUA for diagnostic prevention or treatment purposes require the existence of a serious or life-threatening disease or condition for which the product's known and potential benefits outweigh its known and potential risks. No adequate, approved alternatives to the product are available for diagnosing, preventing, or treating the disease or condition for which it's being issued. The Pfizer-BioNTech and Moderna COVID-19 vaccines are available under EUA for prevention of COVID-19 but remain unapproved. Products and quantity available for

mass vaccination is currently limited.

The FDA expectations for COVID-19 vaccine EUAs were discussed previously at the October 22nd and December 10th and 17th, 2020 Advisory Committee meetings and are described in FDA Guidance, "Emergency Use Authorization for Vaccines to Prevent COVID-19" published in October 2020 and recently updated on February 22nd, 2021.

There are three areas under which our expectations are covered: the first, data to demonstrate manufacturing quality and consistency; clear and compelling safety and efficacy data to support favorable benefit-risk of the vaccine when rapidly deployed for administration to millions of individuals, including healthy people; and plans for further evaluation of vaccine safety and effectiveness, including in ongoing clinical trials, active and passive safety monitoring during use under EUA, and observational studies.

The issuance of an EUA for a COVID-19 Vaccine will specify conditions of use for which benefit-risk

has been determined to be favorable based on review of available data; will provide information to vaccine recipients and healthcare providers by way of prescribing information and fact sheets that will necessarily include our review of the data. An EUA may be revised or revoked if other circumstances arise that warrant changes necessary to protect public health or safety, for example, based on new available information.

This is an overview of today's agenda. Sorry. Yes. Next, we will hear two presentations from our CDC colleagues, Drs. Adam MacNeil and Tom Shimabukuro, and Dr. Steven Anderson from FDA who will present the epidemiology of COVID-19 variants and post marketing surveillance from currently authorized COVID-19 vaccines.

After a ten-minute break, we'll listen to the sponsor's presentation, Janssen, and we'll break for 30 minutes for lunch after that. And after lunch, we'll have the open public hearing which will be followed by the FDA clinical review presentation by our colleagues,

medical officers from FDA Drs. Rachel Zhang and Yosefa Hefter, and voting questions. And the last but not least item in the agenda will be the Committee discussion and voting. After which, we'll adjourn the meeting.

So as a preview and to keep in mind during today's presentations and discussions, here is the question for the Committee. Based on the totality of scientific evidence available, do the benefits of the Janssen COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older?

Thank you for your attention. This concludes my presentation.

DR. ARNOLD MONTO: Thank you, Dr. Allende. Before I open the meeting up to the members for questions, let me ask you about the basis for emergency use relative to the guidelines that appeared this autumn. Are we still working on the basis of 50 percent or more vaccine effectiveness which was the guideline at that point and two months of follow-up for safety? Are those still our considerations?

DR. MARIA ALLENDE: Yes, Dr. Monto. Those are still -- remain our standards. At least a point estimate of 50 percent of risk reduction compared to placebo and a lower bound of least 30 percent are still the standards that we expect.

DR. ARNOLD MONTO: So the standards are exactly the same as in the previous reviews on the 10th of December and the 17th. Okay.

DR. MARIA ALLENDE: Yes, the standards have not changed. Mm-hmm.

DR. ARNOLD MONTO: Please raise your virtual hands those that have questions. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you. Thank you, Arnold. Maria, just curious, regarding what are the expectations after the issuance of an EUA in terms of follow up? Are there routine periodic updates or what? How are you monitoring the status of the EUA with regard to your relationship with the company, the sponsor?

DR. MARIA ALLENDE: Thank you, Mike, for your question. Yes, we expect continuous active and passive

safety reporting and surveillance and also observational studies and months-long follow up of the ongoing study. So it's a mixture of continuing follow up in the current study and reporting by ways of several networks that we have in collaboration with CDC and also observational studies. So the data -- we expect to receive additional data from several of these sources to further evaluate.

DR. ARNOLD MONTO: Dr. Meissner. Okay. Dr. Meissner.

DR. MARIA ALLENDE: I can't hear.

DR. ARNOLD MONTO: You're muted.

DR. CODY MEISSNER: Thank you. Thank you, Arnold. And thank you for that clear presentation. I would like to follow up on Dr. Monto's question. Because the strains of SARS-CoV-2 that are circulating now may be somewhat different than the strains that were circulating during the trials with the messenger RNA and so the efficacy at preventing relatively mild or even moderate disease may be different, but yet, all of the vaccines seem to be equally effective at

preventing very severe disease, intensive care needs, and deaths.

A difficult question I realize, but have you considered -- has the FDA considered that perhaps different endpoints should be considered in terms of granting an EUA in the future as new vaccines apply for an EUA?

DR. MARIA ALLENDE: Thank you for your question. You know, the endpoint is a clinical endpoint because, in the absence in immune correlative protection, the standard is the clinical endpoint. So far, that hasn't changed, and, with the continuing monitoring, we will be able to assess the efficacy of the vaccine, the duration of efficacy, and the efficacy against new circulating strains. And we are engaged in several conversations to implement strategies to monitor and address the issue of variance that are circulating, and I think that we will hear more in the next two presentations about that.

DR. CODY MEISSNER: Thank you.

DR. MARIA ALLENDE: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Chatterjee, please.

DR. ARCHANA CHATTERJEE: Definitely and thank you very much for your presentation as well. I have a question regarding the sponsors applying for a BLA. What is the expected timeline for the sponsors that are receiving authorization under an EUA to apply for a BLA for these vaccines?

DR. MARIA ALLENDE: Our recommendation and expectation is that the follow up should be as long as possible, given all of the circumstances that might affect the participants' time during the study in the follow up with the availability of other vaccines. However, we expect, if possible, a follow up of six months -- a total follow up of six months for safety and effectiveness with several strategies to address those issues of unblinding and placebo crossover to retain, as much as possible, the participants in the study.

DR. ARCHANA CHATTERJEE: Thank you.

DR. ARNOLD MONTO: Dr. Levy.

DR. OFER LEVY: Dr. Allende, thank you for that excellent presentation. A general question about FDA guidance for future EUA for coronavirus vaccines **(AUDIO CUTS OUT FROM 00:42:24 to 00:45:49).**

[BREAK]

EPIDEMIOLOGY OF COVID-19 VARIANTS

MR. MICHAEL KAWCZYNSKI: All right. Welcome back. All right. We just had a quick little -- a little opportunist break there just to get some audio issues. Welcome back to our 164th VRBPAC meeting. Dr. Monto, you want to pick up where we left off?

DR. ARNOLD MONTO: Well, I finally got on again, so yes. It's my pleasure to introduce Dr. Adam MacNeil, who is from the Division of Viral Diseases at the Center for Disease Control and Prevention who will be talking to us about a very important topic, epidemiology of COVID-19 variants.

DR. ADAM MACNEIL: Hi. Good morning.

DR. ARNOLD MONTO: Dr. MacNeil.

DR. ADAM MACNEIL: Hi. Good morning. I'm Adam MacNeil. So I'm with the Division of Viral Diseases at CDC, and I'm a representative on the epidemiology taskforce as part of the COVID-19 response at CDC. So I wanted to start first by giving a brief overview of our current global situation with SARS-CoV-2.

Currently, there's been over 110 million confirmed cases of SARS-CoV-2 with almost 2.5 million deaths. The bulk of the burden has been in the Americas and the European regions of the world. And we are seeing positive trends in the right direction in terms of declining cases, although I would note that there -- these spikes have occurred at various times in various regions. So I think we remain relatively concerned about the current epidemiologic situation.

So I'm going to talk about the various variants of concern. I want to briefly talk about what constitutes or what are the criteria for defining variants, including variants of interest and variants

of concern. Currently, various organizations are developing standardized definitions. This includes WHO. From the United States government standpoint, we have a definition that's currently being reviewed as part of interagency activities, and we hope to have that finalized soon.

But in general, regardless of the formal definition, there are some key criteria that generally meet consensus for helping define particularly a variant of concern. And this concludes at least one of the following: evidence of immune escape, either due to vaccine or natural infection; evidence of convergent evolution; impact with the variant on diagnostics; impact of the variant on therapeutics; evidence of increased transmissibility; or evidence of increased disease severity. For this presentation, I'm going to focus on the epidemiology of three specific variants, which currently have general consensus as being characterized as variants of concern. These variants are the B.1.1.7 variant, which was first identified in the United Kingdom and likely emerged in September of

2020; the B.1.351 variant, which was identified first in South Africa around October of 2020; and the P.1 variant, which was first associated with Brazil and Japan, and identified in January of 2021.

Notably, all three of these variants have two distinct amino acid changes, N501Y and D614G. Importantly, the emergence of these same amino acid changes in all three of these variants is suggestive of convergent evolution -- in other words, suggestive of a potential selective advantage. In a different -- in addition, the B.1.351 and the P.1 variants have a notable amino acid change of E484K. And this amino acid change has been very much associated in vitro with very strong evidence of reduced neutralization to previous infection, as well as vaccination.

In addition, I want to note one characteristic of the B.1.1.7 variant that's relevant to some of the current data we have. This contains a deletion at amino acid 69 and 70 of the spike gene, which impacts the S gene on multiple diagnostic PCR assays, which results in what has been referred to as an S gene

target failure or an SGTF. And due to this distinct pattern, it's allowed as an effective tool for screening or potentially enriching for identification of B.1.1.7 using PCR assays.

So since -- transitioning specifically to B.1.1.7, since being identified in November 2020, B.1.1.7 has rapidly been broadly identified across the globe. Notably, there's a high density and a high overall number of cases of infection of this variant in Western Europe, particularly in the United Kingdom. Although, I would caution when we look at this distribution that in many parts of the world natural coverage with sequencing is relatively limited, so we have to realize this probably does not represent the full distribution of B.1.1.7.

Relatedly, if you look on the table on the right, you can see that in many countries in Western Europe B.1.1.7 has actually become the predominant virus in circulation. So as mentioned, B.1.1.7 was first detected in England of 2020 and likely actually emerged in the southeast part of the country in

September of 2020. The United Kingdom has used the S gene target failure PCR pattern as a way to actively monitor spread of the variant. And we observed in late 2020 a very rapid expansion of this variant throughout the United Kingdom. Based on various modeling studies, it has been estimated that the reproductive number of the B.1.1.7 variant is approximately 1.5 times higher, or in other words, this data suggests that B.1.1.5 -- B.1.1.7 is about 1.5 times higher in terms of transmissibility in comparison to the previous dominant variants.

I also want to briefly touch on the evidence suggesting potential increased severity of disease associated with B.1.1.7. This data is pulled from a previously -- or this evidence is pulled from previously unpublished data that was reviewed by the New and Emerging Viruses Threat Advisory Group in February of 2021, and it was based on a composite analysis of 22 different related analyses of studies. And the data used a combination of either B.1.1.7 confirmed variants based on sequencing or data using

the S gene target failure marker.

Based on review of all the evidence, it was concluded that there was evidence from these analyses of multiple different datasets that have infection with B.1.1.7 that was associated with an increased risk of hospitalization and death compared to infection with non-variant of concern viruses. Results, if you look at this preliminary report, varied. But some outcomes were statistically significant, with ratios of hospitalization and death up to 1.7 times higher for this variant as opposed to baseline viruses. However, it should be noted that one of the key conclusions of this report is the absolute risk of death per infection remains low, even with B.1.1.7.

Moving on, I want to talk a little bit about the global distribution of the B.1.351 variant. This variant was first identified in South Africa in October of 2020, and South Africa continues to have the highest case counts. Although, like I mentioned previously, I caveat this by the fact that many countries currently have limited sequencing coverage. You can see that, in

addition to South Africa, multiple countries in the southern part of the African continent have had cases identified. Similarly, there are a number of cases that have been identified in Western Europe, and small numbers of cases have been reported from the Americas, Asia, as well as Australia.

Looking at this variant, specifically using one case study, a recent MMWR report documented the potential epidemic spread of B.1.351 in Zambia. This figure demonstrates the trend in the overall number of confirmed COVID-19 cases in Zambia. Starting in December, as you can see, a large spike in overall case numbers was noted within the country.

Sequencing performed on the selection of diagnostic specimens from mid-December identified a high proportion of the B.1.351 variant with 22 of 23 specimens being this variant. Notably, these specimens were obtained from four different provinces, indicating likely broad or wide distribution of this variant throughout the country. Similarly, prior to December, no B.1.351 cases were identified among 245 specimens

that were previously sequenced within the country.

Moving on to looking at the global distribution of the P.1 variant, this virus was first identified among travelers from Brazil in January of 2021. And Brazil really remains the epicenter of transmission, which I'll discuss more on the next slide. Additionally, this variant has been identified in North and South America, Western Europe, and there are a small number of cases that have been documented elsewhere.

So I'd like to turn over to the Manaus region of Brazil, which presents interesting and, I would say, quite concerning situation. There was a wide, largely unmitigated outbreak of COVID-19 that occurred within the Manaus region of Brazil in mid-2020. And you can see on this Figure A, on the upper half of this, the large peak in excess mortality that occurred within this region of Brazil in 2020. A study used blood donor serology to estimate the actual seroprevalence of SARS-CoV-2 in Manaus and estimated seroprevalence in October 2020 to be around 76 percent. Notably, even

with waning immunity, one would expect that this high a seroprevalence would likely have put this region in the position to be able to establish herd immunity.

However, a second large peak in hospitalizations and excess mortality began being documented in January 2021, as you can see on the far part of Figure A. P.1 variant was detected in circulation in Manaus on January 12, 2021. And as shown in the previous slide, this really represents kind of the epicenter where now numerous instances of P.1 have been detected in this region. While waning immunity from the previous large outbreak may partly be contributing to this overall second spike, I think it's important to point out that largely this data is probably suggestive of a certain degree of antigenic escape associated with P.1. I would note that a number of further investigations are currently going on to better understand the situation within Manaus.

I'm going to turn over the SARS-CoV-2 situation in the United States now. As of earlier this week, we were hitting around 70,000 new cases being

reported on a daily basis. This is down from a peak of over 300,000 being reported on a daily basis, which occurred in December and January of last year and earlier this year. In total, almost 28 million cases of SARS-CoV-2 have been reported within the United States. So you can see from the curve on the right side of the slide, we are moving in the right direction with a -- certainly, a strong downward trend in the number of cases. However, I would caution we are certainly not out of the woods yet, and we need to continue our focus on mitigation measures and trying to stop the current outbreak.

So as I get into talking about some of the approaches we're taking towards genomic epidemiology within the United States, I want to talk about how we're thinking about this in terms of key objectives and approaches. This can broadly be grouped into three categories: first of all, using genomic epidemiology for situational awareness or surveillance. So this would be to understand the prevalence and spread of variants and potentially use this for broader public

health decisions. I would mention that for surveillance and situational awareness, this does require widespread sampling of representative specimens for sequencing. And the overall number of specimens is largely dependent on the burden of infection.

Second is using genomic epidemiology to allow for novel variant detection. This requires -- the main focus of this is to identify the presence of novel variants for further investigation. And as I'll talk about in a later slide, this is more focused on using a relatively fixed sample size within a defined population for detection of variants.

Finally, we are using genomic epidemiology for focused studies. This includes trying to better understand the transmission, clinical outcomes, and vaccine effectiveness associated with variants. And for these studies, it requires extensive sampling and sequencing within a targeted population.

So I do also want to touch on some of the inherent challenges of using genomic epidemiology to characterize SARS-CoV-2. First of all, in our current

situation, we have to acknowledge that only a small proportion of viruses are being sequenced. And as I'll touch on, we are really rapidly scaling this up, but the reality is, even if we can get to extremely high numbers with current incidents, we may only be sequencing 5 to 10 percent of specimens.

So the reality is that we can have a certain degree of evidence, but we may not ever know the full situation in terms of what is going on with the virus. Second, there is an inherent time lag between sample collection and sequencing results. And while we are trying to push this time lag down, it does remain a significant challenge. So thus far, sequencing is not a rapid diagnostic tool. It has limited current utility from a clinical standpoint for clinical monitoring, and it currently represents a challenge for informing immediate public health action.

Oftentimes, by the time we are able to actually confirm a variant, it may be late in terms of the opportunity for conducting contact tracing. I'd also like to note that we have not yet demonstrated

sequencing as an effective containment strategy. And this is just evidenced by the fact that we have seen broad global spread of these three SARS-CoV-2 variants that I've discussed. Finally, sequencing by itself has limitations in terms of predicting epidemiologic outcomes. So key to mention that sequencing needs to be linked with supporting and immunologic studies, as well as clinical and epidemiologic data. And acquiring clinical epidemiologic data does take substantial sample size numbers and often takes a decent amount of time to fully characterize.

So going on and looking at what sample sizes are needed to actually detect variants of concern. So the -- this approach was adapted from the Influenza Virologic Surveillance Right Size Roadmap, which has really been our long-term approach for estimating sample sizes for influenza surveillance. So this represents a disease agnostic sample size calculator. And I would note that various factors including the actual sampling strategy, variant prevalence, and turnaround time can affect actual numbers.

But to give a rough sense in terms of numbers needed, if we want to have a 95 percent chance of identifying a variant that occurs in 1 out of every 1,000 cases -- so in other words a 0.1 percent prevalence -- we need approximately 3,000 sequences per week. And if you look at the figure, I noted -- as prevalence increases -- so as we get up to 1 percent prevalence and 5 percent prevalence, this actual number needed to sequence becomes smaller. So as prevalence goes up, the number of sequences needed to detect a variant decreases.

So we are currently taking a number of different approaches to evaluate genomic epidemiology of SARS-CoV-2. First is really kind of our backbone surveillance program, which we call National SARS-CoV-2 Strain Surveillance, or NS3, which represents a random selection of specimens submitted by public health laboratories for sequencing at CDC. In addition, we're taking further efforts to scale up sequence numbers by partnering with commercial diagnostic laboratories, conducting focused epidemiologic studies, developing

contracts and partnerships with states and local health departments and universities, and finally by supporting the SPHERES consortium, which represents a consortium of over 160 partners that are working to standardize metadata and ensure that there is a large number of SARS-CoV-2 sequences available in the public space.

So going on and looking at sequences in the public repository, in this slide, I'm showing numbers of sequences from specimens in the U.S. currently available in public repositories. And you can see in the orange line the number of sequences from the United States as currently been submitted to GISAID, which is currently around 100,000. And we do hope that this will rapidly continue to increase as we are scaling up our sequencing efforts within the United States.

Further, I want to note that we have a number of preexisting protocols and study platforms that we are currently adapting to try to better understand epidemiologic and clinical characteristics of the viral variants. And this is -- being able to use these platforms is somewhat dependent on the prevalence of a

variant. So to be able to pull out clinical characteristics of a variant with very low prevalence is challenging. But as we continue to see increasing proportions of all cases that are represented due to variants, we anticipate having further statistical power to be able to tease out various epidemiologic characteristics. Furthermore, I would note that we are conducting surveillance and investigation of vaccine breakthroughs to understand the actual impact that viral variants have on occurrences of vaccine breakthrough.

So looking at actual current numbers of SARS-CoV-2 variant cases detected in the United States, currently, there are approximately 1,600 reported cases of B.1.1.7, 22 cases of B.1.351, and 5 cases P.1. And you can see from these maps the current distribution of these cases. I would note that due to sequence coverage involved looking at the distribution, that these variants are probably much more widespread throughout the country. And I think we have to assume in the absence of other information, that these

variants probably could exist throughout the entire United States.

So there are -- in order to better understand the potential impact of B.1.1.7, assuming increased transmissibility of this variant, we developed mathematical models to look at the dynamics of viral transmission. In this slide, two scenarios are shown. In the figure on the left, a baseline reproductive number of the dominant virus of 1.1 is plotted. And in the right, we used a scenario of a reproductive number with a baseline variant -- a baseline virus of 0.9. The incidents of disease is shown on the Y-axis. In both scenarios, B.1.1.7, as represented in light purple, eventually becomes the dominant virus in late to mid-March. While these are theoretical models, even with a lower reproductive number, which may be closer to the current epidemiologic situation, B.1.1.7 does eventually result in an overall uptick in case counts.

So in these figures, we have used the same modeling assumptions as the previous slide. However, vaccine introduction is additionally added to the

model. As with the previous scenario, B.1.1.7 becomes the dominant virus in mid to late March. However, through scale-up of vaccination, the actual trajectory of case count is substantially blunted.

I would similarly like to briefly pull in some empiric data from a combination of academic partners and a commercial diagnostic laboratory that looked at early introduction and spread of B.1.1.7 in specimens being submitted through their diagnostic network. Based on their evidence, they noted that B.1.1.7 likely arrived in the United States in November of 2020, and multiple introductions occurred. Geographically, B.1.1.7, based on current data, is widespread and confirmed in 44 states.

And this data from early February estimated prevalence around 1 to 2 percent. However, when the actual trajectory of the increase in prevalence was plotted through January and early February, it did appear that the virus was at an exponential growth phase if you look at the proportion of cases due to B.1.1.7. So this is also supportive of a notion that

B.1.1.7 is on a trajectory to potentially become the dominant variant within the United States.

I want to move on and look at the overall burden of infections within the United States so we can think about the impact that viral variants may have on this. So we have started conducting routine seroprevalence surveys using commercial diagnostic specimens starting in around June or July of this year, which we used to generate seroprevalence specimens every two weeks for all states within the United States. So in this slide, I'm showing our seroprevalence estimates from December of 2020. And you can see from this slide that many states are starting to approach close to 25 percent seroprevalence. I would note that seroprevalence may underestimate the overall burden of infection because of potential waning and immunity.

So we have similarly used probabilistic models to try to account for under-detection and under-reporting on infections and estimate the overall burden of infection. Through December of 2020, based on these

models, it's been estimated over 83 million infections have occurred within the United States, with 70 million estimated symptomatic illnesses and 4.1 million hospitalizations. So if you look at this number, 83 million infections, it would land on approximately 25 percent of the U.S. population previously being infected with SARS-CoV-2 by December of 2020.

So how do these estimates stand with regard to herd immunity? So shown in this slide is a figure generated by Omer et al. using empiric data to estimate herd immunity requirement of SARS-CoV-2. So based on estimates of the reproductive number, approximately 60 percent population immunity is necessary to establish herd immunity. So based on our current estimates, which I showed in the previous slides, through around December 2020 we're certainly nowhere close to having herd immunity. I would note since that time, obviously, vaccination has started, and hopefully, this is moving us closer to filling the herd immunity gap.

However, thinking about the potential impact of variants on viral transmission and population

immunity, currently, we know that the U.S. population -- the majority of the U.S. population is not immune to SARS-CoV-2. And variants may affect -- may cause this proportion of the population that is not immune to increase. Waning immunity has potential to continue to contribute of this pool of individuals who may be susceptible to infection or disease. Increased transmissibility of a viral variant would require higher proportions of the population to be immune to establish herd immunity. And decreased effectiveness of a vaccine to protect against infection by a variant virus would -- could result in prolonged or continuous transmission of SARS-CoV-2.

So as I wrap this up, I want to talk about some key public messages to stress. First of all, we know that current mitigation strategies work, and they work against varying viruses. So this includes masking, social distancing, handwashing, quarantine, and public health policies.

Variants demonstrate the need to push -- further push these mitigation measures. Current

epidemiologic data is moving in the right or downward direction. However, potential of increased transmissibility means that adherence to these mitigation measures needs to be higher in order to maintain this downward trend in cases.

Additionally, I will sort of stress the importance of vaccination and monitoring the impact of vaccination. Vaccination provides general protection for the population against SARS-CoV-2. The impact of viral variants on vaccine effectiveness is still being characterized. But even with decreased effectiveness, vaccinations still may provide partial protection against variants. And this underscores the need for robust epidemiologic and virologic surveillance systems to determine if vaccine updates are needed.

So in conclusion, three variants of concern have currently been identified. As SARS-CoV-2 continues to evolve, we have to figure, inherently, additional variants will likely emerge, and this underscores the importance of genomic surveillance. Data suggest that variants may have increased

transmissibility, increased severity, or the ability to evade immune responses from previous viral infections. Epidemiology indicates broad global spread of these variants, and containment of variants has thus far been unsuccessful.

And finally, this underscores the importance of currently well-characterized mitigation measures. This includes use of well-fitted masks, hand hygiene, social distancing, avoiding crowded or poorly ventilated indoor spaces, and, finally, focusing again on ensuring we scale up vaccinations to all those who are eligible to receive the vaccine. Thanks and I would be glad to answer any questions you have.

DR. ARNOLD MONTO: Thank you, Dr. MacNeil. Very important presentation for the rest of our discussion. Dr. Rubin.

DR. ERIC RUBIN: Thanks, Dr. MacNeil. That was very interesting. When it comes specifically to the vaccines and their efficacy, the concern, of course, is preexisting mutations that (audio skip) efficacy, and perhaps the appearance of new mutations

in the vaccinated populations because of the new selective pressures. And it seems to find those you'd have to be systematically sampling the escape mutants -- and that means rather intensively -- and have a representative sample of the population to compare that with so the -- and I wonder about that -- about both those pieces. Are we systematically sampling escape mutants? And the -- in the 3,000, say, sequences we're getting a week of -- that we're getting right now, are they in any way -- do we know they're representative (audio skip)?

DR. ADAM MACNEIL: Yes. Thank you, Dr. Rubin. I think, first, touching on this representative piece. So the underlying goal with the NS3 -- so these 3,000 specimens, is to be broadly representative. As we're standing this up, we -- the proportion of specimens we're receiving from state and jurisdictional labs is proportional to their representative population size.

And we are requesting that these states and jurisdictions try best -- as best as they can to submit random specimens. I would add, on the commercial

laboratory front, is we are scaling up the number of sequencing being generated by commercial labs. Early on a lot of this sequencing was focused on the S-drop pattern and trying to identify B.1.1.7. We have shifted this to have our contracts focus more on having large commercial laboratories doing random specimen sequencing.

So we actually hope to be able to get relatively large numbers to have a representative set of specimens. But, you know, this -- it does remain an ongoing challenge. And, you know, I think inherently we can never hope to be perfectly representative. But I think we are getting relatively close to what we need to be able to have a representative denominator and actually understand what the virus is doing in terms of background circulation.

Regarding systematically looking at viral breakthrough, I would note a couple things. Both CDC, but largely more in the interagency space, we are actively working to combination of acquire and culture variants of concern as they arise, as well as collect

and characterize immunological breakthrough using sera from previously vaccinated individuals. In addition, we have currently established protocol, and we are currently conducting more passive but, from a somewhat active standpoint, also trying to acquire and characterize instances of vaccine breakthrough. And hopefully, by the -- evaluating those, both looking at the serial sequences as well as hopefully being able to acquire serologic samples from some individuals who are in current vaccine breakthrough, we'll continue to better characterize these instances.

DR. ARNOLD MONTO: Okay. Thank you. Dr. Gans.

DR. HALEY GANS: Thank you so much. You started -- this has been a really helpful, informative, thoughtful, and very important discussion. So thank you for bringing this to the forefront. You started to allude to some of the efforts that you're doing to understand breakthrough.

And I was very glad to hear that you're actually trying to get some samples -- some blood

samples from the vaccine. This is a group of people, obviously, that is very well characterized. And so it's an opportunity. You talked about serologic. Can you just discuss a little bit more about the immunity studies that you're going to undergo in terms of how you're looking at this?

Because I think what we're starting to see is some discordance in the humoral and T Cell immunity in some of these people. And so to understand that a little bit better it would be nice to know how that pattern is being evaluated, particularly as it pertains to these variants.

DR. ADAM MACNEIL: Yeah. Thanks. Great question. And I am going to caveat this because I am not working on the laboratory end. But, you know, from a broad standpoint, certainly a number of in vitro studies have focused on the serologic component and looking at correlates of breakthrough from infection.

From a T Cell standpoint, you know, I know this is an area that's been discussed. Obviously, characterizing T Cell responses and even acquiring

specimens from a relevant number of individuals is more challenging from a serologic standpoint. But I know that that is an area that there's also interest. I think we're looking at this from a broad perspective.

I would use -- probably the closest analogy is how we continually characterize influenza and the dynamics between that virus as it's circulating and the vaccine. And I would note this is a combination of CDC as well as a number of other organizations in the interagency space including NIH, FDA, DOD.

DR. ARNOLD MONTO: Dr. Meissner.

DR. CODY MEISSNER: Thank you. I'll add my compliments for a very clear, helpful presentation. I would like to ask you a little bit about serologic correlates of immunity and how that's going to be impacted by these variants. It would be nice if a serologic correlate of immunity could be established so that large efficacy trials, which are so expensive and so time-consuming, weren't necessary.

And particularly thinking about children, if we had a serologic correlate of immunity, that might

make it easier to evaluate vaccine usefulness in the pediatric age group. But it seems to me it's going to be hard to establish a serologic correlate of immunity if these variants continue to emerge because it'll -- the threshold of immunity will probably vary depending on the vaccine and depending on the variant that's circulating. So perhaps you could comment on that.

DR. ADAM MACNEIL: Sure. Thanks. Great question. You know, I think the issues with the variants underscores that exact concern. So, you know, I think we've seen -- and I realize those on the call know the clinical trial data better than I do, but, you know, we've seen particularly with B.1.351 that there's a lot of evidence that the vaccine does not provide as high levels of serologic protection. So as these viruses are evolving, it may be a moving target in terms of what the serologic correlate of protection is.

You know, going back to the E484K amino acid change, you know, I think that was the one -- it was -- it's been -- I would say there's been a logical scientific progression where around December/January

there was anagenic mapping, and this was the -- in essence, the amino acid that showed the highest potential for immune evasion. And then, I think we've seen, analogously, evidence of, as this mutation has been present in both B.1.351 and P.1, there's similar evidence.

So I think there is a certain alignment between the in vitro studies and what we're seeing in vivo. But it's -- it is probably going to be a moving target, I think. That's going to be one of maybe the fundamental questions as this outbreak progresses is how is this virus going to behave?

Are we going to need annual updates like influenza? Will we need annual updates every five years, or will we have broad enough protection to be able to use in essence a steady-state vaccine?

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Meissner, and thank you, Dr. MacNeil. I'm going to have to close the question period right now. This is a topic which we are going to be returning to in our open discussion

this afternoon. So please, if possible, stay around so we can follow up with additional questions at that point.

Now, I'd like to move to another issue: post-marketing surveillance from currently authorized COVID-19 vaccines. This is going to help us decide on what is working and what is not working. And we have a double-barreled presentation: first from CDC, Dr. Shimabukuro from CDC, who is Deputy Director of Immunization Safety Office; and then from FDA, Dr. Steven Anderson who is the Director of the Office of Biostatistics and Epidemiology. And we'll have the two presentations in sequence and the question period following. Please go ahead.

POSTMARKETING SURVEILLANCE FROM CURRENTLY AUTHORIZED COVID-19 VACCINES

DR. TOM SHIMABUKURO: Thank you. This is Tom Shimabukuro. Can you hear me okay?

DR. ARNOLD MONTO: We can.

DR. TOM SHIMABUKURO: All right. Good morning. Today I'm going to do an update on v-safe, one of our CDC's safety monitoring systems; then a Vaccine Adverse Event Reporting System update; a Vaccine Safety Datalink update; and then I'm going to spend some time focusing on COVID-19 vaccine safety in pregnancy.

Starting off with v-safe, so just to remind folks, v-safe is our smartphone-based text and web survey monitoring system that CDC stood up just for COVID-19 vaccine -- the COVID-19 vaccination program. It involves health check-ins that occur daily the first week after vaccination and then weekly and then -- through six weeks, then three, six, and 12 months. And the process starts again when a person gets a second dose.

It's a voluntary, self-enrollment program. If on any health check-in a registrant reports that they received medical care, we will follow-up through our call center with VAERS and take a VAERS report. The questionnaires also allow for identification of

pregnant women. And we also have a pregnancy registry team that conducts follow-up for enrollment into the pregnancy registry.

So as of February 16th is -- that's the analytic period that -- for this presentation -- there are roughly 55 million individuals who had received one or more doses of COVID vaccines in the United States. And we had about 3.9 million registrants in v-safe that had completed at least one health check-in. And that included just over 30,000 individuals that self-reported that they were pregnant on a v-safe health check-in.

So this table is from an MMWR that was recently published. And I apologize if this is a little bit small, but the analysis that I want to draw your attention to is really looking at dose one versus dose one for the two vaccines, the Pfizer-BioNTech vaccine and the Moderna vaccine. And specifically, we're looking reactogenicity, which is collected during week one following the vaccination of dose one day one and -- of Pfizer versus dose one day one of Moderna.

And you can see that the reactogenicity profiles are very similar. Injection site pain is commonly reported. And then systemic reactions are also commonly reported as well, confirming what was observed in the clinical trials. These mRNA vaccines are reactogenic, and this -- the reactogenicity profiles of the two vaccines for dose one day one look very similar.

Then at the time of this analysis for the Pfizer-BioNTech vaccine, we had some dose two data. We didn't for Moderna because of the timing of the rollout and the longer period between doses. But for the Pfizer vaccine, we had information on dose one day one compared to dose two day one. And if you look at the comparisons for the systemic reactions like fatigue, headache, myalgia, chills, fever, joint pain, nausea, there's substantially more self-reported reactogenicity symptoms for dose two compared to dose one, up to three to four-fold higher in some cases. And that's not unexpected. That was observed in the clinical trials. So the v-safe reactogenicity really kind of confirms

the safety profile of these vaccines and confirms that it was similar to what was observed in the preauthorization clinical trials.

Moving on to VAERS, VAERS is our spontaneous reporting or passive surveillance system that's co-managed by CDC and FDA. VAERS is a national system. Basically, anyone who's eligible for a vaccine is in the covered population. It can rapidly detect safety signals and can detect rare adverse events.

The main limitation of VAERS is that it's not designed to assess causality. It accepts all reports from anyone regardless of a plausibility of the vaccine causing the event or the clinical seriousness of the event. It's a hypothesis-generating system to identify potential safety concerns or signals that can be studied in more robust data systems.

So at the time of the data cut off for this analysis, which was February 16th, we had just over 100,000 reports to VAERS, of which 94 percent were non-serious and 6 percent were serious. Serious uses the regulatory definition. So here's two tables showing

the most commonly reported adverse events to VAERS for the Pfizer-BioNTech vaccine on the left and the Moderna on the right. You can see that systemic reactions and local reactions are the most commonly reported adverse events. But importantly, there were no empirical, Bayesian data mining alerts detected for any adverse event COVID-19 vaccine pairs as of the last data mining run that the FDA performed on February 18th.

I just want to draw your attention to a fairly recent publication which updated some of the anaphylaxis reporting rates for the vaccines. This is a little small. I've highlighted a statistic on the bottom there showing that the most current reporting rates we have for the -- for anaphylaxis were 4.7 per million doses administered for the Pfizer-BioNTech vaccine and 2.5 per million doses administered for the Moderna vaccine. So I think the take home message here is that these are rare events. And anaphylaxis, although clinically serious, is treatable. And there is CDC guidance available on identifying, managing, and being prepared at vaccination locations to handle

anaphylaxis when it occurs.

Moving on the Vaccine Safety Datalink, it's a collaboration between CDC and nine participating integrated healthcare organizations. It has electronic health record and administrative data on a covered population of roughly 12 million persons per year. And it also has rapid access to charts to review to confirm cases if need be. As of -- through February 13th, there had been approximately 630,000 doses -- dose one doses of any COVID-19 vaccine administered in VSD and about 200,000 dose two doses.

We do something called Rapid Cycle Analysis in VSD. These are basically weekly analyses of the data as the data accumulates. And I'm showing this slide mainly as a reference slide. This shows all of the pre-specified outcomes for VSD Rapid Cycle Analysis. These are outcomes that we've identified in advance and we are monitoring.

The analysis I'm showing here is an unvaccinated concurrent comparator analysis that's basically comparing vaccinated individuals with

unvaccinated individuals for these adverse events. And they're matched on certain characteristics, vaccinated and unvaccinated individuals. The preliminary results of the unvaccinated concurrent comparator analysis after any dose of an mRNA vaccine showed no statistically significant increased risk detected for any of these pre-specified outcomes.

So what I'm showing here is a different kind of analysis. This is a sequential vaccinated concurrent comparator analysis. This is comparing vaccinated individuals and looking at events and risk interval versus events in control interval. And I'm only showing outcomes for which there is -- there are events in the risk window.

So if you don't see an outcome on here compared to the previous slide, that means there was just no event in the risk interval. In the preliminary results of the sequential vaccinated concurrent comparator analysis was that there were no statistical signals detected. So next steps for VSD RCA, we're going to do a dose-specific analysis; product-specific

analysis; analysis in two risk intervals, 1-21 and 1-42 days; and a historical comparator analysis that's expected to start in the latter half of March.

Moving on to pregnancy, the v-safe pregnancy -- v-safe participants who self-report pregnancy are actively contacted and enrolled. The outcomes of interest include fetal demise, pregnancy complications, maternal intensive care unit admission, adverse birth outcomes, neonatal death, and infant hospitalizations, and major birth defects. So we have currently enrolled just over 1,800 individuals in the v-safe pregnancy registry.

Moving on to VAERS data, as of the 16th there were 154 reports to VAERS. And there were -- the median maternal age in these reports was 33, median gestational age, 13. Just over half of these reports involve vaccination in the first trimester. And you can see the vaccines there below.

Of these 154 reports, most of these -- and in fact, 73 percent were non-pregnancy specific adverse events that you would expect like headache, fatigue,

chills, local reactions. Of the 42 pregnancy or neonatal specific conditions, most were spontaneous abortion or miscarriage. I just want to point out that the frequency of spontaneous abortion and miscarriage is actually quite common, 10 to 20 percent based on age. So there are other maternal vaccination safety activities, which I'm not going to cover in detail. But they include studies and surveillance activities in VSD and in the clinical immunization safety assessment project.

So to sum things up, as of February 16th, just over 55 million doses had been administered in the United States. The reactogenicity profiles of the mRNA vaccines in v-safe are consistent with what was observed in the clinical trials. Systemic and local reactions are most commonly reported to VAERS. Anaphylaxis does occur, though rarely, and there's no safety signals for any serious adverse events. And there are no safety concerns identified among VSD Rapid Cycle Analysis outcomes.

Most reports to VAERS among pregnant women

involve non-pregnancy-specific adverse events. Miscarriage is most frequently reported -- the most frequently reported pregnancy-specific adverse event, but the number was not concerning considering expected background rate. And safety monitoring in pregnant women is ongoing or planned in v-safe, VSD, and CISA. Thank you. That concludes my presentation.

DR. STEVEN ANDERSON: All right. I'm just going to just give an update on FDA monitoring of the COVID-19 vaccine safety and effectiveness work that we're doing. So Tom has presented information from this slide. Just wanted to note the 55 million doses administered. We're using the same set of numbers for our presentation.

Since Tom has already -- this is a slide of our current vaccine surveillance programs. And since Tom has already covered the passive surveillance and VAERS systems, I'm not going to cover that. I'm really going to focus on the bottom portion of this slide, the active surveillance component, talking about our CMS work, our work on background rates, our work on study

protocols, and then talk about next steps.

So just launching into the FDA CMS work, we're going to talk about our Rapid Cycle Analysis, specifically talking about the approach, which is to monitor 20 or more outcomes, which Tom sort of mentioned in his presentation. FDA is identifying -- the elements of our RCA are we're identifying and using 15 possible adverse events of special interest. I wanted to then talk a bit about getting sufficient counts in the CMS database to start the analysis, the background rates, and then talk about where we are as far as conducting the RCA analysis and CMS data.

So these are the adverse events of interest that FDA is focusing on. I just wanted to mention that these have been studied in other vaccines, but they haven't been associated with the COVID-19 vaccine in pre-authorization studies, so some of the things you've seen in previous studies like Guillain-Barré Syndrome with Bell's Palsy, et cetera. I just wanted to talk about the rarity of these events, 1 in 10,000, 1 in 100,000, or less. And so they're rare and so need large

databases in many cases in order to get significant power in order to analyze these with millions -- usually with millions of patients.

The CMS data, just to remind people, I think I've shown this slide at the previous presentations to this committee. The data covers nearly all of the 55 million elderly U.S. beneficiaries over 65 years of age in the United States. All right. So here's the counts that we're getting.

So in the CMS Medicare data, we've got 4.8 million total doses. And just to sort of orient you on the graphics, the far left, as far as the total number, the middle is the first dose. The right bar in the set is the second dose. And as you can see, for Pfizer, there's 2.8 million doses and 2 million doses for the Moderna vaccine. And the time period given for this analysis is listed in the bottom left corner.

All right. So as far as the vaccine counts, what is the age distribution look like? So this is just a check. So you can see that most of the counts end up in the age 65 years of age and older. Medicare

does cover younger populations, persons with disabilities, and kidney disease, and so you'll see some of those represented in the lower age populations in this study.

All right. So background rate analyses, so background rates, why are we talking about them right now? So the background rates for AESIs provide us with information on expected rates or an estimate of baseline for comparison to see if there's an elevated risk of -- for an AESI. Then, we need to compare that to some sort of baseline historical number.

So for our analysis, I think it's important to mention that COVID-19 vaccines are new. So we lack kind of the -- that historical information that you might have for a vaccine like influenza where we have years and years of data where we can understand background rates for these AESIs. But what this work does, in the third bullet point, is it really requires us to go ahead and generate new background rates for the selection of comparator groups.

Just going down to the bottom bullet point, so

we've actually generated information on background rates for four different populations. And I'm sorry this type is small, but what we've done is we've looked at -- in the CMS data of the population overall, the age 65 years of age in that group. And then, we've also looked at influenza vaccinees age 65 years of age and older and gotten the rates for those specific AESIs in that population.

The time periods may be important too, so we've looked at that. So we looked at the pre-COVID period, and that means for the years 2017, 2018, and 2019, and that should give us information prior to COVID. And then, we're also looking at the peri-COVID, or sort of the COVID period, which we think is another important consideration.

And why are we doing that? Well, so in the first bullet point here, the COVID-19 pandemic may have impacted healthcare utilization. And that's been published in the literature that for, like, infections, like -- I'm sorry, for conditions like heart attacks or AMI, reports dropped initially by 50 percent in the

first few months of the pandemic and then initially rose back to sort of more pre-pandemic levels. So that's of interest to us if we're trying to evaluate, what's the relevant background rate to use for the analysis?

So we've assessed background rates in these populations, and what I wanted to show you was some of the results. And these are just sort of representative. So the top three lines on this left graph represents 2017, 2018, and 2019. And then this is for colonoscopies, and as you can see -- and you might have expected this -- but during the first few months of the pandemic, colonoscopies dropped by almost 70 or -- 75 or 80 percent. But then by about September of the fall, they started to climb back up to rates that were equivalent to prior to the pandemic.

Now, if we look at something like stroke in the graph on the right, you can see again those three lines in blue, orange, and gray sort of show you that -- the rates for 2017 through 2019. And by comparison, the line in yellow, you can see there's a dip, again

similar to what colonoscopies but not so -- not such a strong relations- -- not such a strong drop for hemorrhagic strokes. And then what you can see is that it's really popped back up by -- again by late summer to sort of the pre-COVID rates.

So what does that mean for us? So for a majority of the AESIs in our analysis, we collected the pre-COVID-19 background rates among persons 65 years of age and older in our CMS data. For a few of these AESIs, like less than five of those AESIs where the rates didn't recover, then we used the pre-COVID-19 levels for our background rates. And then just to note, the background rates are also being standardized against -- for age and other demographic characteristics.

So I just wanted to talk about where we are as far as our RCA analysis. The FDA's done this foundational work on the counts monitoring and then the background rates. And that work is complete. So we just sort of started to -- on the preliminary runs.

Those are -- have been underway for the last

few days, and we're evaluating our early results. So our expectation is we'll have results probably end of the week, early next week, into the weekend. And then, our expectation is to be able to sort of fine tune our analyses and then conduct runs every one to two weeks to kind of achieve our goal of near-real-time monitoring of safety for these 15 outcomes.

I just wanted to mention that we have the surveillance study protocols that sort of support the work that we've done. The first bullet points we've done looking at the background rates as I've mentioned. The second protocol that we've done is the active monitoring, which is really just describing the rapid cycle analysis protocol used. Each of those protocols were posted on the bestinitiative.org website, and so we received comments for about 10 days on each of those.

And then, I think we posted the latest version or the latest update on February 10th and 11th. So you can go to that website and see those. We're also developing additional protocols for inferential

studies. So if we do signal in these RCAs, we need to follow up with epidemiological studies.

And the goal would be to -- these protocols have the -- those protocols listed that we would be using to follow up on any signals identified in the Rapid Cycle Analysis or any signals identified in VAERS, like the anaphylaxis and others. There's also a testing where we're evaluating the performance of testing codes as well. And that protocol's under development as well. And I just wanted to say sort of at the bottom of this point number two is we're developing a vaccine effectiveness study and obviously, many considerations there, for instance, effectiveness by vaccine, comparative effectiveness by dose, duration between doses, duration of protection, and a number of other factors for considering and developing those protocols.

And then, just to get to the next steps, so I wanted to say that we talked about persons 65 years of age and older. What we need to do then is focus on 18- to 64-year-old persons. So -- and we're going to be

conducting additional Rapid Cycle Analyses. And if you go down to the bullet points in the middle here, we're going be doing these analyses in Optum and then CVS/Healthagen. And that should cover approximately, I think, 20 -- 25 to 30 million persons overall is our hope -- and then to add other claims databases as soon as we can bring those online. And our plan is we would start analyses in late March, so the two databases listed, followed by and subsequent links with other databases.

And again, I think Tom mentioned what they're doing by brand. They're analyzing their AESIs by brand, by risk intervals, doses, et cetera. I just wanted to mention quality assurance. So I think the power of the government approach is that we're able to compare our results that we get with the FDA systems with those of the CDC's VSD, but also the Veteran's Administration is running similar analyses. So we can do this cross-comparison, see what we're getting. If one gets a signal in their system that others don't get, we can do validation of those outcomes and verify

signals that are identified.

And then, I just wanted to acknowledge that this work is a huge amount of work by a number of colleagues and a lot of individuals in CBER, as well as our CDC colleagues, our CMS colleagues, VA colleagues, and many other FDA partners. And with that, I will stop. So thank you very much.

DR. ARNOLD MONTO: Thank you both. We have time for a few questions. Dr. Marasco.

DR. MICHAEL KAWCZYNSKI: Dr. Marasco, please make sure you're unmuted. All right. Let's go to the next --

DR. ARNOLD MONTO: Well, let's --

DR. MICHAEL KAWCZYNSKI: -- one, yeah.

DR. ARNOLD MONTO: Dr. Pergam.

DR. STEVEN PERGAM: Thanks for those presentations from both of you. Dr. Anderson, I wanted to ask you specifically about how you're tracking and how the FDA -- and maybe this is for you Tom as well -- how you guys are monitoring people who are getting a second dose that is not the same as the primary dose of

the vaccines they've received? And I think that's particularly important when we get into the Janssen vaccine that might potentially be a different mechanism. So do you guys have a plan or a system of how you're tracking that information and potential differential effects of that situation?

DR. STEVEN ANDERSON: Sure. I'll ask Rich Forshee also to get on this -- get online as well. So Rich, can you kind of explain for first dose, second dose?

DR. RICH FORSHEE: Absolutely. So thanks for that question. We have been working with the American Medical Association and CMS since the start of 2020 to make sure we had appropriate codes in place to deal with the kinds of situations that you were discussing. So each of the vaccines that receive an EUA is going to have a specific CPT code and not just for the vaccine but also for the administration and the administration by dose.

So currently for the Pfizer-BioNTech and the Moderna vaccine, there are specific CTP codes for first

dose of Pfizer, second dose of Pfizer, first dose of Moderna, second dose of Moderna. And the same thing's going to happen for other vaccines that are approved. So when the claims are submitted, we will know exactly which vaccine and which dose people have received. And so that will allow us to look at some of the safety and effectiveness questions that you outlined with regard to mixing different vaccines. I'll pause there and see if there are any other follow-up questions.

DR. ARNOLD MONTO: Dr. Gans.

DR. HALEY GANS: Hi. Thank you for this very important presentation and actually very satisfying in terms of how you're looking at these. My question for you is one way that we actually look at the vaccine in terms of the safety is actually not only to look at the baseline rate in a population of specific outcomes that you listed very nicely, but is actually to look at those outcomes also from the disease itself, so those with active infections. And I'm wondering if those analyses are going on. Because if you can show differences of known rates of some of these outcomes as

comparison to disease, that's an important marker of how we're steering disease and how safe these are in relation to disease entities.

DR. STEVEN ANDERSON: Tom, did you want to start?

DR. TOM SHIMABUKURO: I think --

DR. STEVEN ANDERSON: Or --

DR. TOM SHIMABUKURO: I was going to ask to repeat the question unless you want to -- go ahead, Steve if you want.

DR. STEVEN ANDERSON: Rich, did you want to take that one as well because --

DR. RICH FORSHEE: Oh. Yes. So I can start that discussion. Is -- we have published a first paper, and we have others in the line -- this characterizing the natural history of the COVID-19, essentially trying to look at the risk factors that put people at greater risk for serious outcomes. And so we're already (audio skip) related outcomes. And then, that will give us a position where we can look at vaccinated versus unvaccinated and some of these

serious COVID-19 outcomes. In fact, a big part of the reason we did the natural history study was to make sure the (audio skip). So, Dr. Gans, is that addressing your question, or is there another dimension to it?

DR. HALEY GANS: Yeah. No. Thank you. I'm encouraged to hear that those studies are in place and will go forward because I think that's a really important (audio skip).

DR. RICH FORSHEE: Oh, go ahead Tom.

DR. TOM SHIMABUKURO: I was just going to mention, and I know that CDC and FDA and the VA apply certain -- this is a little bit different than the question you asked but apply certain exclusion criteria based on history of natural disease so the natural disease doesn't confound our safety monitoring.

DR. RICH FORSHEE: And the only other thing that I was add --

DR. ARNOLD MONTO: I am going to -- okay. I think I'm going to have to break in. We're running over. And this is a very interesting discussion again

that's going to come up again later, especially concerning how we can rapidly figure out vaccine effectiveness against some of the variants prevalent.

So it's time for a break, and since we've been going so well over this period of time, let's try to reconvene 20 minutes past the hour. That's Eastern time at 11:20, which will be 10 minutes break. So break time right now.

MR. MICHAEL KAWCZYNSKI: All right, Dr. Monto. I will get us -- hold on one --

DR. ARNOLD MONTO: 15 minutes.

MR. MICHAEL KAWCZYNSKI: And you'd like how much time, Dr. Monto, for --

DR. ARNOLD MONTO: 10 minutes.

MR. MICHAEL KAWCZYNSKI: 10 minutes. Okay.

[BREAK]

SPONSOR PRESENTATION: EMERGENCY USE AUTHORIZATION APPLICATION FOR COVID-19 VACCINE

MR. MICHAEL KAWCZYNSKI: All right. Welcome back from break. We are now going to go into our sponsor section. So I'd like to bring in our Chair, Dr. Monto.

DR. ARNOLD MONTO: Welcome back from our extended break. Next is our very important sponsor presentation. We're going to hear from the team at Janssen. And I'd like to turn this over to Dr. Johan Van Hoof who will introduce the other members in turn of the Janssen team. Dr. Van Hoof.

DR. JOHAN VAN HOOF: Thank you. Thank you, Mr. Chairman. And good morning. My name is Johan Van Hoof. I'm the head of Janssen's vaccines research and development organization. I want to thank the Committee and FDA for the opportunity to present data from our development program as we seek Emergency Use Authorization for our COVID-19 vaccine candidate.

As we all know, while the FDA has authorized two vaccines for emergency use, there remains an urgent need for additional vaccine availability in order to vaccinate a majority of U.S. population, ensure

protection against disease, and subsequently reduce the burden on the healthcare system. If authorized, Janssen's vaccine candidate would play a critical role in the global effort to fight COVID-19.

Ad26.COV2.S was studied in a large Phase 3 study. We enrolled more than 44,000 participants and conducted a study in multiple countries during the height of the pandemic. It offers substantial protection, especially against severe COVID-19, including hospitalization and death irrespective of the variants. It is well-tolerated and safe. And it is a single-dose regimen with storage and transportation conditions that are compatible within existing distribution channels.

Specifically, Janssen's single-dose vaccine has demonstrated early-onset of protection against symptomatic COVID-19. Particularly important in the context of an outbreak, we observed 85 percent vaccine efficacy against severe COVID-19 globally, including the United States, at least 28 days after vaccination. For this secondary endpoint, the effect was consistent

across all geographic regions, including in South Africa where 95 percent of the strains were an emergent variant of the B.1.351 lineage. Importantly, at the time of analysis there were no COVID-19-related hospitalization in the vaccine group versus 16 in the placebo group. There were no COVID-19-related deaths in the vaccine group compared to five in the placebo group.

In the United States, we have shown 72 percent vaccine efficacy at least 28 days post-vaccination. We enrolled more than 19,000 participants in the U.S. and paid particular attention to include a diverse population. Our primary endpoint was achieved with 66 percent vaccine efficacy for moderate to severe/critical COVID-19 with the overall study population after day 28. And protection was observed as early as two weeks after vaccination. And we saw consistent efficacy across age, comorbidities, race, and ethnic subgroups. These results are particularly important when one considers when and where we studied our vaccine.

Our trial was conducted under challenging epidemiological circumstances. Our study sites were located in areas where COVID-19 incidence was highest and where variants were emerging, including in South Africa, Brazil, and United States. And still, the vaccine efficacy against severe/critical COVID-19 was high.

Based on the sequencing of approximately 72 percent of the COVID-19 cases in our study, it's evident that prevalence of the new variants was close to 70 percent in Brazil and greater than 90 percent in South Africa. Of note, we did not observe the P.1 lineage in our Brazil site. Also in line with what you will hear later, these efficacy rates are based on the total dataset including the non-centrally PCR confirmed cases.

During the last two months, we have all seen that it is critically important to manufacture and distribute vaccines quickly and efficiently. And Janssen's vaccine offers logistical and practical advantages to help simplify distribution and expand

vaccine access. Each person receives a single injection of 0.5 ml. The application of the single-dose regimen offers the ability to vaccinate a population faster. Each vial includes five doses, and no dilution is required.

The vaccine can be stored for three months at normal refrigeration temperatures and has a two-year shelf life when kept frozen. We have continuously improved our manufacturing and formulation processes in start of last spring to prepare for large-scale manufacturing. Based on this, we expect to supply 100 million doses to the U.S. government in the first half of 2021. And it can easily be shipped using existing supply chain infrastructure.

In addition to these key features, it is important to note that in the context of a vaccine that would be administered to millions of people it's reassuring to note that Janssen has substantial clinical experience with more than 193,000 people who have been exposed to our Ad26-based vaccine. These studies and programs are conducted across continents,

including participants of various ages, races, and ethnicities. This also included vaccination of pregnant and breastfeeding women in our Ebola program. Our Ebola vaccine was licensed in Europe in July 2020 and is currently part of a mass vaccination program in Rwanda.

Regular reviews of the safety database have shown overall good tolerability and safety. Local and systemic reactogenicity are in line with what is seen with licensed vaccines. And the database searches focused on adverse events of special interest did not reveal any safety signals.

Let me provide an overview of the key studies in our comprehensive development program which led to the current Emergency Use Application. We conducted numerous animal studies, including non-human primates, to study vaccine immunogenicity and efficacy. Our Phase 1/2a study led to the dose selection for our Phase 3 studies. The 2001 is a Phase 2 trial investigating a range of dosing regimens. Our ongoing (inaudible) Phase 3 trial, COV3001, is examining the

efficacy, safety, and immunogenicity of the single-dose regimen. This is the data being submitted to support our application for emergency use.

Today's presentation shares with you the first group of this ongoing study. Since our initial analysis, some additional information on cases observed has become available which will help to address some of the questions those initial results could have triggered. We will also share this with you today.

We also have a series of planned studies which are not part of the data package for EUA. Let's review those. We are evaluating the efficacy of the two-dose regimen in Study 3009. We will conduct several immunogenicity and safety studies in children from birth up to 17 years of age. The study in adolescents will open for enrollment soon. The start of the study in pregnant women is planned for end March/early April. And we also plan to begin studies in immunocompromised individuals in the third quarter of this year. In addition, Janssen plans several post-authorization observational studies to assess vaccine safety and

effectiveness in the real world. This also includes development of the pregnancy exposure registry.

With this in background, let me present the outline for the rest of our presentation. Professor Hanneke Schuitemaker will describe the vaccine design and immunogenicity data. Dr. Macaya Douoguih will review our efficacy and safety data. And Dr. Greg Poland of the Mayo Clinic will provide a benefit-risk assessment on granting Emergency Use Authorization for Janssen's Ad26 COVID-19 vaccine candidate. All external experts have been compensated for their time preparing for today's study. Let me now turn over the presentation to Professor Schuitemaker.

DR. HANNEKE SCHUITEMAKER: Thank you, Dr. Van Hoof. My name is Hanneke Schuitemaker, and I am the Global Head of Viral Vaccine Discovery and Translational Medicine and the Viral Vaccine Disease Area Stronghold Leader at Janssen. I am also a Professor in Virology at the Amsterdam University Medical Center. In this presentation, I will explain our established AdVac technology platform of which Ad26

is at the core of the Janssen COVID-19 vaccine and provide an overview of how we designed our COVID-19 vaccine candidate and its immunogenicity in nonclinical and clinical studies.

By design, the Ad26 vector is replication incompetent. The E1 region, shown in blue, and the E3 region, shown in yellow, are important in the development of our vector vaccine. By deleting E1 from the adenovirus DNA genome, the virus irreversibly loses the ability to replicate in human cells. We have also deleted most of the E3 gene. This creates more room in the genome for a transgene, shown here in purple, that codes for the protein that triggers the desired immune response.

For the production of the replication incompetent viral vector, we use the well characterized PER.C6 cell line that complements for the missing E1 gene. The vector can only replicate in an E1 complementing cell line and, again, cannot replicate in the human body. Of note, the PER.C6 cell line grows in a medium free of animal components. And, ultimately, a

vial of our Ad26 vaccine additionally only contains a buffer with commonly used ingredients in vaccines. There are no added adjuvants, antibiotics, or preservatives.

We chose to target the immune response against the spike protein of SARS-CoV-2. This was based on knowledge gained from previous SARS-1 experience and literature that show that antibodies directed against the spike can neutralize the virus and that T cells against epitopes in the spike protein play a role in the protection against disease. Therefore, we evaluated multiple transgenes encoding different spike designs allowing us to select the vaccine candidate with optimal stabilization, expression, immunogenicity, and nonclinical efficacy. The selected the spike protein is membrane bound and contains two proline mutations and a knocked out furin cleavage site for optimal stability in its prefusion confirmation. And so our lead candidate was selected based on these factors and also on its optimal manufacturability.

Now, let's take a look at how Ad26.COV2.S may

work in the body. First, a single dose is injected into the muscle in order to deliver the transgene to a diversity of cells. The transgene-encoded spike protein is then expressed on the surface of the cell. Innate immune responses triggered by the Ad26 vector provide the optimal microenvironment for the immune response against the spike protein. Ejected antigen-presenting cells pick up the spike protein and migrate to the lymph node, eliciting both humoral and cellular immune responses.

The CD4+ T helper cell responses are predominantly of the Th1 phenotype and stimulate B cells. Spike-specific antibodies are then produced by plasma cells. These antibodies have SARS-CoV-2 neutralizing activities and/or Fc-mediated antiviral effector function and play a key role in vaccine-elicited protective immunity.

In addition, spike specific CD8+ T cell responses are triggered. CD8+ T cells mature into cytotoxic effector cells with the ability to kill virus-infected cells. This is an important effector

mechanism of vaccine-elicited antiviral immunity. Finally, FDA guidelines classify adenoviral vectors as non-integrating, meaning they do not have the propensity to multiply the host genome.

Let's turn to the nonclinical data. A single dose of Ad26.COV2.S gave full protection against SARS-CoV-2 challenge in non-human primates. We observed near-complete protection against viral replication in the nose and full protection in the lung. This protective efficacy was durable for at least six months. And high-level protection against lung viremia was seen even after vaccination with a four-fold lower dose in the phase of lower antibody titers. In addition, a single dose also gave near-complete protection against viral replication in the lungs of aged non-human primates.

To complement our NHP studies, we tested our vaccine in Syrian golden hamsters where it also demonstrated protective efficacy. And histopathology in animals with low-level breakthrough infection demonstrated no evidence of vaccine-associated enhanced

disease. You can find more information on this in your briefing material. Overall, these results satisfied the FDA guidance criteria to allow for progression to human clinical trials.

Turning now to our Phase 1/2a study, Study 1001 is a randomized, double-blind, placebo-controlled trial and was the first in-human dosing of Ad26.COV2.S. The study initially enrolled two groups of healthy adults ages 18 to 55 and healthy adults 65 years and over. We evaluated two dose levels, $5x10^{10}$ and $1x10^{11}$ virus particle, which were administered intramuscularly in either a one-dose or a two-dose regimen.

As both dose levels demonstrated similar immunogenicity, I will focus on the single vaccination with the lower vaccine dose as this regimen was selected for our first Phase 3 study. The interim analysis was conducted at day 29, which was 28 days after demonstration of the first dose, and evaluated safety and immunogenicity. The study demonstrated similar and durable humoral immunogenicity in adults 18 to 55 years of age and those 65 years and older with a

single dose of Ad26.COV2.S. A neutralizing antibody response was observed in 96 percent of participants by day 29 in both age groups. This response was maintained up to at least day 85, suggesting good durability of humoral immunity.

There are additional features of Ad26.COV2.S-elicited humoral immunity. In line with our platform data, Ad26.COV2.S elicited antibodies also demonstrated non-neutralizing Fc tail mediated functionalities. These could have important antiviral effector function, including against emerging SARS-CoV-2 variants. Indeed, in contrast to neutralizing antibodies, these antibodies are not limited to epitopes in the receptor binding site or N-terminal domain where most of the amino acid substitution induced SARS-CoV-2 lineages seemed to occur.

A common concern is that natural immunity against Ad26 may interfere with the immunogenicity of Ad26-based vaccines. The Phase 3 study demonstrated that Ad26.COV2.S immunogenicity was similar across the highest and low-end countries. This included Brazil

with 33 percent of participants having Ad26 neutralizing antibodies at baseline; South Africa with 69 percent; and the U.S., where Ad26 seroprevalence at baseline was below 2 percent. The results are in line with our experience across our Ad26-based vaccine.

Turning now to cellular immunogenicity, a single dose of Ad26.COV2.S elicited CD4+ and CD8+ T cell responses which could be detected by day 15. Spike-specific CD4+ responses were detected in 71 percent of younger adults and in 69 percent of the older adults and were predominantly of the T helper 1 phenotype. CD8+ T cell responses were detectable in 46 percent of the younger adults and 27 percent of the older adults on day 15, further increasing to 61 percent and 51 percent by day 29. Both CD4+ and CD8+ T cells had a memory phenotype -- with a memory phenotype (audio skip) which is obviously important for anamnestic responses and durability of protective immunity.

In summary, following a single dose of Ad26.COV2.S, neutralizing antibody titers were elicited

in the vast majority of adults independent of age. Titers were detected as early as 14 days post vaccination, which increased in the following weeks and persisted at least up to day 85. This was irrespective of the vaccine dose used. Both CD4+ and CD8+ T cells responses were observed. The Th1 dominance of the CD4+ T cell in combination with the neutralizing antibody response minimizes the risk for vaccine associated enhanced disease.

In addition, both vaccine dose levels had a favorable safety profile with no safety concerns. However, the lower dose had a more favorable reactogenicity profile. Based on these results, the lower vaccine dose of $5x10^{10}$ virus particles of Ad26.COV2.S was selected for the Phase 3 study COV3001.

Thank you. Dr. Douoguih will now present the efficacy and safety data from our clinical trials.

DR. MACAYA DOUOGUIH: Thank you, Professor Schuitemaker. Good morning. My name is Macaya Douoguih. I am the Head of Clinical Development and Medical Affairs for Vaccines at Janssen. This morning

I'll be presenting results from our Phase 3 study, COV3001. Our primary analysis shows that the study met its primary endpoint, demonstrating the ability of a single dose of Ad26.COV2.S to protect against moderate to severe COVID-19 in adults, and that it has an acceptable safety and reactogenicity profile.

From here on I will refer to our vaccine as Ad26. I'll start with the study design. 3001 is a randomized, double-blind, placebo-controlled Phase 3 trial that's evaluating the efficacy, safety, and immunogenicity of a single dose of Ad26. We randomized participants one to one to receive a single injection of either vaccine or saline placebo. Randomization was stratified by site, age, and absence or presence of comorbidities.

The first part of the study consisted of a safety run-in phase. Stage 1a enrolled 2,000 adults up to age 59 without comorbidity. Following a plan safety review, enrollment progressed to Stage 1b to include participants up to 59 years with and without comorbidities. Stage 2a began in parallel to Stage 1a

and enrolled 2,000 participants 60 years and above without comorbidity. Note that Stage 2a took a little bit longer to recruit. After a plan safety review where the DSMB identified no safety concerns, we progressed to Stage 2b to include those 60 years and above both with and without comorbidity. Since those 60 years and older are at higher risk for severe COVID-19, we targeted at least 30 percent of the total population to be in this age range.

The co-primary endpoints are vaccine efficacy to prevent moderate to severe critical COVID-19 with onset at least 14 days post vaccination and also with onset at least 28 days after vaccination. The primary hypothesis is that the lower limit of the 95 percent confidence interval of the point estimate is greater than 30 percent. This had to be met for both co-primary endpoints in order to declare success.

The case definition for moderate COVID-19 was a positive RT-PCR or molecular confirmation of SARS-CoV-2 infection and, at any time during the observation period, at least one new or worsening sign or symptom

as listed in the panel on the left or at least two new or worsening signs or symptoms suggestive of COVID-19 on the right. For example, if a participant had a sore throat and a headache, this was sufficient to be considered moderate.

Here's the case definition for severe/critical COVID-19. For this, participants must have a positive RT-PCR or molecular test confirmation of SARS-CoV-2 infection and any one of these listed signs at any time during the observation period. We have a blinded, clinical severity adjudication committee to evaluate severe and all moderate COVID-19 cases with at least three signs or symptoms. Classification of a case as severe/critical by this committee is considered definitive.

Next, I'll move to the disposition and efficacy results. Beginning with disposition, a total of 44,325 participants were randomized, of which 43,783 received an injection of either Ad26 or placebo making up the full analysis set. This is the safety population. The per protocol population is the primary

efficacy population and includes all participants who were seronegative at the time of injection and had no other major protocol deviation judged to possibly affect the vaccine efficacy. Participants were also excluded when they had a positive PCR test at the day of injection. The per protocol at risk set includes all participants in the per protocol population but excludes those with a positive PCR test between injection through day 14 or day 28.

This slide shows the overall demographics of the study population at baseline. Looking between the two groups we see no relevant differences. Efforts were in place to reach (audio skip) groups with good representation in terms of age, race, ethnicity, and sex.

And I'll just flag for you here the numbers of participants who were 60 years and older across those groups. Enrolling significant numbers of participants in this age range was important for evaluating vaccine efficacy. And as I noted, we had a target of 30 percent for the whole study population. Of note,

nearly 20 percent of the full analysis set were frontline essential workers or healthcare professionals.

And here's the same table but looking at baseline demographics for participants from the U.S. Again, we see no relevant differences between groups. We see a similar proportion of participants 60 and older in the U.S. as we saw globally. And importantly, participants are representative of the U.S. population in terms of race and ethnicity, reflective of the diversity of the population.

Understanding that people who are most at risk for developing severe COVID-19 are those with pre-existing comorbidities, it was important to enroll participants with key risk factors. Approximately 41 percent of those enrolled had at least one comorbidity. This table shows the most common comorbidities across the global population with at least 2 percent in either group. As you can see, participants who are the most vulnerable for developing COVID-19 related symptoms are well represented in the study overall. And then

looking at the U.S. subgroup specifically, the percentages are similar to the overall trial population and are distributed between the vaccine and placebo groups. The full table is presented in the briefing document.

Let's now turn to the co-primary endpoint result. Study 3001 met both of its co-primary endpoints accruing 454 primary endpoint cases between September and January. The co-primary endpoint analysis includes all PCR positive cases that were confirmed at a central laboratory. The vaccine efficacy against moderate and severe/critical COVID-19 is approximately 67 percent after day 14 and 66 percent after day 28.

The lower limit of the 95 percent confidence interval was well above the FDA-requirement of 30 percent. Over 99 percent of accrued cases fell within the defined moderate to severe COVID-19. Therefore, the primary endpoint is representative of nearly all symptomatic COVID-19 cases. When looking at the co-primary endpoints in the U.S., we see the vaccine

efficacy against moderate to severe COVID-19 is 74 percent after day 14 and 72 percent after day 28. Note that the onset of protection was apparent as early as day 14 after vaccination.

Now, here we see the cumulative incidence curves for moderate to severe COVID-19 begin to separate between the Ad26 and placebo groups at around 14 days after vaccination. The circles represent the severe cases for each group. Due to the high COVID-19 incidence rate during the conduct of the study and the time it took for central lab confirmation of local PCR tests, not all cases could be confirmed by the central laboratory at the time of the primary analysis. As a result, there are two datasets.

The first dataset consists of PCR-positive COVID-19 cases confirmed at a central laboratory and is used in the co-primary and secondary efficacy analyses. However, we anticipated that subgroup analyses would require a larger dataset in order to be able to draw a conclusion. And we wanted to look at all confirmed COVID-19 cases that required hospitalizations or led to

death. So we prespecified that a second dataset could be used which included all COVID-19 cases with a positive PCR by any FDA-approved test regardless of central confirmation.

To justify the use of the second dataset, we looked at agreement of the PCR-positive results from the central lab versus all other sources. We found that these datasets had high concordance. We also wanted to test for consistency between the datasets with regards to vaccine efficacy and found that there was less than a one percent difference between them for the co-primary endpoint criteria. This is true for both time points. Therefore, the use of the larger dataset was justified.

All secondary endpoint results can be found in your briefing material. In the interest of time, I will just walk through our key secondary endpoints. Overall, vaccine efficacy against confirmed severe COVID-19 occurring after day 14 was high at approximately 77 percent and increased to about 85 percent after day 14 (sic). There were 14 versus 60

cases of severe COVID-19 occurring after day 14 in the Ad26 group versus placebo respectively and 5 versus 34 cases occurring after day 28 in the Ad26 group versus placebo.

When we look at the cumulative incidence of molecularly confirmed severe COVID-19 cases, we notice three important characteristics. Vaccine efficacy starts at day seven or earlier, indicating early onset of protection. Protection continued to increase over time, and this demonstrates the potential for longevity. Notice that after day 48 there were no more cases in the vaccine group versus 13 in the placebo group.

Analyses do show that vaccine efficacy against severe COVID-19 increases over time, as denoted here by the black line. Looking at day 56, we see an estimated increase to approximately 92 percent with no indication of waning thereafter. The gray area reflects the uncertainty around this estimate which increases beyond the median follow up of 58 days due to the small numbers of participants at those time points.

Data also demonstrate substantial effect on the prevention of COVID-19-related hospitalization with 93 percent vaccine efficacy for all positive PCR cases from any source after day 14 post vaccination. And the protective effect is even more pronounced after day 28 where we see 100 percent vaccine efficacy. Nineteen deaths occurred in the study, three in the Ad26 group and 16 in the placebo group. Five of the deaths in the placebo group were confirmed to be COVID-19 associated and were reported prior to the January 22 cutoff. None of the deaths in the vaccine group were COVID-19 related. A sixth COVID-19-related death occurred in a participant in the placebo group who had a positive SARS-CoV-2 RT-PCR test at baseline. As such, according to protocol this participant is not included in the COVID-19-related deaths.

We did look at deaths after the primary analysis and identified six more between the initial cutoff date and February 5th, two in the vaccine group and four in the placebo. One of the deaths in the placebo group was confirmed to be COVID-19 associated

compared to none in the vaccine group. All COVID-19-associated deaths occurred in South Africa.

We also evaluated the effect of Ad26 against asymptomatic, undetected SARS-CoV-2 infection to gain insight into the potential benefits of vaccination. Based on SARS-CoV-2 and IgG testing alone, 18 participants seroconverted in the Ad26 group compared to the 50 in the placebo group, resulting in a vaccine efficacy of 66 percent. The sensitivity analysis was performed to remove all participants with a high positive serology result at day 71 who had symptoms between day 1 and day 71. Ten seroconversions occurred in the Ad26 group and 37 in the placebo. These findings are preliminary, and while further follow up is needed to assess whether or not they are confirmed in the larger dataset, they do suggest a protective effective vaccine on asymptomatic SARS-CoV-2 infection.

We also performed additional analyses where we looked at vaccine efficacy by key demographics and by country. And here we see that vaccine efficacy against moderate to severe/critical COVID-19 is consistently

observed across all prespecified groups. This analysis includes breakdowns by age, 18 to 59 and 60 and older, by comorbidity, by sex, and by the largest racial and ethnic groups.

We do note that a lower vaccine efficacy point estimate with wide confidence intervals was observed for the subgroup of participants 60 years and older that had comorbidities compared with the overall population. At the same time, our assessment is aligned with that of the FDA, but there's an observed trend of increasing efficacy with narrower confidence intervals as numbers of cases in the analysis increase. And, therefore, we are also aligned with the FDA in that those 60 years and older with comorbidities are similar to any other subgroup and would benefit from vaccination with Ad26.

Across three key countries, vaccine efficacy against moderate to severe COVID-19 was consistently high. The majority of participants were enrolled in the U.S., Brazil, and South Africa. They were also the countries with the highest incidence of moderate to

severe COVID-19 cases in our study. The forest plot illustrates that Ad26 consistently protected against moderate to severe COVID-19. Vaccine efficacy after day 28 ranged from 64 percent to 72 percent across three countries.

The vaccine efficacy against severe COVID-19 was consistently high across these countries as well. Looking at South Africa, for example, protection after day 28 was about 82 percent. Of note, 95 percent of the sequence sample in South Africa were associated with the new, highly transmissible variant from the B.1.351 lineage.

Taking a closer look at South Africa, we found that there were no hospitalizations in the Ad26 group and six in the placebo group. There were no deaths in the Ad26 group and five deaths in the placebo group. These findings suggest that Ad26 is efficacious against this newly emerging and rapidly spreading strain.

To summarize efficacy, a single dose of Ad26 offers substantial protection against COVID-19, including against hospitalization and death. Across

all countries, Study 3001 generated high quality robust data at a time when the incidences of SARS-CoV-2 was increasing and new, highly transmissible variants were emerging. Janssen's vaccine demonstrated 85 percent vaccine efficacy against severe disease with an early onset of protection as early as seven days after vaccination.

Importantly, for the primary analysis there were no COVID-19-related hospitalizations in the vaccine group versus 16 in the placebo group. And there were no COVID-related deaths in the vaccine group compared to five in the placebo group. For protection against moderate to severe disease, there were 66 percent vaccine efficacy across all countries. And the onset of efficacy here was evident as early as day 14, increasing through day 56, especially against severe disease.

In the United States where study participants reflected the diversity of the overall U.S. population, vaccine efficacy against moderate to severe COVID-19 was 72 percent. Protection against all symptomatic

disease was consistent with the primary endpoints. And the high levels of protection were consistent across subgroups, countries, and regions in particular areas of high incidence of circulating variants.

Now, let's turn to safety. A single dose of Ad26 was demonstrated to have an acceptable safety and reactogenicity profile. As expected, results were consistent with the tolerability and safety of our other adenovirus-based vaccine. We also have plans in place for continued safety monitoring following Emergency Use Authorization. Now, re-orienting us to the study population, serious adverse events, medically attended adverse events, adverse events leading to discontinuation and death were collected on the 43,783 participants who make up the full analysis set.

In addition, all solicited and unsolicited adverse events were collected in a subset of individuals, referred to as the safety subset. We conducted our primary analysis after meeting the FDA guidelines for reaching a median follow up of at least two months. The median follow up after vaccination was

58 days. More than half the participants in the full analysis set had at least two months of follow up. In the safety subset, nearly all participants completed the post-vaccination period of day 1 to 29.

Now, I'll turn to the solicited adverse events collected during the seven-day post-vaccination period. Solicited local adverse events, stratified here by grade and age, were transient, and more than 99 percent were Grade 1 and Grade 2 in severity. And all resolved within two to three days after injection. The most frequently reported local adverse event was injection site pain. The frequency of Grade 3 adverse events was very low overall with a higher incidence in the Ad26 group compared to the placebo group.

For participants in the Ad26 group, the most frequently reported Grade 3 event was injection site pain at 0.4 percent. And there were no Grade 4 AEs reported. In the Ad26 group, the frequency of solicited local AEs was similar between those who were seropositive for SARS-CoV-2 at baseline pre-vaccination. And there was a frequency of solicited

systemic AEs was higher in the Ad26 group compared to placebo during the seven-day post-vaccination period. Most were transient and had a median duration of one to two days after vaccination with Ad26.

The most frequently reported symptoms in the Ad26 group were fatigue, headache, and myalgia. Approximately 98 percent of solicited systemic AEs were Grade 1 or Grade 2 in severity. Grade 3 events were infrequent and reported in about 2 percent of participants in the Ad26 group. There were no Grade 4 events reported. Fever was reported in 9 percent of participants in the Ad26 group, with 0.3 percent being Grade 3 among those 18 to 59 years of age and 0.1 in those 60 years and older. All fevers were reported to have started on the day of vaccination or the day after and had a median duration of one day. You'll note that the reactogenicity profile overall is milder in the older age group compared to the younger age group.

Now turning to unsolicited adverse events, as you can see, rates for unsolicited adverse events, serious and non-serious, in the safety subset 28 days

after immunization were balanced between arms. Rates were also balanced in the full analysis set for medically attended adverse events, any SAE, any SAE due to non-COVID-related AEs, or any death. SAEs, medically attended AEs, and deaths were numerically higher in the placebo group. The imbalance between Ad26 and the placebo group is mostly driven by the number of AEs associated with SARS-CoV-2 infection. None of the deaths in the Ad26 group or placebo group were considered causally related to the vaccine. In addition, there was no evidence of vaccine associated enhanced respiratory disease following vaccination with Ad26.

The clinical findings confirm the nonclinical observation of theoretical risk of vaccine associated enhanced respiratory disease with Ad26 is low. Data demonstrate clear Th1 dominant immune responses. Breakthru infections in those receiving vaccine were milder than those in the placebo group. The DSMB continuously monitored all cases of COVID-19 for patterns that are suggestive of vaccine associated

enhanced respiratory disease, and none were found. Janssen analyzed the occurrence of various adverse events of interest by regulatory agencies and medical and scientific organizations such as the Brighton Collaboration. These events include neural, inflammatory, and others, including those where there's a numerical imbalance with numbers in the -- numbers higher in the Ad26 group.

I'll provide more details of hypersensitivity reactions as well as arterial and venous thromboembolic events in my following slide. For the other events of convulsions, tinnitus, peripheral neuropathy, Guillain-Barre Syndrome, and Bell's Palsy, no causal relationship with the Janssen COVID-19 vaccine could be determined. The assessment of causality was confounded by the presence of underlying medical conditions frequently present in individuals with these adverse events of interest. And these events are included for further monitoring in our comprehensive pharmacovigilance plan.

Hypersensitivity adverse events were reported

in 0.4 percent or 77 vaccinated individuals and 0.3 percent or 65 individuals who received placebo. A given participant may have reported more than one sign or symptom. As shown in the table, non-serious dermatologic manifestation, particularly rash and urticaria, were the most common hypersensitivity AEs reported. Rash and urticaria, both localized and, more rarely, generalized, are considered likely related to vaccination. In the events reported as related by the investigator, the mean time to onset after vaccination was about six days. And the mean resolution time was 13 days. The vast majority of events were Grade 1 or Grade 2.

There were two serious adverse events in the Ad26 group and one in the placebo group. A single SAE of hypersensitivity was reported in one vaccine recipient with urticaria beginning two days following vaccination and angioedema of the lips with no respiratory distress which began four days following vaccination. The event was likely related to the vaccine. One SAE of angioedema occurred 23 days after

vaccination and was considered unrelated by the investigator. Both participants recovered without sequalae. The results are similar to what we observed with other Ad26 vaccines.

As of February 22nd, no cases of anaphylaxis meeting the Brighton Collaboration criteria had been reported in our vaccine clinical program. On Wednesday of this week, however, we received preliminary reports of two cases of severe allergic reaction, one of which was anaphylaxis from an ongoing open-label collaborative study in South Africa that has vaccinated approximately 40,000 healthcare workers to date. We will continue to closely monitor for these events as outlined in our pharmacovigilance plan.

The overall incidence of thrombotic and thromboembolic events, arterial and venous, were similar across Ad26 and placebo groups. A numerical imbalance was observed for the venous thromboembolic event. Most of these participants had relevant underlying medical conditions as well as predisposing factors that may have contributed to the occurrence of

these events, such as COVID-19 infection, prior history of DVT, new estrogen use, family history of DVT, prolonged air travel, or stopping anticoagulant. There's insufficient evidence to determine a causal relationship between these events and the Janssen COVID-19 vaccine. These events are included for further monitoring in the pharmacovigilance plan.

In summary, the known and potential benefits of Ad26 outweigh the known and potential risks. Overall, safety data from the 43,783 participants in our Phase 3 study demonstrate that a single dose of Ad26 has an acceptable safety and reactogenicity profile. Reactogenicity was demonstrated to be mild and transient in nature, and Grade 3 events were rare.

Most AEs were mild or moderate and generally resolved within one to two days post vaccination. Adverse events of interest were thoroughly evaluated, and we will continue to monitor for these events in our comprehensive pharmacovigilance program. The safety profile is further supported by data from more than 193,000 individuals who have received at least one dose

of Janssen's Ad26-based vaccines in our other clinical studies and programs.

If authorized, Janssen will amend the 3001 study protocol to facilitate crossover participants who received placebos to receive one dose of the vaccine as fast as operationally possible. All participants will be encouraged to stay in the study for up to two years for ongoing assessment of efficacy, safety, and immunogenicity. The amendment will allow us the opportunity to continue collecting long-term data and assess the duration of protection and immunogenicity of a single dose, comparing the results of two groups vaccinated approximately four to six months apart.

I'll now review our safety and effectiveness monitoring activities in the post authorization period. Janssen has developed safety and effectiveness plans to complement and utilize the U.S. government and other established programs to monitor and quickly identify any potential safety signals. This plan includes surveillance of adverse events following immunization, a prespecified list of AEs of special interest, and

other known concerns associated with vaccines in general.

We plan to identify and assess any new safety signals by monitoring our own global safety database along with reviewing external databases, including the FDA VAERS database. In addition, we will monitor long-term safety and effectiveness by conducting observational and active surveillance studies utilizing health insurance claims databases and electronic health records here in the U.S. and in Europe. For patients who opted in to have digitization of their records, they will be followed long-term for efficacy and safety.

Thank you. I will now invited Dr. Greg Poland of the Mayo Clinic to share his clinical perspective on the benefit-risk profile of Ad26.

DR. GREGORY POLAND: Thank you and good afternoon. I'm Dr. Greg Poland. I am a Professor of Medicine and Director of the Vaccine Research Group at the Mayo Clinic. By way of experience, I've been a practicing internist for nearly 40 years, a PI of

roughly 40 vaccine clinical trials, and exposed to hundreds more in my role as Editor in Chief of the journal *Vaccine*. Unfortunately, my experience also includes a front row seat to this fast-moving and deadly coronavirus, both as a researcher and a care provider. And so I'm very pleased to share my clinical perspective on the positive benefit-risk profile of Janssen's vaccine candidate and its role in protecting more Americans against COVID-19.

As of today, COVID-19 continues to spread at alarming rates, and a large proportion of the U.S. population still needs access to safe and effective vaccines. In fact, we have periodically reached exponential phases of spread where the virus is no longer increasing on a linear scale but is instead periodically spiking at a rapid rate. The consequence of this is that there are limited options to control the virus. In fact, there are only three ways the pandemic can be controlled.

First, a hard lockdown with mandatory masking and social distancing. And we know this has largely

been unpopular and less successful in the United States. Second, the virus mutates to be less transmissible. But, in fact, more transmissible variants are already emerging and circulating in the U.S. and the world. Or third, the development of highly efficacious vaccines that are widely used. We need vaccines that are effective and well tolerated and, importantly, ones that are simple to deploy. Vaccines are our primary weapon in countering and controlling this threat.

So let's turn now to Janssen's COVID-19 vaccine candidate and its one-dose regimen and what it could play in the urgent mass vaccination campaign needed now to fight this global pandemic. Here are some of the key factors. First, it's been studied in the largest COVID-19 vaccine trial to date in multiple countries giving us more data to analyze and confidence in the results. Second, it is a replication incompetent vaccine, meaning that it has been engineered to express the spike protein and cannot propagate in the cells of a vaccinated individual.

Third, it is a nonadjuvanted vaccine. So it does not use additional ingredients that would further increase local reactions such as redness or swelling or systemic reactions such as fever and chills. Fourth, it's compatible within existing vaccine distribution channels. It can be stored for three months at normal refrigerator temperatures and has a two-year shelf life when frozen.

And last, but certainly not least, the Janssen vaccine was specifically studied with a one-dose regimen. When the World Health Organization outlined its target product profile for a vaccine candidate, it identified a strong preference for a single-dose vaccine on outbreak. And certainly this one-dose regimen offers important logistical and practical advantages for mass vaccination campaigns. It can lead to the ability to reach both individual and herd immunity more quickly. Essentially, it simplifies the process. People only have to make one appointment for their complete vaccination.

A one-dose vaccination decreases the burden on

the healthcare system and healthcare providers. And as such, this single-dose regimen also decreases health utilization costs. In addition to these factors, the data demonstrates strong efficacy that offers protection against COVID-19. The pivotal study met both co-primary endpoints, finding that Ad26 is effective against symptomatic COVID-19.

Significantly, the vaccine is highly effective in preventing severe COVID-19. The prevention of hospitalizations and deaths was a particularly important finding when you consider the burden this disease has placed on hospitals and healthcare workers. The findings regarding efficacy against newly emerging variants, such as the highly transmissible strain first identified in South Africa, are also important.

Getting on top of these variants will be critical in our fight to control the virus. Notably, in the large Phase 3 trial if a participant who received the vaccine candidate did experience symptoms after infection, those breakthrough infections were milder, another welcome benefit both for individuals

and the healthcare system. Beyond the protective effects, we also see that a single dose was demonstrated to be safe and well tolerated. And the sponsor has a comprehensive plan in place for ongoing monitoring.

Janssen was very successful in enrolling a diverse study population, including older adults and those over the age of 60 who also had comorbidities. This is important, of course, because these are the individuals most at risk of progressing to severe COVID-19 which results higher rates of morbidity and mortality. The data reviewed today for this trial did not demonstrate safety concerns, including fever, in all of the assessed populations. And this includes older adults with comorbidities such as diabetes, hypertension, and obesity.

In this trial, there were no severe allergic reactions. But as you have heard, two days ago the sponsor was made aware of a case of suspected anaphylaxis in a recently initiated trial with a current enrollment of over 40,000 vaccinated healthcare

workers. Generally, hypersensitivity reactions following immunization were rare and nonserious.

I fully support the sponsor's plan to amend the pivotal study and allow participants who received placebo to cross over to access the vaccine. This will allow continued safety monitoring, diminishing any reason to withdraw from the study and give us longer-term data. And the sponsor's planned studies in special populations, including children and pregnant women, will provide important new data for our consideration.

Finally, let's take a moment to consider a list of attributes that would be ideal for a COVID-19 vaccine, especially one authorized for Emergency Use Authorization and to be used in mass immunization campaigns. We'd like to see an excellent safety profile and protective immunity, ideally with a single dose and balanced immune responses. And we want to avoid vaccine induced immunopathology. In terms of production and shipping, we need a vaccine that can be quickly mass produced with normal refrigerator

temperatures and avoids the need for ultra-cold chain transport and can be stored long-term. Beyond this, we want to see a reasonable duration of immunity and efficacy.

With the data on hand, we now see that the Janssen vaccine candidate checks nearly all the boxes. There are some longer-term items that will need to be further researched. But as discussed, we can expect answers to these important questions as part of the sponsor's ongoing investigation.

In summary, COVID-19 continues to be a deadly pandemic, and we urgently need more vaccines under EUA to protect the millions of Americans who remain at risk. Today, we have seen clear and compelling evidence that the Janssen vaccine candidate is well tolerated, has an acceptable safety profile, and, most importantly, is highly efficacious against COVID-19. To me, it is clear that the known benefits vastly outweigh the known risks, and it meets the criteria for Emergency Use Authorization.

Thank you. And I will turn the microphone

back to Dr. Van Hoof.

DR. JOHAN VAN HOOF: Thank you, Dr. Poland. And before we conclude, I would just want to take a moment to say a few special thanks, certainly to our collaborators at U.S. Department of Health and Human Services, particularly FDA, CDC, and the National Institute of Allergy and Infectious Diseases, as well as the team at BARDA. A special thanks as well to all of the global trial sites and to the many trial participants. Our work would not have been possible without their involvement. Thank you. And we are now ready for your questions.

ADDITIONAL Q & A FOR SPONSOR PRESENTERS

DR. ARNOLD MONTO: I'd like to thank you all for a very clear presentation. I'd like to start off by asking specifically about the issue of the crossover, which you said was going to occur as quickly as possible, giving vaccine to the placebo recipients. This, as I take it, is a unblinding of the study -- in

other words, giving the vaccine only to the placebo recipients, not giving a placebo to the vaccine recipients which would be a blinded crossover.

Also -- and I really don't think we ought to spend a whole lot of time on it -- but I noticed in your briefing materials you were also planning in your 3009, the two-dose study, to give vaccine, again, to the placebo recipients, which will change that design completely. I don't think we want to spend much time on that point. It might come up in the discussion later on. But I do want clarification about that now so we have that to keep in mind.

DR. JOHAN VAN HOOF: Thank you. Indeed, just to make sure that you understand it correctly, we are indeed proposing to do an open label crossover of the people who have received placebo that they would receive a dose. This would happen in the Study 2001 and also in Study 3009. It would be subject of an amendment. And depending on the country, it might take some time for these amendments to be approved by the authorities.

The thinking is that by crossing over the subjects that we can keep subjects in the trial. We should not forget that we have really very sensibly been selecting people that are at significant risk for COVID disease. And thus, there are also some medical challenges on keeping these people on placebo. There were quite some discussions in past already around that topic. We have seen that people (audio skip) study in those countries where the products are approved, especially in U.S. And that was part of the data that has been presented.

We hope by offering the vaccine that we can keep people in the study. Although it's not the ideal design with a placebo group, we still would be able to compare relative efficacies between those people that were vaccinated a few months later than those people that were vaccinated initially and that were differences are to occur, that that could be an indication of wanning protection.

For 3009, we are actually indeed offering a single dose of the vaccine to the group that receives

currently, two doses of placebo. And so that means that that study at that moment is different in design, and at that moment you're comparing two-dose regimen with a single-dose regimen.

DR. ARNOLD MONTO: And do you have enough power to show differences?

DR. JOHAN VAN HOOF: I would ask the -- propose that we -- that I go over to our biostatistician who has been looking at those trial calculations. And I would ask Dr. Bart Spiessens to take the floor. Dr. Spiessens?

DR. BART SPIESSENS: Thank you, Dr. Van Hoof. So indeed, if you look at the 3001 study when we do the placebo crossover -- so we crossover the placebo participants, we do think that based on what see in the Fullman (phonetic) paper and simulations that we have done that we do have sufficient power to make sure that we can detect waning if there would be waning of our vaccine. For the 3009 study, also there we will be comparing the one-dose with the two-dose vaccine. And also there we think we have enough power to make at

least some comparisons if the incidence keeps being high as it is currently the case. Thank you.

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

DR. OFER LEVY: Hello. It's Ofer Levy with the Precision Vaccines Program. Can you see me?

DR. ARNOLD MONTO: No. But we hear you. We hear you.

DR. OFER LEVY: Okay. Good. So I had a question for the sponsor regarding what is known with respect to innate immune activation by the Ad26 vaccine vector. There's evidence in the literature that Ad26 may engage pattern recognition receptors, potentially toll-like receptor nine in the inflammasome, thereby inducing cytokines such as interferons. Is that known for this particular product?

The other related query was did any of the Ad26 clinical trials, either for coronavirus or other indications, assess acute cytokine induction and its potential relationship to adaptive immune responses in the clinical responses? And, finally, we note that

there is some safety data for children from the Ebola program with this vector, and how will this position J&J for pediatric studies? Thank you.

DR. JOHAN VAN HOOF: Thank you. Actually, I will start with the last question. And then I would like to go to Dr. Zahn to comment on your questions on the innate immune responses. With regard to this, indeed we do have extensive experience in pediatrics going down to the age of four months. We have, specifically with our Ebola program, done extensive study going through different ages. We have observed that our immune responses are higher than in adults. There is a tendency for somewhat higher fever rate in the younger children, overall still very manageable.

And so overall we feel that this platform experience encourages us to start fast with our pediatric program. And we are looking into -- as I indicated already, we are looking into starting to vaccinating adolescents as of next week. And so we hope to deescalate in age over the next few months. With regard to the innate responses, Dr. Zahn, can you

respond to this question?

DR. ROLAND ZAHN: Yes. Thank you, Dr. Van Hoof. I don't think you can see my camera? I guess it's not working at this moment. So excuse me for that. I'm Roland Zahn, and I'm the Nonclinical Lead for Viral Vaccines program. And indeed, as you mentioned, for the Ad26 vector there have been multiple innate cytokine pattern recognition receptors described like TLR9 and (inaudible), STING pathways as well as inflammasome pathway.

We have not studied this specifically for this vector. However, in our nonclinical safety studies we have made a few phased reaction after vaccine administration 24 hours later in the circulation. Thank you.

DR. OFER LEVY: Thank you for that, Dr. Zahn. And what were the results of those studies?

DR. ROLAND ZAHN: So we saw a CFP (phonetic) induced, transiently one day after the immunization with Ad26 as a one-time stint of a 11 viral particle dose.

DR. OFER LEVY: Okay.

DR. ARNOLD MONTO: Okay.

DR. OFER LEVY: Thank you. So although this vaccine doesn't have an adjuvant in it, it may be self-adjuvanted. Thank you.

DR. ARNOLD MONTO: Okay. Dr. Offit.

DR. PAUL OFFIT: Yes. Thank you. And thank you all for a very clear presentation. I'm trying to get a better understanding of kind of the strategy moving forward with this vaccine. Dr. Poland made an excellent case for all the advantages of the single-dose vaccine. But you're doing with that COV3009 trial -- you're doing through those trials presumably because, as you showed in that Phase 1/2a trial that was reported in the *New England Journal of Medicine* by Dr. Sadoff and others, that with that second dose you had a sort of 2.6 to 2.9 increase in neutralizing antibodies which may well confer more protection.

Was that the case? I mean, as we move forward with this vaccine and we find that with two doses we have a better clinical response, does this then become

a two-dose trial -- a two-dose vaccine rather? In other words, for those who got, say, a single-dose starting a couple weeks from now, then six or eight months from now, when we have the data for the two-dose trial, are we asking them to come back for a second dose? I'm just trying to understand how you're positioning this.

DR. JOHAN VAN HOOF: Hi there. The question is clear. When we start the 2nd September and we had the data from our nonhuman primates model, it actually did show that we had full protection in the lung with a single dose, but we also had protection in those monkeys even four months after vaccination. Combined with the responses we had observed in humans, we decided to evaluate in parallel two vaccination schedules. First one is really testing the single-dose regimen and then the two-dose regimen.

Why did we choose a single-dose regimen? Because also based off all the discussions of the months that preceded, including guidance from WHO and others, it's clear that in a situation of an outbreak

in a raging epidemic the big challenge is to get the epidemic under control. And that is where a single-dose regimen with rapid onset of protection is highly preferred.

We do feel that with (audio skip) study, where we did that, it really has efficacy against severe disease, specifically against hospitalization and death. That with that, they fit that profile (audio skip) an epidemic where you have mass vaccination programs there's so much operational advantage in having a single-dose regimen in addition to also be able to vaccinate more people with the same supply that we do feel that this regimen is really extremely well positioned for use in outbreak situation.

Now, indeed there is a -- remains to be seen what the benefits will be in terms of an additional dose versus a single-dose regimen. It can be indeed that the efficacy could be higher, specifically for moderate. For severe, hospitalization, and death, it should be very difficult to be (audio skip). So I do think that is the judge is still out on what and how

the data look and what to do with it.

The other point is that, of course, for -- even for a single-dose regimen of the other vaccines the big question mark still is how long first protection lasts and at what moment will it be needed? And so we do feel that also those data will help us to determine this somewhat. But, again, the current situation with the emergency use, we do think that there's requirements that the single-dose regimen has to fulfill.

DR. PAUL OFFIT: No. I agree with that. And thank you for that answer. One quick follow up if I might, Dr. Monto.

DR. ARNOLD MONTO: Very quick because we've got some deadlines ahead of us. Go ahead. Go ahead, Paul.

DR. PAUL OFFIT: Okay. Sorry. You can see where the messaging is, right? If you bring out a single-dose vaccine and say this is a single-dose vaccine and then later find that something is better enough -- I mean, clinically better enough to say that

we recommend a second dose, you can see where that would be confusing to people, where they are thinking maybe "I didn't get what I needed." But in any case, that's all. It's a messaging challenge is all. Thank you. Thanks, Dr. Monto.

DR. JOHAN VAN HOOF: You're welcome. Thank you.

DR. ARNOLD MONTO: Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you. Yes. Specifically in relationship to the seropositivity with regard to Ad26 that you highlighted, it could, looking across the different populations -- there isn't any close impact on efficacy.

But I'm wondering if you were able to discern any differences in terms of some of the immuno- (audio skip) predict or not someone with a (audio skip) is previously exposed to Ad26's (audio skip) have less of a risk that may wane quick or may respond differently forward in terms of the overall efficacy, for example, the broader spectrum with regard to some of the variants' activities that you saw?

DR. JOHAN VAN HOOF: Right. That's a good question. So with interference with pre-existing immunities (audio skip) as Professor Schuitemaker, we have clearly seen in this that the immune responses where this was (audio skip) of South Africa this prevalence of people being seropositive at baseline. This is a (audio skip) our other Ad26-based vaccines where we have seen there is really no significant interference with the pre-existing immunity against the vector.

This seems to be a big difference with what has been reported for the adeno 5 vectors. The big difference probably is led in the fact that these titers are -- in the people that are pre-immune are perhaps clearly lower than the titer that you see with Ad5 seropositivity at baseline. So overall, from this program it is in line with what we are seeing with our other programs.

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

DR. PATRICK MOORE: Thank you. I want to follow up on Dr. Kurilla's question. First, a very

quick comment on unblinding. And I'm not picking on your vaccine because I've asked the same thing of the other vaccine makers. I really suggest that you try to do the MPRTP-(audio skip) (phonetic) on all the participants before you unblind them or at the time of unblinding. So that we have a better idea of virus shedding after vaccination. And potentially if you have the samples then you can (audio skip) later about variants.

But my question in follow up to Dr. Kurilla's question, which was really quite good, is that adenovirus latency and persistence is a black box. This, as you've pointed out, is a natural infection. And, presumably, some people will have prolonged infection, other people not with Ad26 after exposure. Do you have any evidence or data on the persistence of the vaccine strain or whether it's cleared from all vaccinees within days, weeks, months, any data that would help us evaluate that?

DR. JOHAN VAN HOOF: Yes. Thank you for that question, and I'll go back to Dr. Zahn to discuss the

biodistribution data that we know from there. I would like to reiterate there was something which was already said before, that is the adeno 26 here is a nonreplicating vector. So there is no multiplication in the vaccinee's body. So we could --

DR. PATRICK MOORE: Now let me just clarify that. It is not -- it will not -- it cannot, presumably, from theoretically what we know, make infectious virions. But in terms of persisting as a latent, either episome or pseudo-episome, I'm not certain that we can say anything about that. You haven't deleted, for instance, the end terminal repeats or any other way that virus may use to persist long-term. So I caution about using that phrasing that it's -- it's not a dead virus.

DR. JOHAN VAN HOOF: I refer to Dr. Zahn to answer the details of your question. Dr. Zahn?

DR. ROLAND ZAHN: Yes. I'm Roland Zahn. Thank you for the question. Indeed, we have obviously looked into biodistribution of Ad26. We have not done specific biodistribution studies with Ad26.COV2.S but

with multiple other Ad26 vaccine vectors. And we've seen that in rabbits, which we use as a main species for these distribution studies that the vector DNA is mainly localized at the injection site and then distributed to a (inaudible) node and a bit to the spleen. Here we have seen that the vector DNA is cleared from these cases within 90 to 180 days. And that's a similar pattern as has been observed for other adenoviral vectors. So the vector seems to be cleared from the organism by a natural mechanism like division of cells or by immune mechanisms of infected cells. Thank you.

DR. ARNOLD MONTO: Okay. We're going to have to go on. We have a hard start for the opening public hearing at 1:10 p.m. Eastern. So we are going to have to limit questions right now to, let's say, two more. And I'll call on Dr. McInnes.

DR. PAMELA MCINNES: Thank you, Arnold. Can you hear me?

DR. ARNOLD MONTO: Yes.

DR. PAMELA MCINNES: I have a question,

please, regarding the case definitions in the description of accompanying statistics. So in the briefing document, the sponsor does define -- under 7.1.1.5, they define moderate COVID-19, severe/critical COVID-19, and mild COVID-19. Yet when we look at the analyses, we have these pooled -- what I presume are pooled -- and the description says something about protection against moderate to severe COVID-19. There is no case definition for moderate to severe COVID-19.

So I want the clarification, please. These are ranked data -- graded data. Is this a pooling of moderate and the severe pools to come up with this moderate to severe?

DR. JOHAN VAN HOOF: That is correct indeed.

DR. PAMELA MCINNES: Sorry, could you repeat that, please?

DR. JOHAN VAN HOOF: That is indeed correct. So moderate to severe is adding the moderate and severe together.

DR. PAMELA MCINNES: So it's pooled -- so it's "and," moderate "and" severe pooled together with an

analysis run on that?

DR. JOHAN VAN HOOF: Yep.

DR. PAMELA MCINNES: Thank you.

DR. ARNOLD MONTO: Dr. Hildreth.

DR. JAMES HILDRETH: Okay. Yes. I had a question about the T cell response to Ad26. The participants made -- all of them made a strong antibody responses -- neutralizing antibody responses. But I noticed that the response by CD4+ T cells was only about two-thirds of them. How does that compare to your other Ad26 vaccines that you've developed?

DR. JOHAN VAN HOOF: Thank you. That question I'm going to refer to Professor Schuitemaker. Professor Schuitemaker?

DR. HANNEKE SCHUITEMAKER: Yes. In our other programs we have seen similar, we call it good CD4+ T cell responses. Also if we compare for other vaccines, these are a high responder rate. And also for our CD8+ T cell, we see good responder rates also as compared to other vaccines. So does that address your question?

DR. JAMES HILDRETH: I was asking the question

because I think T cells are important for durable responses. And I know that some of your vaccines you say it lasts for two years. So I wondered if those individuals have a higher T cell response than you see here?

DR. HANNEKE SCHUITEMAKER: Yes. And, indeed, we see durability of viral responses that indeed correlated with the group CD4 cell responses for the humoral immunity. But also, we see a prolonged durability of our CD8+ T cell responses, which is really a feature of the platform to your point. Yeah.

DR. JAMES HILDRETH: Thank you. Okay. Thank you.

DR. ARNOLD MONTO: All right. One final question. I promise final from Dr. Kim before our very short lunch break.

DR. DAVID KIM: I have a question for Dr. Douoguih. I noted that one death in the Ad26 group was excluded -- she was -- because a subject had tested positive for the infection by PCR at the start of the study. How many other subjects in the study had

positive COVID test at the start of the study, and how were they distributed -- that is, demographics and other information and such?

DR. JOHAN VAN HOOF: Dr. Douoguih?

DR. MACAYA DOUOGUIH: Yes. Sorry. Can you hear me okay?

UNIDENTIFIED MALE: Yep.

UNIDENTIFIED MALE: Yes.

DR. MACAYA DOUOGUIH: Yes. So that's true in the placebo group. We did have one PCR positive at base which, as I said, we wanted to exclude those in our primary efficacy analysis. In terms of evidence, so we looked at seropositivity at baseline in all of our participants and (inaudible) as well. And, overall, we saw that about 9.6 percent were seropositive at study entry. And I'm just checking to see if we have more specific numbers on PCR. I don't see those here. Maybe I can just ask Dr. Spiessens if he perhaps has that information?

DR. BART SPIESSENS: Yeah. Thank you, Dr. Douoguih. So, indeed, we had 9.6 percent of the

subjects that were SARS-CoV-2 positive at baseline, and they were well balanced between the placebo group and the vaccine group. Thank you.

DR. ARNOLD MONTO: Okay. Well, thank you. I apologize because of our technical problems which increased the time we had at the break -- previous break that we didn't have as much time as we had hoped for questions here. I would ask the Janssen team to please be available at the start of our broad discussion time for us in the afternoon because we are certain to have some additional questions for you. Right now, we're going to adjourn for a very brief lunch and start up at 1:10 hard start for the Open Public Hearing. So we'll see you at 1:10, Open Public Hearing.

[LUNCH BREAK]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCYZNSKI: Welcome to the FDA's

164th VRBPAC meeting. We are now going to be moving into our OPH session, so with that, Dr. Monto, would you please take it away?

DR. ARNOLD MONTO: Welcome to the Open Public Hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if

you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Over.

DR. PRABHA ATREYA: Good afternoon, everyone. This is Dr. Prabha Atreya. I am the designated federal officer for this meeting. So we're going to be starting the Open Public Hearing speakers and Open Public Hearing session, and we will start with Dr. Diana Zuckerman. Dr. Zuckerman, take it away. Thank you. You have three minutes.

DR. DIANA ZUCKERMAN: Thank you. Can you hear me?

DR. PRABHA ATREYA: Yes, please.

DR. DIANA ZUCKERMAN: I'm Dr. Diana Zuckerman, president of the National Center for Health Research. Next slide. Our center scrutinizes the safety and effectiveness of medical products, and we don't accept funding from companies that make those products. However, I inherited J&J stock, so my criticisms today are counter to my financial interests.

I'm trained in epidemiology, was a former faculty member and researcher at Vassar, Yale, and Harvard; a former fellow in bioethics at Penn; and also worked at HHS. Please skip the next slide and go to the one titled "Preventing Serious COVID." I'm concerned about the hype that this vaccine is effective specifically against moderate and severe COVID. Those are PR claims that are misleading. Not all symptomatic cases are moderate or severe. The other two vaccine companies just counted cases and severe cases. Since Janssen reported only four mild cases, what the company calls "moderate" cases is almost identical to what the other two companies called "cases," and they do include mild symptoms.

All seven deaths in the study were in the placebo arm and were in South Africa, so let's focus on severe COVID in terms of hospitalization and medical interventions as the FDA did on page 33 of their briefing document. Ten study participants developed severe COVID at least two weeks after their shots, and only five developed severe COVID at least four weeks

after their shots. Most were in the placebo group, but these are very small numbers. And the differences are not statistically significant. It's misleading to tell the public that nobody who was vaccinated was hospitalized unless you also tell them that only five people in the placebo group were hospitalized. The data indicate that the vaccine is effective but doesn't prove that the vaccine is especially effective against moderate and severe COVID. Next slide.

After 28 days, there were zero COVID cases for ages 75 and older in the vaccine arm and four cases in the placebo arm, too few to draw conclusions about efficacy in the oldest patients. Next slide. The vaccine is effective, but the median follow up is only eight weeks after the shot. Does human immunity last only two months or four months or a year? We won't know unless the randomized control trial is continued.

Last slide, in conclusion, the FDA guidance for COVID vaccine approval specified at least a year or two of follow up. FDA's guidance for EUA drastically shortened that to a median of two months, and that's

exactly what the companies provided. The companies said that the double blinded studies would continue after the EUA, but that no longer seems likely. And FDA said today that approval might be based on six months.

As soon as a vaccine is authorized, we start losing the placebo group. If FDA let's that happen, that's a huge loss for public health and a huge loss of information about how we can stay safe. The crossover design is something, but unless it allows at least six months of data, we will really be limited in what we know. So at the very least let's be very honest with the public about what we do know and what we won't know. Thanks very much for the opportunity to speak today.

DR. PRABHA ATREYA: Thank you, Dr. Zuckerman. The next speaker is Dr. William Fitzsimmons.

DR. WILLIAM FITZSIMMONS: I am William Fitzsimmons. I have no financial relationships to disclose, and with my collaborator Anthony Coniglio, I'd like to thank you for the opportunity to make two

points: first support for the Janssen EUA and expansion of the Moderna and Pfizer-BioNTech EUAs to allow single dose administration; secondly, a recommendation for advancing the registration trial methodology so that active controlled noninferiority studies can be used for new vaccine approvals. Next slide, please, slide two.

The Janssen single dose efficacy rate for preventing moderate to severe COVID-19 is 66 percent. The single dose efficacy rate of the Moderna vaccine over 28 days post-dose was 69.5 percent, which includes the first two weeks post-dose. Although the single dose 28-day efficacy data with the Pfizer vaccine is not directly available, we know that the 21-day efficacy of single dose is 52.4 percent and is well over 80 percent in the third and fourth week after first dose. Next slide, slide three.

We support the EUA application for the Janssen vaccine, and the same scientific rationale would indicate that the EUAs for the Moderna and Pfizer vaccine be expanded to include a single dose

administration option. Next slide, slide four. We ask that the FDA and the Advisory Committee advance methodological work to enable the performance of active controlled noninferiority trials. With this event, randomized to placebo have experienced significantly more severe infections, including COVID-19 related death as seen in seven participants receiving placebo in the Janssen study. Reports from ongoing placebo-controlled studies indicate some participants are requesting to leave the study or are receiving vaccination under the current EUAs, both of which compromise the trials. Next slide, slide five.

Pfizer and Moderna data demonstrate that it should be feasible to propose a noninferiority margin, and the FDA guidance document indicates a relative efficacy noninferiority margin when comparing a new vaccine to an effective vaccine. Next slide, slide six. Additional considerations for future COVID-19 vaccine registration trials include inclusion of patient populations, for example, cancer, autoimmune disease, and transplant recipients that were previously

excluded from trials but are at increased risk of COVID-19 morbidity and mortality; antibody testing in these populations; and systematic protocol defined testing for asymptomatic infection and transmissibility.

In summary, we support approval of a Janssen EUA and expansion of Moderna and Pfizer-BioNTech EUAs to allow public health professionals to optimize vaccination for the prevention of severe infection, hospitalization and death as quickly as possible. It is also vital that we reexamine the design and methodologies to facilitate the use of active controlled noninferiority designs. Thank you very much.

DR. PRABHA ATREYA: The next speaker is Dr. Dasgupta.

DR. NABARUN DASGUPTA: Good afternoon. I'm a side effects surveillance scientist at the University of North Carolina in Chapel Hill. Dr. Lazard, Dr. Brownstein, and I have no conflicts to disclose. Next slide, please.

This Committee and FDA need reliable information on side effects, and the systems described by Dr. Shimabukuro and Dr. Anderson this morning are groundbreaking. Seriously, y'all, much respect. But there are two areas for improvement. Therefore, I'll share what we learned from deploying government adverse event reporting apps for drugs and medical devices across 13 countries in Europe, North America, and Africa.

From the MMWR, early v-safe reporters had a median age of 46, and 69 percent were women, aiming to reflect the vaccination eligible health care workforce, but there's more to the story. In our apps, the earliest adopters matched exactly this demographic profile. Many were nurses who already knew about the importance of adverse event reporting. It was much harder to get run of the mill patients to report because we weren't tuned into their motivations. When we asked, their answer was clear. "Show that someone truly cares about our well-being."

So to get sustained reporting from patients

via digital tools we had to tap into motivations that were different from those of early adopters. There are two main reason why patients report. The first is altruism, to prevent side effects in other. The second is social validation because initial concerns often get dismissed by clinicians. We learned the hard way that too often surveillance systems take valuable information and give patients little in return. Next slide, please.

This leads to our second point. Elderly African-Americans have exceptionally high COVID morbidity and lower rates of digital access. Many have lived experiences of mistreatment by the healthcare system. Their adequate representation in health data is a form of social justice and equity. To especially gather their perspective, Sentinel sites may be needed to supplement existing efforts beyond the digital divide. The key thing missing in the current data picture is community-based Sentinel sampling with the active participation of marginalized populations. Next slide, please.

Can I just come out and say it? The public doesn't know what safety science is or that it even exists. To meet people where they are, we built crowdsourcing tools like Outbreaks Near Me that partner with companies like Facebook, SurveyMonkey, and Google to get population level insights that are not available elsewhere. These tools can be adopted for in-person data collection. Next slide, please.

Final points, the real-world data slides today betray the natural impulse to parse differences between vaccines. Patients do it too. Choice can improve pro-social behavior among those who are hesitant. Choosing between vaccines can be an expression of identity. In turn, expression of identity restores a sense of agency. We anticipate patient choice will be part of the endgame as we try to reach those with lingering reservations into next year. Having a third vaccine will help create choices for patients and caregivers and get all of us vaccinated. Last night, *The Lancet* published our article detailing these comments. Last slide, please. We can be reached here if you have any

questions. Thank you for your time.

DR. PRABHA ATREYA: Thank you, Dr. Dasgupta. Next speaker is Kermit Kubitz.

MR. KERMIT KUBITZ: Good afternoon. I am Kermit Kubitz, and I support EUA for the Janssen vaccine because of the need for additional vaccines and clear positive benefit-risk. So far, the path to vaccination is neither frictionless nor fast.

My prior comments to the Ad-Com addressed the need to approve the Pfizer vaccine. Since then, my 84- and 86-year-old sisters have been vaccinated, but my 88-year-old brother, a Korean War era Navy veteran, has not. He lives alone with caregivers coming in. His medical provider, Peninsula Family Medical Center in Tacoma, Washington, reported to me their, quote, great disappointment and frustration, unquote, that they would not be receiving the COVID-19 vaccine because state officials had chosen to divert the vaccine to other areas deemed more beneficial to the public. So having been vaccinated with the Moderna vaccine myself, I will have to travel to Tacoma to try to navigate the

vaccine highway for my brother with the VA and the state of Washington. We need more vaccines.

Page 2, a structured benefit-risk strongly supports emergency use of a Janssen vaccine. The pandemic is a serious disease. The only alternative, the Pfizer and Moderna vaccines, are not fully licensed and limited in supply. The benefits as revealed in the FDA and sponsor briefing documents are efficacy above 70 percent with virtually complete protection against COVID related hospital and deaths. The risks are limited as shown by limited adverse events among 40,000 trial participants and low overall fever rates. The conclusion is that a well understood method of production vaccine with high efficacy justifies EUA.

Page 3, my recommendations are to note that adenovirus vaccines may have lesser efficacy in older adults with prior multiple adenovirus infections. It may be desirable to include an adjuvant or booster in future or fully licensed vaccines to promote more antigens and efficacy. In any case, it is important to approve the Janssen vaccine and move forward with

community immunity. Thanks to Dr. Messonnier on the annual anniversary of her warning February 25th, 2020 that we should plan for community spread and remote learning and working. Thank you. Bye.

DR. PRABHA ATREYA: Thank you, Mr. Kubitz. The next speaker is Dr. Kevin Latinis.

DR. KEVIN LATINIS: Thank you, Committee, for allowing me to talk about serology testing and COVID-19 infection and vaccine monitoring. I'm Kevin Latinis. I trained in immunology and rheumatology in the medical scientist training programs at the University of Iowa and Wash-U in St. Louis. Going forward we should continue to monitor safety and efficacy of vaccinations and determine need, timing, and safety of booster vaccinations. To do this our best tool is serologic conversation. Next slide.

What do serology tests tell us? They tell us that we have developed immunity to COVID-19. To produce IgG antibodies, our immune system must recognize and respond to COVID-19 proteins by both B cells and T cells. The process of switching from IgM

to IgG cannot occur without T cell help, a hallmark of adaptive immunity. As you have seen in data from all vaccine trials, IgG has strong correlation with neutralization assays and T cell assays. Please return to my previous slide.

Assays have improved significantly. Improve specificities and the increasingly high prevalence of immunity to COVID-19 have eliminated early problems with false positives. I propose the EUA assays of highest value are those that measure IgG; those that measure quantifiable levels of antibody; those that detect spike proteins, in particular the receptor binding domain; and those that are inexpensive and available for high throughput capacities.

Next, the CDC recommendations on use of serology testing, last updated in November, need to include using serology to establish a threshold for protection and to monitor maintenance of immunity. From a clinical perspective, vaccine studies evaluate homogenous populations of healthy individuals. They lack large amounts of data on significant variability

in regard to age extremes, immunologic comorbidities and medical treatments, factors that impact immunity. Vaccines, like drugs, are medical treatments. They come with relative risks and benefits that need to be assessed and monitored.

So what can we hypothesize? One, that some people may not respond with durable immunity; two, that some people may hyper-react; three, that at some point immunity after infection and after vaccination is likely to wane. In these cases, serology testing is very helpful to track immunity.

I will close with two cases demonstrating why serology testing is a valuable tool. One, a 32-year-old lupus patient had COVID in the fall. She received her first vaccine dose in January and had significant and lingering post-vaccination symptoms. Testing for lupus activity revealed a lupus flare with a critical drop in her platelets. Serology testing showed evidence of antibodies, so I recommended postponing her second vaccine dose until her lupus has stabilized and her serology's waned.

Second, a 67-year-old woman with severe autoimmune disease treated with immune modifying medications received both vaccine doses in January. Serology testing this week showed she had not seroconverted, so my plan is to continue monitoring her serology over the next few months and if persistently negative, revaccinate with the vaccine supplies are no longer limited. Thank you for your time.

DR. PRABHA ATREYA: Thank you, Dr. Latinis. The next speaker is Dr. David Berger.

DR. DAVID BERGER: Hello. I'm a board-certified pediatrician in Tampa, Florida, and I specialize in preconception infancy and wellness. And I am also a patient vaccine consultant. I also serve as an associate professor at the University of South Florida College of Nursing and am the senior medical advisor of the Vaccine Consideration Project. Thank you for inviting me back to present to this Committee. I have no conflicts of interest. To the technical staff, please note that I will not be using slide number 11.

Before I start my presentation, I again want to express significant frustration with this process which required us to submit slides and written comments before the vaccine data was available to the public. If the FDA truly values our input, it would give us sufficient time to review the data. Now, if you can please go to slide number 3 and start my presentation.

My comments today are about the use of COVID-19 vaccines in pregnant women and people of childbearing age. No studies of pregnant women have been published. Americans are asking if they should get a vaccine if pregnant or trying to conceive. Each will weigh the options and need more information, and we must be open and honest with them about what is known and not known. Next slide, number 4.

Morbidity associated with COVID-19 in pregnant women has been established with increased ICU admissions, pre-term births and admissions to a neonatal ICU. Next slide, 5. Ongoing hesitancy relative to vaccine continues. In a recent survey, at least one-third of people aged 15 to 50 say they would

probably or definitely not take a vaccine even if determined to be safe and free of charge. Multiple polls have also shown women are more likely to have vaccine hesitancy than men. Therefore, large numbers of women of childbearing age have vaccine hesitancy. Next slide, 6.

Hesitancy and confusion has likely increased due to conflicting statements from various organizations. Next slide, 7. We have learned that adenoviral vector DNA vaccines such as this one enters the nucleus where the human DNA resides. Messenger RNA vaccines do not enter the nucleus. Next slide, number 8. This difference has led to questions about whether this vaccine could interfere with pregnancy, especially from conception through early fetal development. Upon finally being able to review the data two days ago and with only eight pregnant women included in the trials, safety and effectiveness conclusions cannot be made about this vaccine and pregnancy. Next slide, number 9.

After researching this issue over the past two

weeks with my research team, we could find no medical research or scientific opinion addressing whether a human embryo could be negatively impacted by this type of vaccine. I did locate a CDC article showing adenovirus can enter sperm, and I found one mouse study indicating adenovirus vector DNA does not show up in the DNA of mouse offspring. Yesterday, a vaccine researcher I spoke with suggested that the amount of vaccine particles injected into the arm that could reach testicles or the uterus may not be enough to be consequential.

As per the Agency's mission statement, the FDA is responsible for protecting the public health by ensuring the safety, efficacy, and security of human drugs. Applying this directive to COVID-19 vaccines in people of childbearing age, I believe the FDA has a responsibility to proceed with caution as more data is gathered. However the FDA decides to proceed, we can empower people by providing the information necessary to weigh the benefits and risks of taking a vaccine. Thus, decisions are very personal, and their decision

should be respected. Transparency on the part of the manufacturers and the government needs to be better. It should not be so hard to find information.

In the end, it all comes down to --

MR. MICHAEL KAWCYZNSKI: Time, sir.

DR. DAVID BERGER: -- informed consent.

DR. PRABHA ATREYA: Okay. Thank you, Dr. Berger.

MR. MICHAEL KAWCYZNSKI: Did you want to wrap up?

DR. DAVID BERGER: Yes, if I could just wrap up. I just have three more sentences. So informed consent by definition means individuals must be fully informed so they consent to taking or not taking the vaccine. Next and last slide, the Vaccine Considerations Project is building a repository of information related to vaccine safety concerns and efficacy. We will continue to tackle the issues of most concern to the public and share whatever information we find. Please reach out to us if you wish to join our endeavor. Thank you for your time.

DR. PRABHA ATREYA: Thank you, Dr. Berger. The next speaker is Jared Krupnick.

MR. JARED KRUPNICK: I have no financial relationships to disclose. Hi, I'm Jared Krupnick. I'm the president of Uniting for Action and the founder of the Vaccine Considerations Project. We're working to make sure that all health and safety concerns are given due consideration. Thank you very much for this opportunity. Next slide, please.

Specifically, we're here today to address preventing health inequities. There's a prevailing concern that differences in efficacy between different vaccines could exacerbate health inequities. A solution is for the FDA to provide critical information for the public. I wasn't sure if this was within the FDA's mission, so I looked it up. Next slide, please.

The mission says in part the FDA is responsible for "helping the public get the accurate science-based information they need to use medical products," in this case vaccines, "to maintain and improve their health." Next slide, please. There are

scientific differences between the vaccines. Currently, many public health experts are saying the important statistics are that each of the vaccines prevent hospitalizations and deaths. Those are indeed very important benefits of all the vaccines, but there are other severe potential impacts within families and communities beyond hospitalizations and death. Next slide, please.

Some severe and potentially devastating consequences for individual families and communities include more missed work, more spread to non-vaccinated family members, more long-term health impacts. Next slide, please. The FDA needs to provide information about the differences in the vaccines to people to allow them to provide an informed consent. It erodes credibility to on one hand repeatedly say "Trust the science. Trust the science," and then when it comes to vaccine differences to effectively say, "Ignore the science." Next slide, please.

If it's found that marginalized communities are faring worse in part due to vaccine differences, it

will further deepen mistrust and skepticism and decrease vaccine uptake. Next slide, please. Here's just a simple example of the type of comparative data that would be important for people to know. For families who are one missed paycheck away from going hungry or from losing their home, the difference in the science are critical for them to know. I implore the FDA to not just publish data but to take ownership of ensuring that every individual who is considering a vaccine have all of the best scientific information they can have to make informed decisions for themselves and their family. Next slide, please.

Our national team of professionals and graduate students are actively evaluating concerns and working to provide the information individuals need to make informed choices. We encourage everyone who shares our intentions to join our efforts, so go to vaccineconsiderations.com for more information related to this and to Dr. Berger's presentation and to sign up to receive more information or to join our team. Thank you very much.

DR. PRABHA ATREYA: Thank you, Mr. Krupnick. The next speaker is Benjamin Newton.

MR. BENJAMIN NEWTON: Hi. Thank you so much. I'm here to talk about how we can save the most lives. I have a financial interest in Moderna, and if you follow my recommendations, I will be harmed financially. I encourage you to approve this vaccine. Many people with PEG allergies need it. It's an important first dose. Next slide.

You can see that the J&J vaccine is insufficient to stop the spread of the South Africa variant based upon South African efficacy. You need 100 percent vaccination rate, which is unlikely. Next slide. The tested vaccine doses are not magic. Dosing and regimen for all vaccines was decided for commercial reasons based upon what was known at the time the study commenced.

Sero-bridging is a real and accepted practice at the FDA and CDC. It's actually required by the EUA filing. I would encourage us to use all what we know about biology and not just what was tested so we can

actually follow the science. Next slide.

The MRNA vaccines boost; the adenovirus vaccines don't boost effectively. The one dose efficacy is listed at the top, and you can see the boost increase for Pfizer and Moderna is 16-fold and 7-fold, which is fantastic. Next slide. What this leads to is some amazing vaccine supply math. Doubling the dose provides less than twice the protection. Each additional shot increases protection 10-fold. This means that for any supply of vaccine every person in the world can be fully protected.

The right questions to ask are what is the manufacturing capacity? How many people -- how many doses will each person require? And what we see if we ask those questions on the next slide is that using the single dose size for Pfizer and Moderna and the American doses currently produced per month for Pfizer and Moderna, using sero-bridging we can see that a one microgram dose for Pfizer and a 1.5 microgram dose for Moderna is sufficient for 90 percent efficacy. That leads to 2.2 billion people protected each month, which

is enough to bring COVID to an end in a very short period of time. Next slide.

Ethics, COVID has led to a lot of ethical issues and difficult ethical choices. And we've all had to make them. Since the last time I spoke to VRBPAC, 900,000 people have died of COVID. Next slide. Right here what we have is a regulatory bottleneck -- we should be on slide 8 here -- not a manufacturing bottleneck. I encourage each of you to have political courage, lower the doses for Moderna and Pfizer.

Who's doing this already? Britain has already figured this out. Moncef Slaoui already commented on the logical extension. I've put together a YouTube video. It's about as interesting as watching paint dry to talk about any questions you might have. I do thank you for your time and service. Everyone without a vaccine has the same R0 as an antivaxxer. While you've listened to me speak, six additional people have died of COVID. I urge you to act with all due haste. Thank you very much for your time.

DR. PRABHA ATREYA: Thank you, Dr. Newton.

The next speaker is Dr. Sidney Wolfe.

DR. SIDNEY WOLFE: I'm Dr. Sidney Wolfe, the Public Citizen's Health Research Group. I have no conflicts of interest. I support granting an EUA for Janssen vaccine despite decreased efficacy in older people with comorbidities.

With the current EUA availability of two COVID vaccines, a third probably next week, it will be neither practically nor ethically feasible to continue recruiting new participants to placebo controlled trials unless they will ultimately get vaccinated whether initially randomized to the vaccine or placebo group. On December 10th before your Committee, I stated that, quote, "An important unresolved conflict exists. If an EUA is granted for widespread use, should the 19,000 participants in the Pfizer trial who received a placebo be notified of this and be offered a vaccine by Pfizer, clearly encouraging them to stay in the trial? Status uniformed trial participants might otherwise leave the trial to try and get vaccinated with Pfizer or any other EUA available vaccine."

Parenthetically, a couple thousand people have left the Janssen trial for exactly this reason.

The unblinding vaccine providing proposal has important advantages. Once an EUA's granted, the ethical obligation to both inform all placebo recipients of their status and offer them the vaccine within the context of the clinical trial is met. The originally vaccinated group could be compared with the newly vaccinated group to continually compare rates of new COVID infection with increase duration of vaccination as well as adverse reactions. Pfizer's stated preference was, quote -- this is during the Pfizer hearing on the 10th of December -- "was that such individuals be vaccinated with the study -- within the study in order that both safety and efficacy data can be continued to be collected. We believe this approach will minimize the number of current participants who choose to withdraw from the study once a vaccine is available and will maximize the collection of data that can inform long term safety and efficacy of the Pfizer vaccine."

Now, two and a half months later than December 10th, Janssen now proposes that, quote -- this is their slide 62 this morning -- "upon authorization by regulatory authority, all placebo participants will receive one dose of their vaccine." If granted by the FDA for Janssen's and subsequent EUA granted COVID-19 vaccines, all placebo participants will later get a vaccine. But what about the 19,000 Pfizer subjects and 15,000 Moderna subjects who were randomized to placebo groups? At the time of EUA authorizations, both companies had similarly Moderna like -- I just quoted from Pfizer -- had similarly expressed their preference to subjects previously given placebos be notified of this and offered a vaccine.

As of now, how many of the original 34,000 Pfizer and Moderna placebo recipients have been notified of the status and offered a vaccine, and what will occur and when will this occur for the almost 20,000 Janssen placebo recipients who were risking their lives, as were the people without knowing it in the Pfizer/Moderna studies in order to find out that

they are eligible for an EUA?

MR. MICHAEL KAWCZYNSKI: Time.

DR. SIDNEY WOLFE: Thank you very much.

DR. PRABHA ATREYA: Thank you, Dr. Wolfe. The next speaker for presenters did not submit any slides for their presentation, so we will only hear their verbal comments. Thank you. The next speaker is Kim Witczak.

MS. KIM WITCZAK: Good afternoon. My name's Kim Witczak, and I'm speaking on behalf of Woody Matters, a drug safety organization started after the death of my husband due to an undisclosed side effect of antidepressants. We represent the voice of families who live every day with the consequences of the current drug safety system, effective and accessible medical treatments.

There is an excitement in the air. You can feel the energy of excitement growing. People are looking for hope, and these vaccines seem to be providing it. Hope is a powerful motivator, but what is hope based on?

On the surface, the efficacy of J&J's vaccine may not be as high as the other two investigational vaccines on the market, but it is one shot and doesn't need the extreme preservation like the others. Since it is all but guaranteed that J&J will receive emergency authorization this weekend, I'm going to use my time to address some general concerns I have. The public has not been explained what emergency use authorization really means. Most assume it means FDA approval. We may never have FDA approval on any of these vaccines, especially if we lose the placebo control group on the ongoing phase 3 clinical trials. These vaccines need to continually be framed as investigational, and we are learning as we go in the real world with all the risks that that entails.

It seems EUA has become the new standard. With new variants popping up there will be an endless market for potential booster shots. Warp speed testing, then deploy and hope for the best seems to be the new acceptable strategy. Is the public being given trust informed consent and made aware that these

vaccines are still investigational and may not stop transmission, may not stop your life, has not been tested on all types of people like those with immune efficiencies and those who are pregnant? And now, we are seeing celebrities, politicians, influencers joining in on the mass vaccination effort while telling the public the shots are safe.

Speaking of safe, how can the public be assured that harms and adverse events are being taken seriously? The adverse events that we have seen occur in the short term are being quickly dismissed and accepted as "The vaccine is working. It's priming our immune systems."

I would personally (audio skip) workers that experienced horrific side effects after their first shot. They took the proper reporting measures to the FDA, CDC, and the companies. To this day, none of them have been contacted or followed up by the companies. However, contrast this with the *Reuters* story from earlier this week with the headline "First Month of Shots Find No Safety Issues with Pfizer-BioNTech,

Moderna Vaccines." Of course, we still no nothing about the long-term impact on our immune systems, fertility, and other health related issues.

Ultimately, in this current pandemic environment the public is the real-world clinical trial. It is one big human experiment. And thank you for your time and I appreciate your careful consideration of my comments.

DR. PRABHA ATREYA: Thank you, Ms. Witczak. The next speaker is Ms. Ann Lewandowski.

MS. ANN LEWANDOWSKI: Hello. My name is Ann Lewandowski, and I'm the executive director of the Wisconsin Immunization Neighborhood. I have no conflicts. I would like to begin by thanking the sponsors and members of VRBPAC for their time today.

As a public health professional, I am thrilled to see a one dose stable vaccine that can be distributed to hard-to-reach communities. I'm also thrilled to see that some groups are providing high acceptability of this vaccine. I am deeply appreciative that the sponsor included transmission

data claims to help us communicate to the public that these vaccines do more to protect not just the individual. They help protect the community.

We support the five-dose vial size as appropriate for small clinic locations and trying to get into hard-to-reach communities. We ask that you consider an acceptable minimum order size and shipping amounts for other vaccines. We very much expect to support doctor office and other suggestions that clear messaging should be made for the public on whether or not this may turn into a two-dose series in the future.

Like others, I support the comments that many of these populations do not have adequate data. We must help the public understand where data exists and what gaps may be and at what timeframe these questions and data gaps may be clarified. Of particular interest, as many already noted, autoimmune disease and pregnancies are critical for many people in the United States as they make decisions to be vaccinated. Thank you.

DR. PRABHA ATREYA: Hello?

MR. MICHAEL KAWCZYNSKI: Yeah. Prabha, we're back on track now. Prabha?

DR. PRABHA ATREYA: Okay. The next speaker is Ms. Sarah Christopherson.

MS. SARAH CHRISTOPHERSON: Hi. Thank you.

DR. PRABHA ATREYA: Could you just speak up a little bit? The volume is low.

MS. SARAH CHRISTOPHERSON: All right. I will take off my headset, then. My name is Sarah Christopherson. I am the policy advocacy director at the National Women's Health Network, a nonprofit advocacy organization that has been bringing the voices of women to the FDA for 45 years. We are supported by our members and do not accept financial support from drug or device makers, and I have no conflicts of interest to disclose.

We believe that an emergency use authorization based on the data presented this week is appropriated under the current circumstances. A one dose vaccine effective in preventing severe disease, including against several known variants, that can be stored for

three months at normal refrigeration temperatures with fewer logistical constraints has the potential to markedly reduce hospitalizations and death. With two authorized vaccines currently on the market, we now have real world data about how logistical challenges and distribution have hampered equitable access.

The Janssen vaccine represents a big leap forward for access, particularly in low income, rural and other underserved communities. However, because it's difficult to make an apples-to-apples comparison between vaccines authorized based on data collected before new variants are believed to have been in widespread circulation and today's data, there is a significant concern that headline numbers are already leading to a sense among the public that there are first- and second-class vaccines, with the latter relegated to low income, rural, or otherwise marginalized communities. That has the potential to exacerbate existing mistrust. Public health authorities must address these perceptions head on.

And secondly, and as we've heard in previous

meetings of this Committee, CDC data indicate that Black and indigenous people living in the U.S. are roughly four times more likely to be hospitalized from COVID-19 and roughly three times more likely to die from the virus than their white counterparts. Racism, both systemic and interpersonal, healthcare disparities, and increased workplace exposure are all factors. When examining today's clinical trial data, we see that the data for racial and ethnic groups track closely with each group's share of the U.S. population but do not account for the disproportionate impact of the pandemic on different communities. Given that disparity's impact, which was already well established at the time the trials were begun, the sponsor should have sought to enroll Black, Latino, and indigenous participants relative to their vulnerability to the virus, not share of total population. Thank you for your consideration.

DR. PRABHA ATREYA: Thank you very much. The next speaker is Ms. Lynda Dee.

MS. LYNDA DEE: Hi, my name is Lynda Dee. I'm

from AIDS Action Baltimore. I've been a community rep on a number of antiviral advisory committee hearings, and I have no financial relationship with the sponsor. I support the EU application given the risk-benefit ratio presented here.

Back in October, I had a laundry list of issue, many of which have been addressed by the sponsor, including the intention to use an open label crossover study for phase 3 placebo arm participants. I'm actually surprised by the large number of people between 65 and 74, the many racial and ethnic minorities, and people with pre-existing COVID-19 outcome affecting morbidities. I mean, I've never seen this before in 35 years of doing this work -- this many. At least we've started to enroll the correct people in the studies here.

Some data was also provided on pregnancy outcomes for trial participants, and the sponsor intends to conduct a trial in children, pregnant women, and immunocompromised people. People with HIV were included at the outset of the study, and at least some

study data was provided. There are many people with HIV who are interested in being vaccine study participants. I hope all sponsors will do a better job of recruiting people with HIV for future studies. Outreach to the HIV community will undoubtedly help recruitment.

Ad26 has lower efficacy than the messenger RNA vaccines. This may be affected by the location of the studies, but there is benefit regarding hospitalizations and death. There is also great benefit in no rate limiting storage or transportation requirements and a one dose regimen, although the results of two dose studies will be very important. And I also share Dr. Offit's concerns about two dose vaccine regimen.

Hopefully, efficacy in people 60 and over with, quote, comorbidities will be confirmed. Thromboembolic events possibly related to the use of Ad26 is concerning and should be followed carefully. The sponsor will also be studying real world effectiveness and evolving viral variants using genetic

sequencing and immunogenicity data. The FDA should require specific duration entrant's admission in the studies. The Agency should also make similar study recommendations for all the above for future studies and further address both authorization, BLA and post marketing requirements.

The FDA's planned guidance update is a great start. I'm committing to using every opportunity to stress for the record that the government must address both vaccine hesitancy issues and vaccination access digital divide issues to promote trust and enroll more people of color and other underrepresented people in vaccine trial. To do otherwise would be a disgraceful continuation of generational neglect. Once again, I'd like to thank the FDA for their tireless work and VRBPAC members for your dedicated service and commitment and for the opportunity to comment.

DR. PRABHA ATREYA: Thank you, Ms. Dee. The next speaker is Ms. Nissa Shaffi.

MS. NISSA SHAFFI: Yes, good afternoon. I'm Nissa Shaffi. I'm present today on behalf of the

National Consumers League. I have no conflicts of interest to disclose.

Our organization extends its gratitude to the Vaccines and Related Biological Products Advisory Committee for the opportunity to amplify consumer voices regarding Janssen Biotech COVID-19 vaccine. For over 120 years, NCL has championed efforts to increase vaccine education, safety, and access for consumers. As consumer advocates, we thank that Food and Drug Administration for their commitment to fostering public trust throughout the development and approval of a vaccine for COVID-19. We were also encouraged by the transparency and opportunities for engagement afforded to the public during this process.

Consumers are relying on the FDA more than ever for guidance pertaining to treatments for COVID-19, and preserving their confidence in the Agency is of vital importance at this time. Emergency Use Authorization, while not intended to replace randomized clinical trials, has been a critical component to the nation's pandemic strategy. NCL appreciates the FDA's

recognition of clinical trials as a vital component to demonstrating safety and efficacy of a treatment.

We are encouraged by reports indicating that the Janssen Biotech vaccine has proven to be effective against hospitalization and death from COVID-19. The added benefit of another vaccine is to decrease virus mutation. Presently, three far more contagious variants of COVID-19 spreads and enhance our efforts to quell the virus. We are reassured that the Janssen vaccine has demonstrated efficacy against certain variants. As new data is collected, we call on the FDA to perform post-market surveillance to monitor ongoing efficacy. Vaccine efficacy and social determinates of health remain critical obstacles in the vaccine roll out process. The Janssen Biotech single shot vaccine has the potential to increase access for hard-to-reach communities, bringing us closer to heard immunity.

This week we marked a grim milestone as half a million Americans have now perished from this relentless virus. Amidst this last but continued development of vaccines for COVID-19 has provided the

nation with much needed hope and respite. As the Committee deliberates on the Janssen Biotech COVID-19 vaccine, we request the Agency to consider the benefits of its release for historically disadvantaged communities for which this vaccine would be logistically more acceptable than the prior two vaccines.

Thank you to the Committee for your considerations of our views, your consumer education work. NCL will continue to support the FDA in its efforts to develop a safe, effective, and expedited pathway for the vaccine for COVID-19. Thank you.

DR. PRABHA ATREYA: Thank you, Ms. Shaffi. The next speaker is Dr. Peter Doshi.

DR. PETER DOSHI: Hello and thank you. I'm Peter Doshi. I'm on the faculty at the University of Maryland and a medical journal editor at the *BMJ*. I have no relevant conflicts of interest. No one's paid for my attendance, and these comments are my own.

First point, I'm nervous about the prospect of there never being a COVID vaccine that meets the FDA's

approval standard. The Agency has already authorized two COVID vaccines as meeting the EUA standard of "may be effective." Granting another EUA to Janssen would begin to create a kind of marketplace of vaccines good enough to be authorized but never approved. The briefing documents say that Janssen's seeking an EUA, but they don't say why. My question is if Janssen is fully confident in the data, why not seek a full approval, a BLA?

Looking forward, I worry about FDA lowering its approval standards. Last June, FDA outlined its expectations for an approvable vaccine saying participant follow up should continue, quote, for at least one to two years. We know Moderna and Pfizer can't meet this standard as placebo recipients are already being vaccinated, and in its briefing document Janssen says that if an EUA is granted, they will unblind their trial.

It's quickly seeming that the only way a vaccine will ever be approved is if FDA lowers its standards to the "may be effective" standard of the

EUA. Is this what we want? If the FDA now believes that a few months of follow up is sufficient to be certain benefit outweighs risk, the Agency needs to tell us why it changed its mind. We thankfully have a waning epidemic in the U.S. right now, and manufacturing capacity of already EUA vaccines continues to grow. The argument that we don't have the luxury of time to demand better evidence doesn't hold as much water as it might have two months ago.

Second, I worry about process. The way it's supposed to work is the FDA asks the Advisory Committee for its honest, independent view, but the media reporting on this suggests an EUA is a foregone conclusion. I want to know if FDA is doing anything to ensure Advisory Committee members can truly vote their mind and not bow to the pressure that there's only one right decision.

Third, it's unreasonable to accept Janssen's labelling of its primary endpoint "moderate to severe critical COVID-19" because it includes what most would call mild disease. A lab positive test plus two

symptoms like cough and headache would be sufficient. Everyone knows that the majority of COVID cases are mild. Yet, it Janssen's trial there were only four cases of mild COVID compared with 390 so-called moderate cases, see page 17. Clearly Janssen's "moderate" is what everybody else would call mild.

The case definition of severe COVID also needs scrutiny as PCR positive cases with no other symptoms other than blood oxygen saturation of 93 percent or less would qualify. There's a real urgency to stand back right now and look at the forest view as well as the trees, and I urge the Committee to consider the effect FDA's decisions may have on the entire regulatory approval process. Thank you.

DR. PRABHA ATREYA: Thank you, Dr. Doshi. The next speaker is Dr. Robert Kaplan.

DR. ROBERT KAPLAN: -- faculty member at the -- hello, this is Robert Kaplan. I am a distinguished professor emeritus at the UCLA Fielding School of Public Health, and I'm also a faculty member at the Clinical Excellence Research Center at the Stanford

University School of Medicine. I'm employed by Stanford, and they have no conflicts of interest to report.

With colleagues I've reviewed the data prior to the EUA hearings for Johnson, Pfizer, and the Moderna vaccines. We consider this to be part of our responsibility as academic research scientists, but as interested scientists we have some concerns. The public has been saturated with non-peer reviewed press releases that shape public opinion and have created very high expectations. We believe that constructive feedback improves and clarifies data interpretation. The scientific community has embraced an open data movement that emphasizes posting of data for re-analysis by independent scientist like us.

None of these safeguards are in place with the EUA reviews. The briefing document is excellent, but it raises many questions, which various colleagues have commented on today. We have concerns because EUAs are for emergencies, and they should be temporary. EUA might use a lower standard to speed early

dissemination, but continuing the use should depend on emerging data. The trials have included between 30,000 and 44,000 participants, large sample sizes.

However, we have more experience. 66 million doses have now been administered in the U.S., yet we don't have access to data on how many people have been infected post-vaccine. We have minimal information about serious adverse reactions outside of trials. Now, v-safe and VAERS certainly are a step in the right direction, but they don't use representative samples from the population.

So what needs to be done? First, we need more transparency. Some of the vaccines have been developed at public expense and are being paid for using public resources. Therefore, the data should be made public. We need independent analyses by investigators who are not employed by the manufacturers. Importantly, the data must be available more than 48 hours prior to these hearings.

Second, the public access surveillance system should be a condition of the EUA. During the EUA,

there should be continuous monitoring post-vaccination for COVID cases, deaths, and serious adverse reactions. This could be done on a population basis or based on true representative samples of vaccine recipients.

And third, we need to preserve control groups. There's been a precipitous decline in COVID cases in countries that have and have not started vaccine programs. Without control groups, we won't be able to figure out causation. In the interest of transparency, please remember that if it is in the public interest it should be in the public domain. Thanks again for listening today.

DR. PRABHA ATREYA: Thank you, Dr. Kaplan. The next speaker and the last speaker of the open public hearing session is Mr. Michael Ward.

MR. MICHAEL WARD: Hello and good afternoon. My name is Michael Ward, and I am the vice president of public policy at the Alliance for Aging Research. I have no financial conflicts to disclose. The alliance is one of three convening members of the COVID-19 Vaccine Education and Equity Project, along with

Healthy Women and the National Caucus and Center on Black Aging. As you can see at COVIDvaccineproject.org, we are joined by more than 175 leading organizations representing a wide range of patients, professionals, and diverse communities.

We are focused on promoting widespread and equitable access to COVID-19 vaccinations and information, especially in hard hit communities. As an organization committed to advocating on behalf of older Americans, the Alliance is thankful that the scientists and researchers at Janssen have successfully developed a safe, effective vaccine. Moreover, we appreciate that individuals aged 60 and older and people of color were prioritized in study design, resulting in significant enrollment of clinical trial participants from groups disproportionately susceptible to severe outcomes and death from COVID-19.

We are impressed that the vaccines thus far have been so effective. However, the primary endpoints in the Janssen trial differ from previously authorized COVID-19 vaccines, as did levels of community

transmission and the documented presence of emerging variants during the trial period. We hope the FDA and other agencies within HHS will work with us and others to shape messaging and communicate the encouraging takeaway that all FDA authorized vaccines will prevent many from contracting SARS-CoV-2 and prevent most serious medical complications arising from COVID-19.

Further, the ability of the Janssen vaccine to provide protection against severe disease and death resulting from the B1351 variant is critical. We also appreciate the preliminary data made available by Janssen regarding the impact of a range of comorbidities on efficacy. We encourage monitoring for the age 60 and older population that has pre-existing conditions, especially hypertension and diabetes, across all COVID-19 vaccines with larger subgroups of patients. Such comorbidities are endemic, and proving the understanding of the influence of these comorbidities will be helpful not only for the Janssen vaccine but as other COVID-19 vaccines are developed and updated.

Janssen is conducting a second clinical trial to test the two-shot regimen of this vaccine. As Dr. Offit noted this morning, stakeholders should begin evaluating policy issues now around the results of the ongoing ensemble 2 trial. For example, as the two-shot regimen induces an enhanced level of protection, will patients who received a single shot be given the option to receive a second shot? What level of enhance protection will merit reserving a percentage of available vaccine to enable distribution of a second shot given current excess demand? These are not easy questions but ones worth considering as soon as possible.

In conclusion, the Alliance is thankful that an additional tool may be hopefully available soon in our fight to end this pandemic. We encourage the Agency to work in concert with colleagues throughout HHS to advance public confidence and ensure equitable vaccine access. Thank you.

DR. PRABHA ATREYA: Thank you, Mr. Ward. This concludes the Open Public Hearing session, and then we

will go into the regular session. Dr. Monto, would you introduce the next speaker, Dr. Rachel Zhang and Dr. Yosefa Hefter? Thank you very much.

DR. ARNOLD MONTO: Yes, it's my pleasure to introduce for the FDA presentation and describing the voting questions which will follow our discussion -- the FDA presentations are being given by Rachel Zhang and Yosefa Hefter. Please.

FDA PRESENTATION AND VOTING QUESTIONS

DR. RACHEL ZHANG: Thank you very much. All right. So first I'll give a brief introduction of the Janssen COVID-19 vaccine and take you through the clinical development program to date. Then, we will take a closer look at the efficacy data from the phase 3 study. Then, I'll turn it over to Dr. Hefter to take you through the safety data, the pharmacovigilance plan, and summarize the benefit-risk assessment in context of the proposed use under EUA.

So the Janssen COVID-19 vaccine is a

recombinant replication-incompetent adenovirus type 26 vectored vaccine which encodes the SARS-CoV-2 spike protein. Produced in PER.C6 cells, the vaccine's administered intramuscularly, a single dose regimen at the dose of $5x10^{10}$ viral particles. The proposed indication under EUA is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older.

Shown here are the ongoing studies for the Janssen COVID-19 vaccine. All the studies are randomized, double blinded, and placebo controlled. I will give you a brief overview of each study, except for study 1002, which is a phase 1 non-U.S. IND study, and then focus on study 3001, which is the study submitted to support the EUA application.

Study 1001 is an ongoing phase 1/2 safety and immunogenicity study in approximately 1,000 participants with two-thirds of the participants between the ages of 18 to 55 and one-third 65 years of age and older. The study assessed two dose levels and a one and two dose vaccination regimen. Interim study

results showed that a single dose at $5x10^{10}$ viral particles was able to induce SARS-CoV-2 binding and neutralizing antibodies in both age cohorts.

There was a Th1-skewed CD4 T-cell response solicited. The safety profile supported further clinical development, and results from this phase 1 study, are (inaudible) for further initiation of the phase 3 study 3001. The study was initiated on July 22nd, 2020. Review of the SAEs from studies up to the time of the EUA request revealed no safety concerns to date.

Study 2001 is an ongoing phase 2 study in healthy adults and adolescents. Enrollment of the adolescent cohort has not yet started. Four different dose levels will be tested in this study at both one and two dose regimens. Interim immunogenicity assessments at day 29 show the vaccine elicited SARS-CoV-2 neutralizing antibodies in the adult cohort consistent with results from study 1001. This study was initiated on August 31st, 2020, and review of SAEs from this study up to the time of EUA submission

revealed no safety concerns to date.

Study 3009 is an ongoing phase 3 efficacy, safety, and immunogenicity study of a two-dose vaccine regimen spaced 56 days apart in approximately 30,000 participants. This will be a multinational study and will include sites in North and South America, Africa, Asia, and Europe. The study was initiated on November 16th, 2020, and enrollment is still ongoing. No safety concerns have been identified to date based on review of blinded SAE reports up to the time of the EUA submission.

3001 is the study used to support the EUA application. This is an ongoing phase 3 efficacy, safety, and immunogenicity study in 44,325 participants across the U.S., South Africa, and six countries in Latin America. Participants are stratified by two pre-specified age cohorts and randomized one to one to receive a single dose of vaccine at $5x10^{10}$ viral particles or a saline placebo. Enrollment was staggered in stages based on age and comorbidity so that participants without comorbidities were enrolled

earlier than those with comorbidities. The protocol specified that at least 30 percent of the study population would be participants 60 years of age and older. The study was initiated on September 21st, 2020, and the total planned study duration is two years.

This slide summarizes the scheduled visits and assessments for study 3001. Primary analysis was triggered on January 22nd when there was a median follow up of 58 days in the overall study population. Active surveillance for COVID-19 is conducted via an e-diary with prompts twice weekly for the first year of the study and then bi-weekly thereafter. Solicited local and systemic adverse reactions are collected for seven days post-vaccination, and unsolicited adverse events through 28 days post-vaccination in the safety subset. All participants will be followed for medically attended AEs for the first six months after vaccination, and SAEs and medically attended AEs leading to study discontinuation will be followed for the entire study duration of two years. Blood samples

will be collected at scheduled visits for immunogenicity assessments and for the asymptomatic infection endpoint.

Shown here are the case definitions for moderate COVID-19, which is a positive SARS-CoV-2 PCR plus any one of the following new or worsening respiratory symptoms as listed on the left-hand side or any two of the following new or worsening systemic symptoms as listed on the righthand side. The case definition for severe/critical COVID-19 is defined as a positive SARS-CoV-2 PCR plus any one of the following new or worsening signs or symptoms as listed in the box with a specific parameters for each further specified in the protocol. All cases meeting the severe/critical definition and all cases meeting the moderate case definition as shown in the previous slide that included more than three signs and/or symptoms were evaluated by an independent blinded adjudication committee. Only cases adjudicated as severe by the adjudication committee were included in a severe/critical COVID-19 endpoint.

The study included co-primary efficacy endpoints of vaccine efficacy to prevent protocol defined moderate to severe/critical COVID-19 confirmed by the central laboratory occurring at least 14 days and at least 28 days after vaccination. The original study protocol had a single primary endpoint of onset at least 14 days after vaccination, and a 28-day endpoint was added as a co-primary endpoint in December while the study was ongoing.

The primary efficacy success criterion if met is a null hypothesis of VE less than or equal to 30 percent is rejected and the VE point estimate of 50 percent or greater for both co-primary endpoints. The primary efficacy analysis would be triggered with an accrual of at least 42 moderate to severe/critical COVID-19 cases, at least six moderate to severe/critical COVID-19 cases among participants 60 years of age and older, and at least five severe/critical cases of COVID-19 in the placebo group with a favorable vaccine to placebo split for both primary endpoints. To align with the median follow up

requirement as specified in FDA's guidance document, the primary analysis was not conducted until at least 50 percent of the participants in the study have had eight weeks follow up post vaccination.

Secondary endpoints evaluated in the study include vaccine efficacy to prevent any symptomatic COVID-19, including mild, moderate, and severe disease, COVID-19 per FDA harmonized case definition; efficacy against severe/critical COVID-19; COVID-19 requiring medical intervention; COVID-19 related death; and asymptomatic COVID-19 as inferred through seroconversion using serology against a nucleocapsid protein. The protocol specified that COVID-19 cases diagnosed by a positive SARS-CoV-2 PCR obtained using an FDA authorized test at a local laboratory be sent to the central laboratory at the University of Washington for confirmation. The statistical analysis plan further stipulated that the primary analysis would be triggered and based on the centrally confirmed cases at the time of data cutoff. Due to the high incidence rate of COVID-19 during the study, not all positive PCR

test accrued by the time of the trigger for the primary analysis had been confirmed by the central laboratory.

At the time of the primary analysis, about 70 percent of the accrued cases have undergone the central confirmation process. Another 18 percent were in the shipping process, and 12 percent were received by central laboratory but still being processed. At the time of the data cutoff, there was high concordance observed between the local PCR results and central lab confirmation at around 90.3 percent. The majority of discordant cases were those with low viral loads, which may have been impacted by the freeze-thaw cycle during the shipping process. In today's discussion, we will present only results from centrally confirmed cases for the primary efficacy analysis as specified by the protocol. For subgroup analyses, we will also include results from those cases of positive PCR from a local laboratory and still awaiting confirmation by the central laboratory to increase the number of cases and the precision of the estimates.

The study analysis populations are shown in

the table on this slide. The full analysis set included all randomized participants with a documented study vaccine administration. The per-protocol set used for the efficacy analysis included all participants in the full analysis set who had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The safety subset is a subset of participants used for the analysis of solicited adverse reactions and unsolicited adverse events through 28 days post-vaccination.

At the time of the primary analysis, the median follow up duration for all participants in the efficacy and safety analysis populations was eight weeks post vaccination. Phased enrollment by age group and comorbidity resulted in differences in follow up duration between participants in these groups with approximately a two-week difference in the median follow up time between the first group enrolled, which are trial participants 18 to 59 without comorbidities, and the last group enrolled, which are participants 60 years and older with comorbidities.

Next, we will take a closer look at the efficacy results from study 3001. This table shows the demographic characteristics of the per-protocol set, which was the population used for the analysis of efficacy. The demographic characteristics among vaccine and placebo participants were similar. The median age in the study was 53 with about 20 percent of participants 65 years of age and older. There was a slightly higher percentage of males compared to females. 62 percent of participants were white. 17 percent were Black or African-American; 8 percent Alaska native or American Indian, including American Indians from Latin America countries; 3 percent Asian; and 0.3 percent native Hawaiian or Pacific Islander.

In terms of ethnicity, 45 percent identified as Hispanic or Latino. About 47 of participants are in study sites in the U.S., 40 percent in Latin America countries of which a majority are in Brazil; and about 13 percent in South Africa. About 40 percent of participants had one or more comorbid conditions associated with an increased risk of progression to

severe COVID-19 as listed by the CDC at the time of study initiation. Overall, the demographics in the U.S. participants in the study are similar to the global demographics as shown in these slides, except for some variations in race and ethnicity composition.

This table shows the disposition of the participants from the study. The proportion of participants excluded from the per-protocol set were balanced between the treatment groups with the vast majority of those excluded due to positive baseline SARS-CoV-2 status. Overall, few participants were discontinued or lost to follow up.

As of the data cost date for the primary analysis, 5.3 percent of participants in the vaccine group and 5.8 percent of participants in the placebo group were unblinded by request as they became eligible to receive an authorized COVID-19 vaccine under EUA. A slightly greater proportion of participants 60 years of age and older were unblinded at 6.6 percent compared to those 18 to 59 years of age at 4.4 percent. And the vast majority, about 93 percent of participants who

were unblinded, were from U.S. study sites.

Shown here are the co-primary efficacy endpoints of protocol defined moderate to severe/critical COVID-19 confirmed by the central laboratory with onset at least 14 days and at least 28 days after vaccination. In the overall study population, vaccine efficacy after 14 days was 66.9 percent, with a lower bound of 59, and 66.1 percent, with a lower bound of 55 after 28 days. Efficacy for the two pre-specified age cohorts of 18 to 59 and 60 years and older were comparable with the efficacy in the overall population.

For the subgroup analyses, centrally confirmed cases as well as cases with positive local PCR which are still awaiting confirmation by the central lab were included. As shown here, efficacy was similar across different age groups and sex. There was some variation in efficacy across geographic regions, which will be discussed in further detail in a later slide. Efficacy across race and ethnicity were generally consistent with that observed in the overall study population, but

a small number of participants and cases of some racial groups resulted in large confidence intervals around a point estimate and limited the interpretation of those results.

When looking across age groups and comorbidities, there was a lower efficacy point estimate observed in the subgroup of participants 60 years of age and older with comorbidities with onset at least 28 days after vaccination. However, the confidence intervals are wide, and the uncertainty of the point estimate is large. This wide confidence interval may be attributable to a lower number of cases due to the shorter follow up duration in this subgroup compared to the other subgroups and with a slightly greater proportion of participants in this subgroup who were unblinded due to eligibility for an authorized COVID-19 vaccine under EUA compared to the younger cohorts. There was also overall a smaller number of participants in this subgroup compared to the other subgroups.

The VE estimate increased, and the confidence

interval narrowed as the number of cases included in this analysis increased. For example, when looking at the VE at the 14-day endpoint, which included all cases in the 28-day endpoint, and when comparing centrally confirmed cases only to this analysis which includes non-centrally confirmed cases as well, this indicates that the apparent lower VE in this subgroup potentially reflects imprecision associated with a smaller number of cases.

There was a lower efficacy estimate for participants with comorbidities compared to those without but only for the endpoint of onset at least 28 days post vaccination, which, similar to what was discussed in the last slide, may be reflective of a smaller number of cases. For a majority of individual comorbid conditions, interpretation of the results is limited by the small sample size, low incidence of COVID-19 in the subgroup. However, for subgroups with higher incidence of COVID-19, such as in participants with obesity, the VE appeared to be similar to the VE estimate in the overall study population.

The study included a little more than 4,000 subjects who were SARS-Cov-2 seropositive at baseline. The number of cases observed in this subgroup was small, and at this time there is insufficient data to evaluate vaccine efficacy in previously infected individuals. Efficacy against any symptomatic COVID-19, including mild disease, and efficacy based on a less restrictive case definition -- the FDA Harmonized case definition -- with onset at least 14 days or 28 days after vaccination were overall similar to results obtained for the primary efficacy analysis of efficacy against moderate to severe/critical COVID-19. There were only four centrally confirmed mild COVID-19 cases, one in the vaccine group, three in the placebo group with onset at least 14 days post vaccination indicating that the moderate to severe/critical primary efficacy endpoint definition captured almost all cases of symptomatic COVID-19.

Vaccine efficacy against centrally confirmed adjudicated severe/critical COVID-19 cases in the overall study population with onset at least 14 days

after vaccination was 76.7 percent, with a lower bound of 54.6, and 85.4 percent, with a lower bound of 54.2 after 28 days. Point estimates of efficacy against severe/critical disease were lower with wide confidence intervals in participants 60 years of age and older compared to the younger participants when evaluating only centrally confirmed cases. When non-centrally confirmed cases were also included, the VE estimate for participants 60 years of age an older increased, and the confidence interval narrowed and was more similar to the efficacy estimates for the younger cohort and the overall population.

The endpoint of COVID-19 requiring medical intervention is defined as participant requiring hospitalization, ICU admission, mechanical ventilation, and/or ECMO. A post-hoc analysis of all COVID-19 related hospitalizations was performed by counting all hospitalizations recorded in medical resource utilization forms, SAE forms, and clinical event listings such as during a severe/critical COVID-19 episode, in the setting of a positive PCR at the onset

of the COVID-19 episode or onset of the adverse events. These date indicate vaccine efficacy and a prevention of severe COVID-19 requiring medical intervention with no COVId-19 related hospitalizations seen in the vaccine group following 28 days after vaccination. In the subgroup of participants 60 years of age and older with comorbidities, after 14 days post-vaccination two out of the 22 moderate to severe COVID-19 cases in vaccine recipients resulted in hospitalization, both prior to 28 days, compared to 11 hospitalizations out of 53 cases in the placebo recipients with five occurring after 28 days.

As of February 5th, 2021, which is an additional two weeks after the primary analysis data cutoff date, there were a total of 25 deaths reported in this study, with five in the vaccine arm and 20 in the placebo arm. Of these, there were seven COVID-19 related deaths all in participants in the placebo group and from study sites in South Africa. One death was in a participant who was SARS-CoV-2 PCR positive at baseline and who developed symptoms ten days after

vaccination. As you can see in this table, all subjects had one or more comorbidities, which may be associated with an increased risk of more severe COVID-19.

Asymptomatic infection was defined as a participant who does not fulfill criteria for suspected COVID-19 based on signs and symptoms and has a positive SARS-Cov-2 PCR or developed a positive serology based on SARS-CoV-2 nucleocapsid serology during the study. There is no scheduled PCR screening specified in the protocol, so most of the data would be based on N-serology collected at scheduled time points.

Based on available day 29 N-serology data, efficacy for this endpoint was modest with wide confidence intervals across from zero. Day 71 N-serology results are only available from a subset of approximately 2,800 subjects, which is a very small proportion of the overall study population. Available serology is also not evenly distributed across demographic groups and geographic locations. Data's limited at this time to make a conclusion about vaccine

efficacy against asymptomatic infection, and also note that the protocol specified this endpoint will only be evaluated once 15,000 samples from day 71 are accrued. So what is done has been an interim analysis.

During the conduct of this study from study initiation on September 21st through the data cutoff date of January 22nd, new SARS-CoV-2 variants emerged in geographic regions where the study took place. In a subsequent analysis of vaccine efficacy against moderate to severe/critical COVID-19 in the United States, South Africa, and Brazil there was lower efficacy observed in South Africa compared to the United States. Vaccine efficacy against severe/critical COVID-19 was comparably high across the three countries, although, there was a wide confidence interval around the point estimates for United States and Brazil.

Doing sequencing of COVID-19 cases in the study to inform the vaccine efficacy analysis by region is incomplete at this time. As of February 12th, 71.7 percent of cases which had been centrally confirmed by

the data cutoff date of January 22nd have been sequenced. Only samples with a sufficient viral load were able to be sequenced. Prioritization for sequencing was given to moderate to severe/critical cases and cases with onset at least 14 days after vaccination. As of February 12th, there were no cases identified from the study to be from B.1.1.7 or P.1 lineages.

In the United States, 73.5 percent of cases have been sequenced, of which 96 percent were identified as the SARS-CoV-2 Wuhan H1 variant D614G. In South Africa, 66.7 percent of cases have been sequenced of which 94 percent were identified as the B1351 variant. In Brazil, 69 percent of cases have been sequenced of which 69 percent were identified as the variant of the P2 linage and 30 percent were identified as the Wuhan variant. Because strength sequencing of COVID-19 cases in the study is incomplete at the time of this analysis and due to selection bias involved in prioritizing the cases to be sequenced first, vaccine efficacy against the specific SARS-CoV-2

variants cannot be evaluated at this time.

So in summary, the data from the primary efficacy analysis with the cutoff date of January 22nd, 2021 and the median follow up for efficacy of eight weeks post vaccination met the pre-specified success criteria established in the study protocol. Efficacy of the vaccine to prevent protocol defined moderate to severe/critical COVID-19 occurring at least 14 days after vaccination was 66.9 percent with a lower bound of 59 and 66.1 percent with a lower bound of 55 at least 28 days after vaccination. Efficacy against a key secondary endpoint of prevention of severe/critical COVID-19 was 76.7 percent with a lower bound of 54.6 for onset at least 14 days after vaccination and 85.4 percent with a lower bound of 54.2 for onset at least 28 days after vaccination.

There was efficacy against COVID-19 requiring medical intervention with two COVID-19 related hospitalizations in the vaccine group after 14 days compared to 29 in the placebo group. After 28 days, there were no COVID-19 related hospitalizations in the

vaccine group compared to 16 in the placebo group. Efficacy outcomes across demographic subgroups are generally consistent with the efficacy seen in the overall study populations. Although, vaccine efficacy in participants 60 years of age and older was overall similar to observed in younger participants, a lower efficacy estimate against prevention of COVID-19 with onset at least 28 days was seen in the subgroup of participants 60 years of age and older with comorbidities. However, for this and several other subgroups the VE estimate increased and the confidence interval narrowed with inclusion of more cases indicating that the observed results potential reflect imprecision associated with a smaller number of cases in this subgroup. This vaccine was effective in reducing COVID-19 related hospitalizations in this subgroup.

Finally, there was country to country variation in vaccine efficacy in the setting of different predominant variant strains circulating around the time of the study, so the confidence

intervals were overlapping. And efficacy was more similar across countries when evaluating the endpoint of prevention of severe/critical COVID-19. So with that, I will turn it over to Dr. Hefter who will take you through the rest of the presentation.

DR. YOSEFA HEFTER: Thank you, Dr. Zhang. I want to start by going over the safety monitoring in study 3001. This is a graphical depiction of the monitoring throughout the study. Solicited adverse reactions were collected via an e-diary for seven days after vaccination in the safety subset, which included 6,736 participants. Unsolicited adverse events were also collected in the safety subset for 28 days after vaccination and recorded in electronic case report form at the day 29 visit.

Medically attended adverse events are captured through six months post vaccination. Serious adverse events and adverse events leading to study discontinuation are captured through the entire study period. In addition, spontaneous reports of AEs to investigators regardless of seriousness or severity

were recorded in the case report form at any time. The arrow in the middle of this slide marks the approximate safety evaluations completed prior to the data cutoff point.

Here we have the disposition in the safety population. This is overall similar to what was previously presented by Dr. Zhang for the efficacy population. Follow up duration, unblinding to treatment and discontinuations occurred at similar rates between treatment arms. In the safety subset, the population for analysis of solicited and unsolicited adverse events was about 15 percent of the total safety population. 99.9 percent of individuals in the safety subset completed follow up through day 29.

Subjects in the safety subset were enrolled in three tier one countries. The tier one countries were selected based on rapid startup capacity and protected incidence rates for COVID-19 that would allow for rapid efficacy signal detection. At the site level, investigators questioned participants on their

willingness to be part of the safety subset. Selection and randomization of the participants was then completed through a web-based randomization system.

The demographics of the subset were similar to those of the entire safety population, the full analysis set, with respect to sex and age. However, a larger percentage of participants in the safety subset were white, 83.4 percent, compared to the full analysis at 58.7 percent. Geographically, the safety subset was limited to the participants in the United States, South Africa, and Brazil. Fewer participants in the safety subset compared to the full analysis set were seropositive at baseline, 4.5 percent compared to 9.6, and had at least one comorbidity, 34.1 percent versus 40.8.

Here you can see the rates of solicited local reactions broken down by age group. The most commonly reported solicited local reaction was pain. Grade 3 events were rare for solicited local reactions. Overall, there was a lower rate of solicited reactions in the older cohort compared to the younger age group.

Among participants in the vaccine group, the overall rate of local adverse reactions was similar between those who were seronegative for SARS-CoV-2 at baseline and those who were seropositive. The same was true for each individual adverse reaction.

Here are the rates of solicited systemic reaction also broken down by age group. The most commonly reported solicited systemic reactions were headache, fatigue, and myalgia. These systemic reactions were Grade 3. Again, you can see that the rates were higher in the younger cohort compared to the older cohort. As with the solicited local reactions, for systemic reactions in vaccine recipients there was no significant difference among those who were seropositive or seronegative at baseline.

This is a broad overview of all unsolicited adverse events collected through the protocol specified method. Overall, rates of medically attended adverse events and serious adverse events were balanced between groups. This remained true when you looked by age cohorts as well.

Through the data cutoff, 19 deaths were reported with three in the vaccine group. There were no vaccine related deaths. There were also no AEs that lead to study discontinuation. Unsolicited AEs within the safety subset were reported at similar rates in the 28 days following vaccine, 13.1 percent in the vaccine group and 12 percent in the placebo group.

This table shows the breakdown of unsolicited AEs in the first 28 days in the safety subset by system organ class and preferred term. Events that occurred in at least 1 percent of vaccine recipients are included. By preferred term, the most commonly reported unsolicited adverse event in the vaccine group was chills. As this was not recorded in the solicited adverse reaction, this may represent vaccine reactogenicity.

FDA conducted standard measure queries, or SMQs, using FDA developed software to evaluate for constellations of unsolicited adverse events. The SMQs were conducted on adverse events that could represent various conditions, including but not limited to

allergic, neurologic, inflammatory, and autoimmune disorders. The SMQs were conducted on all adverse events that were reported in the full analysis set. These included adverse events collected through protocol specified method as well as voluntary reports from participants.

Here we highlight several adverse events which had a higher frequency in the vaccine group compared to placebo. Under the SMQ of embolic and thrombotic events, there was a small imbalance of cases reported in the vaccine group compared to the placebo group. This imbalance was driven by genus events. Specifically, deep vein thrombosis was reported in six vaccine recipients compared to two placebo recipients. Five events in the vaccine group and two events in the placebo group were within 28 days of vaccination.

Pulmonary embolism was reported in four vaccine recipients and one placebo recipients. Two events in the vaccine group and the event in the placebo group were within 28 days. There was one report of sinus venous thrombosis in the vaccine group.

Causality assessment of these events was confounded by the presence of underlying medical conditions and other risk factors in participants. As such, FDA's assessment is that vaccine cannot be excluded as a contributing factor to these events.

Tinnitus was reported in six vaccine recipients and no placebo recipients. Of the events in the vaccine group, three occurred on the day of vaccination or the day after. Of note, in the phase 1 study 1002 an FAE of hearing loss was reported in a 21-year-old who experienced sudden hearing loss associated with tinnitus on day 34. Hearing improved and the event resolved by day 69. Causality assessment of these tinnitus events was also confounded by the presence of risk factors in participants in study 3001. In FDA's assessment the vaccine cannot be excluded as a contributing factor to these events. Overall, rashes were reported more frequently in vaccine recipients than placebo recipients. Urticaria specifically was reported in five vaccine recipients compared to one placebo recipient in the seven days following

vaccination.

Moving to serious adverse events, according to study investigators seven serious adverse events were considered related to the vaccine. I will go through FDA's assessment of these events. In FDA's assessment, three of these events were considered likely related to the vaccine.

The first is a 42-year-old male who experienced hypersensitivity following the vaccine. On day three he began to have urticaria which became more confused over the following days. On day five, he had angioedema of the lips and reported sensation of an itchy tight throat. He did not experience any respiratory distress, and he was not hypoxic. The event did not meet branding criteria for anaphylaxis.

The second event was pain in the injected arm on day one which progressed to include more of the upper extremity. Electroconductive study conducted on day 15 showed intact sensor and motor nerves in the effected region and no degradation of muscles. The subject's symptoms as well as assessment were ongoing

at the time of data cutoff.

The third event was extreme generalized weakness in a 35-year-old male associated with multiple systemic symptoms including fever and headache. The subject was hospitalized for evaluation where a mild elevation in CPK consistent with myositis was noted and a demyelinating disorder was excluded. Symptoms resolved by day four.

Four SAEs were considered to have an indeterminate but not likely relationship to vaccine in FDA's assessment. This included two cases of facial paralyzes considered SAEs on the basis of medical importance by the investigator. These occurred on days three and 16. Two events of facial paralysis were also noted in the placebo group in a similar timeframe on days two and 29. One additional case of facial paralysis was reported in the vaccine group on day 19. However, review of the clinical information revealed no facial asymmetry as well as intact cranial nerves, making the diagnosis of facial paralysis unlikely.

Reports of Guillain-Barre syndrome were also

balanced between vaccine and placebo arms with one event happening in each group on days 16 and 10, respectively. There was a case of pericarditis in a 68-year-old male 16 days following vaccination. No etiology for the diagnosis was determined. While the vaccine cannot be excluded as the cause of this event, review of the Ad26 safety database did not reveal cases of pericarditis or carditis. In addition to the SAEs already mentioned, yesterday Janssen reported to the FDA that an anaphylactic reaction the details of which are still under investigation had occurred in an individual who received the Janssen COVID-19 vaccine as a participant in another ongoing study.

Prior to the data cutoff, 19 deaths were reported with three in vaccine group and 16 in the placebo group. An additional six deaths were reported between January 22nd and February 5th, two in the vaccine group and four in the placebo group. None of the deaths were considered related to the vaccine. The deaths in the vaccine group were as follows.

A 61-year-old was diagnosed with pneumonia on

day 13 and died on day 24. A 42-year-old individual with HIV was hospitalized with a lung abscess and died on day 59 following prolonged hospitalization. And a 66-year-old woke up with shortness of breath on day 45 and died prior to EMS arrival. No autopsy was performed, and a cause of death is unknown. The two deaths following data cutoff were also considered unrelated and included an individual who collapsed at home and an individual who died from decompensated heart disease. In the placebo group, six deaths prior to data cutoff and one following were related to COVID-19.

Any participants of childbearing potential were screened for pregnancy prior to vaccination. Participants were excluded if they were pregnant or planned to become pregnant within three months of vaccine administration. Eight pregnancies were reported through the January 22nd, 2021 cutoff, four vaccine and four placebo. In seven participants, vaccination was withing 30 days of the last menstrual period, and in one vaccine recipient vaccination was

prior to LMP. Among vaccine recipients, one spontaneous abortion and one ectopic pregnancy was reported. Two pregnancies were ongoing with outcomes unknown at this time.

To summarize the safety data, the information provided by the sponsor with safety data available in greater than 42,000 participants with a median safety follow up of 68 days was adequate for review and to make conclusions about the safety of the Janssen COVID-19 vaccine in the context of the proposed indication on population for intended use under EUA. Reactogenicity particularly injection site pain, headache, fatigue, and myalgias were frequent but mostly mild to moderate. Overall, less reactogenicity was seen in the age cohort 60 years and older. A single SAE of hypersensitivity was seen in the vaccine group, as well as more cases of urticaria. Finally, we noted numerical imbalances in thromboembolic events and tinnitus. The assessment of causality for these events was confounded by the presence of risk factors in participants, and vaccine cannot be excluded as a contributing factor to these

events.

We will now move to the pharmacovigilance plan and future studies. Janssen submitted a pharmacovigilance plan to monitor safety concerns that could be associated with the Ad26.COV2 vaccine. Important potential risks include vaccine associated disease, anaphylaxis, and thromboembolic events. Important missing information includes use in pregnancy and lactation, use in immunocompromised individuals, use in individuals with autoimmune or inflammatory disorders, use in frail individuals with comorbidity, interaction with other vaccines, long-term safety, and use in pediatrics.

Pharmacovigilance activities include adverse event reporting. Adverse event reporting under the EUA may come from vaccine recipients, vaccination providers, or the sponsor. First, vaccine recipients will be notified that AEs can be reported to VAERS through the factsheet for recipients and caregivers. Another source of AE reports from recipients is the v-safe program, which is a smartphone-based program that

uses text messaging and web surveys from the CDC to check in with vaccine recipients for health problems after vaccination.

Reports from vaccine recipients are voluntary. AE reporting by vaccine providers and the sponsor is mandatory. Both the sponsor and vaccine providers administrating the Janssen COVID-19 vaccine must report to VAERS the following information associated with the vaccine: vaccine administration errors, whether or not associated with an adverse event; serious adverse event irrespective of attribution to vaccination; cases involving inflammatory syndrome in children or adults; and cases of COVID-19 that result in hospitalization or death.

In addition, the applicant will also conduct periodic aggregate review of safety data and submit periodic safety reports at monthly intervals for FDA review. Each periodic safety report is required to contain a narrative summary and an analysis of adverse events submitted during the reporting interval, including interval and cumulative counts by age group,

special population, and adverse events of special interest, newly identified safety concerns in the interval, and actions taken since the last report because of adverse experiences. Both FDA and CDC will take a collaborative and complementary approach on reviewing AEs.

FDA will individually review all serious adverse events on a daily basis. FDA will also examine other sources for AEs, such as the literature, and will perform data mining to determine if AEs are disproportionately reported for the candidate vaccine compared to all other vaccines in VAERS. Any potential safety signals identified will be investigated.

The sponsor provided description of studies they are currently planning on conducting. These studies include completing a long-term follow up from ongoing clinical trials, as well as the following active surveillance study; a pregnancy study which will be conducted as a multi-country observational prospective cohort study of pregnant women vaccinated with Ad26.COV2.S in order to assess the occurrence of

obstetrical, neonatal outcomes among women administered the vaccine during pregnancy; an active surveillance study of safety which will be conducted as a retrospective, observational, propensity-scored matched cohort study using health insurance claims and electronic health records in order to assess the risk of developing prespecified adverse events of special interest during specific risk windows following administration of the Janssen COVID-19 vaccine. An active surveillance study of effectiveness will also be conducted as a retrospective observational propensity-scored matched cohort study using health insurance claims and electronic health records in order to estimate the effectiveness of Ad26.COV2.S to prevent medically attended COVID-19 in individuals who are vaccinated according to national immunization recommendations. The sponsor has provided protocols and milestone dates for these studies, and FDA is reviewing the protocols and will provide feedback.

Finally, I will review the overall risk-benefit assessment. The benefits of the Janssen COVID-

19 vaccine include reduced risk of symptomatic COVID-19 14 days following vaccination as well reduced risk of severe critical COVID-19 at least 14 days following vaccination. This includes a reduction in COVID-19 related deaths and hospitalization. The efficacy against severe critical disease was similar across demographic regions. Overall, the efficacy was generally consistent across demographic groups. Finally, as the vaccine is administered as a single dose, it may provide operational benefits to mass vaccination campaign.

The risks associated with the Janssen COVID-19 vaccine include reactogenicity, especially injection site pain, headache, fatigue, and myalgias. An SAE of hypersensitivity as well as nonserious urticaria were reported and likely associated with the vaccine. Finally, the vaccine cannot be excluded as a contributing factor to thromboembolic events and events of tinnitus.

There remain several data gaps and areas of unknown risk including the duration of protection;

efficacy against asymptomatic infection, transmission, and new variants; safety in subpopulations such as pregnant and lactating women, pediatrics, immunocompromised individuals, and individuals with SARS-CoV-2 infection; and information on adverse events that are uncommon or need longer follow up to detect. Finally, at this time the evidence suggests risk of vaccine enhanced disease is low, but a longer follow up duration is needed to fully assess this risk.

With that, I will conclude with the voting question for the VRBPAC members. Based on the totality of the scientific evidence available, do the benefits of the Janssen COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older? And that concludes my presentation.

DR. ARNOLD MONTO: Thanks to both of you. I must complement you not only on the presentation but on the briefing document, which was very comprehensive and easy to follow. Before we go on to a few questions, we're going to have a break. And then we're going to continue in the first part of the discussion with a

question period for both you if the members wish to do so and for others.

I wanted to ask you, Dr. Zhang, specifically about the difference between the endpoints "moderate" and "severe" versus the Harmonized case definition. There seemed to be only four cases that were different -- four additional cases. So can we conclude that really the moderate and severe case definition is just about equivalent to all asymptomatic cases?

DR. RACHEL ZHANG: Yes, you are correct, Dr. Monto. When looking at mild cases -- centrally confirmed mild cases, there are only four additional cases included, so really the efficacy estimates for moderate to severe were based on any severity or based on the FDA Harmonized definition was basically the same.

DR. ARNOLD MONTO: Okay. Could I ask your help? I'm having a technical issue right now.

MR. MICHAEL KAWCZYNSKI: Yup. The next person we have is Dr. Cody Meissner.

DR. ARNOLD MONTO: Okay. I'm back.

MR. MICHAEL KAWCZYNSKI: Go ahead and turn your camera on.

DR. CODY MEISSNER: Okay. I don't know if my video is on or not.

MR. MICHAEL KAWCZYNSKI: That's okay. Go ahead, Dr. Meissner.

DR. CODY MEISSNER: Okay.

DR. ARNOLD MONTO: We can hear you.

DR. CODY MEISSNER: Okay. Thank you. First of all, I want to make an acknowledgment, and then I have a question for the FDA. First of all -- let me get myself back in here. First of all, I want to second Dr. Monto's comment about the FDA. This has been an extraordinary amount of data that has been digested. I believe it was submitted to the FDA on February 4th, so that's 22 days ago. And to get all of this data in such a presentable form is remarkable, and I just want to thank -- I want to thank you all for what you've done, Dr. Zhang and Dr. Hefter and everybody else at CBER.

Second point I'd like to make briefly is there

were comments in the public hearing about wide confidence intervals in some of the endpoints. But remember that's inevitable. This was a very large study with over 43,000 subjects enrolled and randomized. And as you break down each group by smaller and smaller numbers, the confidence intervals are going to be wider because there will be fewer events.

So in view of the urgency of having information about an additional vaccine, I think the Janssen team has done a remarkable job in getting this data to us and to the FDA. And I think in particular their representation of different races in the trial is really -- I think it's the best that we've seen among the three submissions. So all I can say is I think a lot of people have done a remarkable job.

The question I have relates to study 2001, and, Dr. Zhang, I think maybe you can comment on this. There were 660 individuals 12 to 17 years of age who were enrolled in that safety and immunogenicity study. And I didn't see any suggestion of additional attempts

to generate efficacy data. And can you comment on how the FDA is going to deal with that information? Is that -- my concerns is that that should not be a basis on which an EUA should be administered to adolescents, or at least I think we have to exercise caution in using that as a sufficient basis to address an EUA. Over. Thank you.

DR. RACHEL ZHANG: Thank you for that question, Dr. Meissner. So just to clarify, the study 2001, the adolescent cohort has not yet been enrolled, so those subjects have not been included in the study yet. And that study is -- you're correct. It's just a safety immunogenicity study with secondary exploratory endpoints for efficacy to be included. And of course, we're still in discussion with all the sponsors about pediatric plans and what will be the basis for the indication down to those age ranges.

DR. CODY MEISSNER: Okay. Thank you. And who -- I'm sorry. Who was just speaking?

DR. RACHEL ZHANG: Oh, it was Rachel Zhang.

DR. CODY MEISSNER: Oh, okay. I guess it's a

delay.

DR. ARNOLD MONTO: Okay. Let's move on to Dr. Hildreth.

DR. JAMES HILDRETH: Yes. I have a question about the percentages of American Indians and Alaska Natives included in the trials. According to the data from the sponsor, on a global basis there were 10 percent of such individuals enrolled. When they showed the data for the U.S., it was only 1 percent, and I don't really understand how that can be -- they can have 10 percent on a global level, and it drops by 90 percent when you look at the U.S. itself. Can you explain that disparity to me, please? Thank you.

DR. RACHEL ZHANG: Thank you for that question. So yes, I think that the terminology may not be totally encompassing, but the American Indian/Alaska Native population shown in the slides includes the American Indian population in Latin American countries as well, so those populations in South America and Central America as well. So also, 1 percent, you're right, came from the U.S. study sites, and the rest are

from mostly the South American/Central American sites.

DR. JAMES HILDRETH: Okay. Thank you.

DR. ARNOLD MONTO: Okay. Two more questions and then we're going to go into our break. And at the discussion -- when the discussion starts, we'll have a free for all. We'll be asking questions both of you, FDA group, and also of the sponsor, so that's the only way we can attempt to stay on schedule. So next, Dr. Rubin.

DR. ERIC RUBIN: Hi, thanks. That was a terrific presentation, and I echo what everyone else said. Just a quick question about the testing, the PCR test isn't that complicated, and is it so important to have the centrally confirmed testing? How often were there discrepancies between what was acquired locally and the central adjudication?

DR. RACHEL ZHANG: Thank you for that question. So yes, the protocol was set out that way that all the tests should be shipped to University of Washington for central confirmation. When looking at the tests that had already undergone that central

confirmation process, there was a high concordance rate in the tests. So those tested positive in the local laboratory and those at the central laboratory is 90.3 percent.

So as mentioned in the presentation, most of the discordant results were those samples with very low viral loads and probably with a prolonged shipping time from some regions where the study was conducted to the University of Washington. The freeze-thaw cycle might have impacted those samples as well. But all of the tests used in the local laboratories were all FDA authorized tests as well.

DR. ARNOLD MONTO: Okay. Before the break, we'll hear Dr. Sawyer.

MR. MICHAEL KAWYCZYNSKI: Your mic may be muted, Dr. Sawyer. There you go. Go ahead.

DR. MARK SAWYER: My question relates to a slide in Dr. -- it's on the same topic of the PCR testing. It relates to a slide in Dr. Zhang's presentation as well as Table 18 in the briefing document. Although there's concordance, as you just

stated, in general between the testing done at the sites and the centrally confirmed testing, in this table all of the differences appear to be in the placebo group, which seems a little bit odd. Are we to interpret in general that one of these tests is more sensitive and the other is less specific, or how are you interpreting the differences?

DR. RACHEL ZHANG: I'm sorry. I'll have to find the table you're referring to, but the tests, as I mentioned, both used in the local laboratory and at the central laboratory, University of Washington, are all FDA authorized. And 99.9 percent sensitivity and I think similar specificity as well. So in terms of the samples analyzed, like I mentioned in the presentation and in our briefing document, there was some selection bias involved in which samples got sequenced first. So again, those samples with more severe cases, samples that had onset 14 days or after -- so treating the samples that would have met the primary endpoint basically were selected to be sequenced first to try to generate as much data as possible.

So because of the selection bias in prioritizing which samples were sequenced first -- sorry, now I'm talking about something else. We're talking about PCR results. So I apologize. I'll have to find the table that you're talking about, but I don't remember there being a very big difference between the vaccine and placebo groups in terms of PCR testing results.

DR. ARNOLD MONTO: Okay. Thank you. We're going to take a 10-minute break now. When we come back, we're going to be hearing from Dr. Peter Marks before we go into a general question and answer session, and I hope the Janssen team is also going to be available because the Committee has residual questions they want to ask. So 10-minute break. Thank you.

[BREAK]

COMMITTEE DISCUSSION AND VOTING

MR. MICHAEL KAWCZYNSKI: Just be a second as

we are going to come back. All right. Welcome back to our 164th meeting of the VRBPAC Advisory Committee. So, Arnold -- Dr. Monto, I'm going to hand it back to you.

DR. ARNOLD MONTO: Right. And it's my pleasure to introduce Dr. Peter Marks, the head of the Center for Biologics Evaluation and Research, familiarly called CBER. Dr. Marks.

DR. PETER MARKS: Thanks very much, Dr. Monto. So I just want to take a moment here for those who might not have been here this morning to thank everyone once again. I really want to thank the Committee members for the time in going through a lot of data. I also want to thank the sponsor for a very clear presentation and for their participation in this process, our public speakers, and the FDA staff who really have worked tirelessly over the past month after working the month before and the month before with these various Emergency Use Authorizations, so a tremendous amount of work and a tremendous amount of thanks to all of them.

I'll also call out the Advisory Committee staff. Dr. Atreya and her staff have done an incredible job putting together all the logistics here to make this happen. A lot of planning has to go into these meetings. And then having them get executed is really a lot, a lot of work. So thank you so much for all you've done here.

Just to finish off here, I just want to thank everyone from the Committee. We'll look forward to a very robust discussion this afternoon. We're looking forward to hearing the Committee's dialog, and I'm going to just turn it over to Dr. Monto now. Thank you so much and have a good rest of the afternoon discussion.

DR. ARNOLD MONTO: Right. Thank you, Dr. Marks. We're going to try to have some question and answers for a limited time. We'll say about 10 minutes to finish up the questions on the FDA report and then about 20 minutes questions for the sponsor that are hanging over since their presentation. So let's just go ahead, and I see Dr. Fuller's got her hand raised.

Dr. Fuller.

DR. OVETA FULLER: Amazing. I'm first in line. Look at that. Thank you, Dr. Monto. This is actually --

DR. ARNOLD MONTO: Sometimes you're lucky.

DR. OVETA FULLER: Look at that. Yes. This is for the Janssen group as well as for Dr. Marks. And I asked this question this morning. Clearly the reduction of disease and moderate to severe to hospitalization is critical for ending this pandemic, but in the long run we really do have to stop infection in order that we don't give the coronavirus the many opportunities to mutate and to actually adapt to get to a best fit for itself. So I want to commend Janssen for doing the global study including people around the world, but we know that nobody's going to be safe until we're all able to shut down the virus replication.

So in that light, what is happening with both the Pfizer and Moderna studies to follow the asymptomatic infections and shedding as well as for Janssen? What are you going to do? I think that was

in your Table 7.166. Could you tell us if you got additional data or you're planning -- what studies you're planning to follow the vaccine effect also on infection asymptomatically in shedding?

DR. ARNOLD MONTO: If I can -- right. If I can interrupt, I just -- this gives me the opportunity to give us all an admonition. We are reviewing the Janssen vaccine here, so we need to be very specific in what we are looking at. So when getting answers to your question, let's talk about what is going on with this vaccine. So FDA, I think you had mentioned --

DR. OVETA FULLER: My question includes this vaccine.

DR. ARNOLD MONTO: Right. This vaccine. Right.

DR. OVETA FULLER: Right. It includes this one --

DR. ARNOLD MONTO: FDA -- I understand there are global questions, but that's not our remit right now. Rachel?

DR. RACHEL ZHANG: All right. So I'll

actually defer to Janssen to talk about what their plans are in terms of asymptomatic infection and transmission studies.

DR. JOHAN VAN HOOF: Can I comment on this question?

DR. ARNOLD MONTO: Yes, please.

DR. JOHAN VAN HOOF: Yeah. So --

DR. ARNOLD MONTO: We try to be orderly, but things never turn out to be orderly during the discussion.

DR. JOHAN VAN HOOF: No problem at all. So as already discussed in the presentation, the way that we want to address this is to look at non-symptomatic seroconversion against N protein. As indicated, we do have preliminary data on that that actually are limited to about 1,300 samples in the placebo group and 1,300 samples in the active group. And where we do see that we have, depending on how you look exactly, about 70 percent -- we observed 70 percent efficacy.

However, we want also to stress that these are preliminary data, a point that was made also by the

colleagues from FDA. It's a limited number of samples, and also in the study protocol we have plans to do this once we have at least 15,000 people. And we look at the time point between day 29 and month six. So it is certainly part of our plan to continue to do this, to take those samples and to look at asymptomatic infection.

With the preliminary data that we have today, I come at this from two perspectives. On one hand, it suggests if it's confirmed then indeed it has impact on -- or it presents asymptomatic infection to the last degree. And the other point is that sometimes it was hypothesized that eventually you can shift all of your symptomatic patients into the non-symptomatic, so people without symptoms. In which case, you could eventually even increase transmission. And certainly, that seems not be to the case.

So completely, we have an active plan. We will do that based on seroconversion between day 29 and month six, and the preliminary data we have are very encouraging.

DR. OVETA FULLER: All right. Thank you.

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

DR. OFER LEVY: Yes. I wanted to thank the FDA representatives for their most recent presentation at this hearing. I had a general question. For some of the imbalances seen with adverse effect, such as tinnitus for example, I'm wondering whether FDA also looked at the broader pool of data for the AdVAC26 platform and whether that gave any guidance as to whether such imbalances were seen in other vaccine studies with the same adenovirus 26 platform. Thank you.

DR. YOSEFA HEFTER: Hi, yeah. Thank you for that question. So we did look across for tinnitus across the development program of the COVID-19 vaccine. Because it's reported as an AESI, it doesn't come up as a serious adverse event throughout. But there were no SAEs that were notable -- you know, that were reported aside from the one that I had previously mentioned that occurred in the phase 1 study and then one additional

event of tinnitus that occurred in the ongoing two dose study arm. And that remains blinded. I would defer to Janssen to report on the larger safety database for all of Ad26 vaccines.

DR. JOHAN VAN HOOF: We have indeed --

DR. ARNOLD MONTO: Go ahead. Go ahead, Dr. Van Hoof.

DR. JOHAN VAN HOOF: I just wanted to suggest to look into the platform database. We have actually done a screen on that particular phenomenon, tinnitus, and we have not seen that previously when we reviewed the platform.

DR. OFER LEVY: Thank you.

DR. ARNOLD MONTO: Okay. Thank you. Dr. Chatterjee.

MR. MICHAEL KAWCZYNSKI: Arnold, we had a little -- we have some question just to clarify. The questions right now are for FDA -- the FDA portion; correct? That's where we're focused right now.

DR. ARNOLD MONTO: We're trying to do that.

MR. MICHAEL KAWCZYNSKI: Okay. So if the FDA

representatives could both keep their cameras on, that would be great, and that would help guide -- there we go. Thank you.

DR. ARNOLD MONTO: To discipline the Committee is rather difficult. Dr. Chatterjee, is this for FDA?

DR. ARCHANA CHATTERJEE: Yes.

DR. ARNOLD MONTO: Okay.

DR. ARCHANA CHATTERJEE: So my question is I had trouble with the briefing document trying to distinguish between where the cutoff was for severe disease. Was it -- because the way the data were presented it was moderate to severe and then severe/critical. And so I couldn't figure out is this a continuum? Where's the cutoff?

DR. RACHEL ZHANG: Thank you for that question. Yes, there is a cutoff, and in our briefing document and in one of the slides in my presentation there is a separate analysis for just severe/critical disease. And as I mentioned in the presentation, for it to meet that severe/critical disease endpoint it has to undergo adjudication by a blinded, independent

adjudication committee. And what their decision is based on when they review the data, that is the final determination of whether that case is severe or not. So it is a distinct endpoint.

DR. ARCHANA CHATTERJEE: So when they're talking about moderate to severe disease, that is separate from the critical -- severe/critical; right? And that's dependent on the adjudication committee? Is that correct?

DR. RACHEL ZHANG: The moderate to severe disease endpoint includes all the severe disease.

DR. ARCHANA CHATTERJEE: Okay. Got it. Thank you.

DR. ARNOLD MONTO: Okay. Dr. Lee, is this for FDA?

DR. JEANNETTE LEE: Yes. Yes, sir, it is.

DR. ARNOLD MONTO: Okay.

DR. JEANNETTE LEE: So my question to the FDA is I did notice in the document that you indicated about 70 percent or over 70 percent of the -- you had the strain sequencing on that. And so I think one of

my questions is obviously we haven't seen that before. When we see these results again at some point, will we be able to see the efficacy by strain because obviously there's a lot of interest in that? Thank you.

DR. RACHEL ZHANG: So I'll defer to Janssen to talk about their plans for finishing up the sequencing and what kind of analysis we can get.

DR. ARNOLD MONTO: Okay. We try to segregate by -- but it doesn't work. Dr. Van Hoof.

DR. JOHAN VAN HOOF: Thank you for that question. Indeed it is our aim to continue the sequencing of the cases that we observe. Sometimes there might be challenges because you need to have a minimum amount of viral load to make viable sequencing, but we certainly want to get it at a higher percentage than what we have now. And all of that would be intended then to be sufficient to do the strain efficacy analysis, and it's our intent to include this in the BLA we plan to submit later this year.

DR. JEANNETTE LEE: Okay. Thank you.

DR. ARNOLD MONTO: Dr. Gans.

DR. HAYLEY GANS: Thank you so much. My camera doesn't seem to be working.

DR. ARNOLD MONTO: We can still hear you.

DR. HAYLEY GANS: I wasn't clear who we could ask questions and who may have this data, so if it's all right, I'd like to just go ahead and ask my questions. And then people can defer to whomever. Is that all right?

DR. ARNOLD MONTO: That's okay.

DR. HAYLEY GANS: Okay. Thank you.

DR. ARNOLD MONTO: Discipling the group is impossible.

DR. HAYLEY GANS: Yeah. It's just hard because we don't know the timeline. Anyway, there is, as has been mentioned a couple of times, a little bit of discordance between immune responses. And the real questions are if an individual doesn't have an antibody response, which was some of the individuals, do they have a T cell response? So in essence is there individuals who have no response to the vaccine, and what percentage of it? I assume that it's low.

And in that vein as we're trying to understand the immunity to these vaccines and how that pertains to the efficacy of the vaccines, is there any immune data from those who had infection, so particularly those who were hospitalized or had more severe? Were there actually attempts at sketching further immunologic studies on them so we can understand had their antibodies dropped, had their T cell responses dropped? And in addition, are those being correlated to whether or not people actually had whatever levels of antibodies?

I think there was some very brief mention of there was some correlates of the level of antibody and then disease. But that would be important to know so we understand in the future how to boost individuals moving forward. And I did hope that -- I hear a lot about pediatric studies. I know they're in the works. If we could get a better timeline on that because we're getting a lot of questions about when these studies may then be completed. Thank you.

DR. ARNOLD MONTO: Okay. I think this is for

Dr. Van Hoof.

DR. JOHAN VAN HOOF: Thank you. Your first question related to the immune read out and the correlates of protection, and it certainly is a very typical question. It is also part of the objectives of this trial. It's actually a work that is planned to be done in collaboration with NIAID, and we've asked Professor Peter Gilbert, who is a specialist in doing correlates of protection. That work is -- it has started, but it's still a work in progress so too early to report back on.

We have seen in our non-human primate studies that there was a correlation between the neutralizing titers and the protection. Although, this was not absolute, which might imply, indeed, that the cell mediated immunity is an important component. And again, in the future we'll need to tell us going forward. In general with the platform, we have seen that usually good responders on the humeral side with also good response on the cellular side, although sometimes you do see these discordances.

DR. ARNOLD MONTO: Okay. Dr. Hildreth. You're muted.

DR. JAMES HILDRETH: Sorry about that. Thank you, Dr. Monto. I'd like to follow up on a comment that Dr. Poland made about the breakthrough infections of those that got the vaccine being milder, and can you refer us or me to the data that confirms that, that the breakthrough infections had a milder disease when they got the vaccine?

DR. JOHAN VAN HOOF: There's actually a figure which is in the briefing documents, and it's Figure 16, page 65, which actually looked at the amount of symptoms that people had when they had breakthrough infections. And you see that in general if there are breakthrough infections, people present with less symptoms.

DR. JAMES HILDRETH: Page -- I'm sorry, page 65?

DR. JOHAN VAN HOOF: Yeah. This is -- I don't know if our team could pull up a slide that actually shows this. Let me --

DR. JAMES HILDRETH: I think that's a fairly important point that needs to be made when this is discussed with the public to know that the breakthrough infections were milder. That seems a very important point that needs to be made.

DR. JOHAN VAN HOOF: There's some technical challenge because I see it in the system that it is up, but I don't see it appearing in the Adobe.

DR. JAMES HILDRETH: Okay. I'll find it.

MR. MICHAEL KAWCZYNSKI: We're waiting for Ted to connect his -- but that's all right.

DR. JAMES HILDRETH: I'll find it. Thank you.

MR. MICHAEL KAWCZYNSKI: Arnold, go ahead. Arnold, that comment that just came in so we can keep on track, is it open now to both -- like I said, they wanted to know because we are --

DR. ARNOLD MONTO: I capitulate. I think it's open to both. Let's do this. Are there any questions specific to the FDA? And then we can really focus on questions for the next few minutes for the sponsor. So any of those four or five people who have their hands

raised right now who really want to talk to the FDA.

MR. MICHAEL KAWCZYNSKI: Go ahead and unmute then if you want to talk.

DR. ARNOLD MONTO: Dr. Perlman, do you want to talk to the FDA? You're next.

MR. MICHAEL KAWCZYNSKI: Dr. Kim.

DR. ARNOLD MONTO: Dr. Kim. Okay.

MR. MICHAEL KAWCZYNSKI: Dr. Kim, don't forget to unmute your own phone.

DR. ARNOLD MONTO: Still muted.

MR. MICHAEL KAWCZYNSKI: Your phone, not your camera your phone, Dr. Kim. No, not yet. All right. Let's go to one of those while Dr. Kim's getting his phone -- he muted himself in his phone. That's all right. You there, Dr. Kim? Go ahead, Dr. Monto.

DR. ARNOLD MONTO: Okay. Dr. Moore. I'm just going to go down the list from now on. I've given up. I tried.

DR. PATRICK MOORE: I have a question that I'd like to ask generally to the FDA because I don't know the answer.

DR. ARNOLD MONTO: Okay. Good.

DR. PATRICK MOORE: And you may not know the answer to this either, but live adenovirus vaccines are very old, right? They were invented in the 1960s.

DR. ARNOLD MONTO: The military has used them a lot.

DR. PATRICK MOORE: I'm sorry?

DR. ARNOLD MONTO: I said the military has used adenovirus vaccines a lot.

DR. PATRICK MOORE: Right. And my impression is that they have a tremendous safety profile, but I'm not an expert on this. Is there anything that we know from the history of adenovirus-based vaccines that we should be particularly worried about because now we're taking two things that we know something about? One is adenovirus vaccines and, two, SARS-CoV-2 spike protein vaccines, which at least we have four months' worth of data on, and putting them together. And neither one of them raises tremendous concerns to me in terms of the general science behind the vaccines, but I could be missing something. I'm just asking is there any

institutional memory of these vaccines and other questions that have been raised. And should we be concerned in a particular way about these vaccines?

DR. RACHEL ZHANG: I'll see if anyone else from the FDA wants to opine on this. It's certainly a little outside the scope of this EUA review.

DR. PATRICK MOORE: I think that answers my question. Thank you very much. And by the way, just a tremendous job.

DR. ARNOLD MONTO: Okay. Why don't we at this point -- because I promised the Committee they would be able to ask questions of the Janssen team since we had to terminate our questions, Dr. Hefter, Dr. Zhang, you're off the hook for now, and we're going to move to a few questions to the Janssen team. We're not going to allow an unlimited number of questions because we really do need time for our own discussion before the vote. So Dr. Hildreth, you have another question, or was yours answered?

DR. JAMES HILDRETH: Thank you. Mine was answered.

DR. ARNOLD MONTO: Okay. Dr. Kurilla. You're muted.

MR. MICHAEL KAWCZYNSKI: Dr. Kurilla, you muted your own phone. Are you unmuted now? Oh, it says you don't have your audio connected, Dr. Kurilla. There you go. We're down here. I'll unmute you right now. Hold on. I gotcha. Give me one second. And now you can talk. Go ahead.

DR. MICHAEL KURILLA: Thank you. So in looking at the cellular immunity that you measured, it looked like there was evidence that well after 28 days you were continuing to see increases in some cases. And I'm wondering from some of the earlier studies, the phase 1/2 where you may have longer data, are you continuing to collect immunogenicity data from those groups, and does that suggest -- does that at least provide the potential for estimating when you might need to boost or possibly also the duration that you may see from a single dose? Any clues or insights from that?

MR. MICHAEL KAWCZYNSKI: Dr. Van Hoof, did you

mute yourself again?

DR. JOHAN VAN HOOF: Sorry, I had.

MR. MICHAEL KAWCZYNSKI: There you go. Yes.

DR. JOHAN VAN HOOF: So indeed to your question, we have designed our phase 1 study such that we do monitor these subjects over the next 24 months and that we will monitor their cell mediated immunity and the immunological responses which will help us at least to some extent in guiding us when a boost might be needed. We do know historically from the platform experience that we do see quite good persistence even after one to two years. We have seen that with our Ebola vaccine, which was a two dose vaccine, but also with Zika we see good persistence at least up to one year.

DR. ARNOLD MONTO: Okay. Dr. Pergam.

DR. STEVEN PERGAM: Hopefully, you can hear me since it seems like muting's been a problem.

DR. ARNOLD MONTO: We can.

DR. STEVEN PERGAM: Okay. Good. So just a question about the vector itself and looking at

immunity to the vector over time. Most of the adenovirus vaccines that you've done have been short term prime boost or just a single dose. It's not really been long term where you've gone back and re-vaccinated. Is there a plan to look at the Ad26 immunity over the longer course to see if it might preclude or might limit the boost of responses at a later date?

DR. JOHAN VAN HOOF: This is a very important question indeed, and we do have an HIV vaccine program that is running where we are in a clinical proof of concept study in South Africa. We also have a phase 3 one in the western world, and that's a study in which we give up to four injections. And we do see that as you continue to give injections you do see a continued rise in antibody levels.

We also have experience with people who were vaccinated several years ago with a prototype of the HIV vaccine that we have boosted several years later, and it seems to be no problem at all to get that booster response. But it's certainly a very valid

point. These vectors are immunogenic to some extent, but it looks like the overall viral load that you get with the vaccine is sufficient to overcome that eventual interim.

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

DR. STANLEY PERLMAN: So I have a question about one group of patients, namely the ones who are greater than 60 with the comorbidities who have only -- not a great protection rate. So there's a few parts to this that I find -- well, I don't know really what the answer is. So we talked a little bit about immune responses, and I know that you're going to be looking at that. But do we expect this population to respond to adenovirus as well as people who are not over 60 with comorbidities? And do you think that when you go to the two-dose regimen will this help with this group? As it is now, I worry that the people who receive this, they will feel like they're getting a vaccine that doesn't work as well. So we don't want to have to classes of recipients or feel like we're increasing health inequities.

DR. JOHAN VAN HOOF: This certainly a question that is very important, and we actually -- once we had that observation, we went deep into the details to really understand the numbers. And perhaps I can share a few slides, essentially, which are in line with the observations that were already shared by the colleagues from FDA.

As you see, this is actually the forest plot data that give the efficacies. They're all within a somewhat different way. On the top, you see those after 14 days, on the bottom at the 28 days. You see actually that when you have a sufficient number of cases -- also for the people over 60 with comorbidities you have quite decent vaccine efficacies for the moderate and severe with (inaudible) confidence intervals that are quite good. It is when you go to the 28 days that it's lower, and you go really into that category with over 60 with comorbidities where you observe that lowest point estimate. However, as already indicated by FDA, we have that very wide confidence interval which is linked actually to the

very low numbers.

What you see on the righthand side is there was a statistical analysis made across proportional hazard test, and the P values indicated that there was no evidence of statistical significance when the three-way interaction was checked, so age and comorbidities. Of course, that is -- the question here is how is this, and then an interesting finding which I would like to share is when we looked closely to the Kaplan-Meier curves. And I'll guide you here through the slide itself.

You do see in blue the active group. The dotted line is the overall study population. The full line is the population that received the vaccine, so that cohort with comorbidities, and the gray lines -- dotted line are overall study population. And then the full gray line is over 60.

And what you do see is, first, the split for the people over 60 with comorbidities is exactly the same moment, and the trajectory is really very similar to the trajectory for the overall population. So for

me, this really indicates that there's something real that's happening here, not that much with the vaccine line as with the placebo line, which in our view, to the point made earlier, is really linked to that overall shorter follow up because you do see a significant drop of the population that is available for that duration of follow up.

Now, what is also important but not seen here is that when we look, then, to those cases and we look individually, then we see that those are somewhat randomly distributed over different countries. There was two countries where there was sufficient numbers to reach efficacy. It was the U.S. and South Africa, and in both cases, it was around 70 percent with regards to the moderate and severe.

Now, what is certainly very reassuring and also our colleagues from the FDA have mentioned this is that when you look really to what is important for this population with regard to severe endpoints, then we did see very clearly that we had a higher frequency, 82 percent, seeing two versus 11 hospitalizations after

day 14, so statistically significant with confidence interval of zero, which was really very encouraging. And we also see zero against five after day 28, which is in line with the observation of hospitalization for the rest of the study population. In addition -- and this is, of course, not statistically relevant because it's only two cases -- but it is encouraging to see that you have no case of deaths in this population due to COVID while you have two that was related to -- that was in the placebo group it was COVID related.

Of course, one of the challenges that we have is that despite having 44,000 people, once you go doing several analyses of subgroups of subgroups, you end up with low numbers. Even if you take all of these together, we do feel that specifically these numbers that are in front of us give us sufficient confidence to say, yes, this population will benefit also from this vaccine. Thank you.

DR. ARNOLD MONTO: Okay. I've got about eight hands raised, and we really need to close out the discussion. So I'm just going to call on Dr. Marasco

to have the final question.

DR. WAYNE MARASCO: Sure. Can you hear me now?

DR. ARNOLD MONTO: We can.

DR. WAYNE MARASCO: Okay. Good. Fine. Thank you. Well, I didn't get to introduce myself earlier, but I work in the Dana-Farber Cancer Institute. And my question's really related to the patients that we see. So there's a large number of patients with checkpoint blockade inhibitors and in different stages of chemotherapy or with a distant history of cancer. So how do you plan to roll out the vaccine to these particular patients, or are you planning on studying them at all?

DR. JOHAN VAN HOOF: Yeah. We're actually planning on studying them, and we're already in discussion with some centers that have expressed interest to start these studies as soon as possible. Out of principle, we didn't want to start those studies before we had evidence of particularly not put them unnecessary at risk. But based on the efficacy now

observed and under the assumption that the Emergency Use was approved, we would certainly start these studies.

DR. ARNOLD MONTO: Okay. So thank you very much. We're going to move now to the general discussion. There may still be questions for the sponsor, so it's not too late. Where you are, please stand by. And why don't we start our general discussion, and I'll call on Dr. Rubin to lead us off.

DR. ERIC RUBIN: Thank you. Thank you. I'm having some problems with my webcam. It won't seem to turn on.

DR. ARNOLD MONTO: We hear you, though.

DR. ERIC RUBIN: Great. Thanks. I guess my biggest concern -- and it doesn't really speak to the approval as much as how we use the vaccine. There is this ongoing study with two doses. If that proves to be superior, what do we do? Because we have a vaccine now that has good efficacy that everyone's going to compare to the existing vaccines and say it does not look quite as good. We have a second dose that might

well -- and after what we just heard from Dr. Van Hoof, there might well be a better response.

But we're going to have a large number of people who've gotten a single dose out there. What do we do for them, including the participants in the trial? We won't have a way of capturing the way that we do for the -- that we do for the current vaccines because it's sort of built into the program. It seems like a big logistical problem.

DR. ARNOLD MONTO: The simple answer from an FDA standpoint -- and we may want to ask our colleagues at FDA to comment -- is that this is something that the ACIP will need to consider -- that what is in front of us is whether this vaccine as a one dose formulation should be approved. But I see this also as an issue, especially if the two-dose formulation in study 3009 proves to be more efficacious. Other comments? Dr. Gruber, please.

MR. MICHAEL KAWCZYNSKI: Dr. Gruber, please unmute your own phone. Dr. Gruber, please unmute your own phone.

DR. MARION GRUBER: Yes. Can you hear me now?

MR. MICHAEL KAWCZYNSKI: Yes, we can. Thank you.

DR. MARION GRUBER: Okay. I am sorry about that. So I just wanted to make a general comment. I mean, it is something that we have -- the FDA has been discussing internally. We have now these data from a clinical study that evaluated one dose, and we have a study ongoing where two doses are evaluated. I think what we need to keep in mind in addition to have conversations also with other health policy makers in ACIP is that these -- if authorized, this is an emergency use authorization to really mitigate, hopefully, the devastating effect of the current pandemic.

The question about, you know, if data show that two doses are going to be more effective than one dose, you can really, you know, address it by looking at a biologics license application and see what the proposed application would be approved there. And if, god forbid, this pandemic drags out, then we'll have to

have these Emergency Use Authorizations in effect and we have data then to see that or to demonstrate that two doses work better than one dose, there's always the provision to amend the Emergency Use Authorization to allow two doses. I understand that there are logistical issues and operational issues that need to be sorted out. But from a regulatory perspective, I think we have means to address that. Over.

DR. ARNOLD MONTO: Okay. Thank you. I think that clarifies the situation. It's still a difficult situation, but -- Dr. Kim.

DR. DAVID KIM: Yes, thank you. So in the briefing document today and during today's presentations and discussion, Janssen championed Ad26's effectiveness against moderate to severe COVID. I'd like Janssen to reconsider this claim. Earlier this afternoon and during OPH, two of the commenters -- I believe they were Drs. Doshi and Zuckerman -- mentioned basically a total lack of mild COVID cases in the study. And honestly, you had mentioned this as well, Dr. Monto.

And Dr. Zhang during her presentation discussed the lack of mild cases, and this is basically a case -- basically a situation where Janssen's definition of mild case versus moderate case are inconsistent with FDA's and what CDC -- as well as the other two vaccine manufacturers for whom the EUAs were administered -- were different. So the mild case is defined as one -- a single symptom, whereas a moderate case was defined as two or more symptoms by Janssen. And for others, we're talking about a situation where the standard definition of symptomatic COVID is two or more of the symptoms.

So I would like to see Janssen revise their claim or their position in saying -- instead of saying there's a 67 percent moderate to severe COVID vaccine effectiveness, that they be consistent with what's currently in use for FDA and others by saying that 67 percent vaccine effectiveness applies to symptomatic COVID. Just something that'd I'd like us to have some consistency in this.

DR. ARNOLD MONTO: Dr. Gruber, would you care

to comment, or should we go to Dr. Van Hoof?

DR. MARION GRUBER: Yes, I think I would like for Dr. Van Hoof to take a stab at that. I mean, all I want to say is it's really difficult because these were pre-specified case definitions, and the primary analysis was really, you know, yeah, specified looking at these definitions. So going back now retrospectively and change that I think will provide with difficulties, but I also would like to give the sponsor a chance to comment on that.

DR. JOHAN VAN HOOF: Thank you, Dr. Gruber. No, no. I fully agree. Well, basically for methodological reasons it would not be wise to go back. A good thing is that we do have as part of the analysis also looked at protection against symptomatic infection and also protection against COVID infection according to the FDA definition. We will make sure that in our publications those numbers are also mentioned such that there is less potential for confusion. So from that perspective, I hope that that will help also to avoid confusion.

DR. ARNOLD MONTO: Right. I think that would be a great help if both are presented.

DR. JOHAN VAN HOOF: Yeah.

DR. ARNOLD MONTO: So whoever is reading the briefing document can do -- can figure it out.

DR. JOHAN VAN HOOF: Sure. I would like to -- on the two versus one doses. As I said before, we still need to wait to see what the two doses will give us, incremental value. And we overall feel that the efficacy we see and hospitalizations and death and critical disease that one dose already delivers quite a lot on the promise. Thank you.

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

DR. JAMES HILDRETH: Oh, I don't have a question. I'm sorry.

DR. ARNOLD MONTO: Okay. Could you put your hand down?

DR. JAMES HILDRETH: Yes, sir.

DR. ARNOLD MONTO: Okay. Thank you. Dr. McInnes.

DR. PAMELA MCINNES: Hello. Thank you,

Arnold. So this question about the case definitions I think is very important to be able to report out by the FDA a concordant definition. And it sort of comes from my question before lunch today about the case definitions and how you'd lump thing together, and that I think leads to some confusion.

My actual question, though, pertains to your placebo and to your actual description of your vaccine. I presumed that you probably used saline as a placebo, but a search for the word "saline" in your briefing document for the sponsor does not reveal anything. So I'd like to please know what your placebo was.

And then I have a question in regards what your vaccine actually looks like and how you handled blinding. And the reason this comes up is because in the FDA document they describe the product as being colorless to slightly yellow, clear to very opalescent, which I'm not really sure what that is actually looking like. I don't think there is a description of the vaccine in the sponsor's briefing document. If in fact it is not clear or colorless and a match to whatever

the placebo is, how did you handle blinding, please?

DR. JOHAN VAN HOOF: Yes. So it's a very good question, and all of the vaccines were prepared by a pharmacist who was unblinded but was independent from the study and who was also accountable for the vaccine preparation. Because of differences in appearances, there was also a blinding tape -- so a translucent yellow tape that was wrapped around the syringe after the following of the suspension. And then the masked syringes was handed over to the nurse who administered then the vaccine to the participant in the blinded fashion.

DR. PAMELA MCINNES: And was it saline?

DR. JOHAN VAN HOOF: It is the same vessel as we used for the vaccine.

DR. PAMELA MCINNES: It's a buffer? It's a vehicle or a buffer?

DR. JOHAN VAN HOOF: It's a buffer, but let me double check with the experts.

DR. PAMELA MCINNES: Thank you.

DR. JOHAN VAN HOOF: Thank you. Thank you.

Yeah, it is.

DR. ARNOLD MONTO: It is.

DR. JOHAN VAN HOOF: I will come back to it when I have final confirmation. I have some communication challenges here working virtual. Sorry.

DR. ARNOLD MONTO: Okay. Dr. Rubin?

DR. ERIC RUBIN: Please -- sorry, my hand shouldn't have been up.

DR. ARNOLD MONTO: Okay. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes. I have a comment to offer, Dr. Monto, and then I have a couple of questions as well. The questions are very brief, I promise, and so is the comment. The comment is with regard to the concerns around the two dose versus the one dose. I think that we are in such a fluid situation that what happens two, four, six months down the road is going to be very difficult for anybody to really say for sure. We currently have two two-dose vaccines that have been authorized and are being used, but there's already discussion about will you need a booster dose and how will we figure out, you know, how

to give those booster doses. So I think this is going to evolve over time. Can people hear me?

DR. ARNOLD MONTO: Yes, we can.

DR. ARCHANA CHATTERJEE: Okay. Thank you. The questions I have -- they're actually two and fairly easy. The first one is in the 3001 study I noticed that taste and smell changes were not included in the moderate to severe or severe to critical case definitions, and I was just curious about why that was the case.

DR. ARNOLD MONTO: Dr. Van Hoof, I'm afraid you can't leave.

DR. JOHAN VAN HOOF: Could you repeat the question, please? I didn't fully understand it.

DR. ARNOLD MONTO: Please repeat, Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yeah. Changes to taste and smell, which are pretty common symptoms for people who have COVID, they don't appear to have been included in the case definitions for the moderate to severe or severe/critical cases. I was just curious

why they were not included. Because when I looked at the list that was (audio skip) DART they were not there.

DR. JOHAN VAN HOOF: I'm pulling up now the definition of the -- that was used, and as you will see change to olfaction and taste is actually part of the definition. It's part of the definition, so you might have overlooked it.

DR. ARCHANA CHATTERJEE: Yeah. I'm sorry. I can't tell you where I saw it, but I did make a note when I was reading the briefing document. The other question is with regard to the distribution based on sex. So in several of the tables it said 45 percent male and 45 percent female, and I was just curious where the other 10 percent went. Were they not reported, or were they other gender or something?

DR. JOHAN VAN HOOF: I'm going to refer to Dr. Douoguih for that question if he has more details on that. Meanwhile, I need to correct myself in an earlier question. The placebo used was indeed saline. I was wrong. It was saline that was used, but it was

taped like I described. Yeah. Can Dr. Spiessens who is our statistician comment on collecting information on the gender? Yeah?

DR. BART SPIESSENS: Yes, I can, Dr. Van Hoof. Thank you. Hi, I'm Bart Spiessens. I'm a clinical biostatistician at Janssen. So I assume that the 45 percent that you refer to is that in each -- both the vaccine group as well as in the placebo group there were 45 percent of females. But there were then approximately 55 percent of males in each of the two groups. Is that the percentage that you refer to?

DR. ARCHANA CHATTERJEE: Again, I don't have the reference unfortunately of the actual chart -- the table, but I did see for both of them it said 45 percent. So that confused me. Maybe it was just the females.

DR. JOHAN VAN HOOF: It is actually indeed a strange way of putting it on the table, I agree. And where it mentions on the line is sex, female, 45 percent. And it's assuming the 55 percent is indeed male.

DR. ARCHANA CHATTERJEE: Okay. Thanks for the clarification.

DR. ARNOLD MONTO: Okay. Dr. Offit.

DR. PAUL OFFIT: Yeah. I have just a practical question but one that I get asked a lot. I notice that in your trial -- in your briefing document 26 percent of younger patients took antipyretics around the time of getting vaccinated. There are studies -- one in the Czech Republic, another in Australia -- looking at influenza vaccine as well as a variety of other vaccines showing that that can lower the immune response. I just wonder whether you had any data on whether or not the choice to use antipyretics in any way affected the immune response.

DR. JOHAN VAN HOOF: I'll immediately go to Dr. Douoguih for the question, but I do know that we actually did screen, indeed, intensively, the literature about impact on use of antipyretics on immune responses. What's most striking is that there's no consistent report, but indeed when it's taken prophylactically it seems to impact. When it's taken

reactively, it seems to be less clear. We have never recommended the use prophylactically, but we did recommend once there was fever starting or headache starting to use an antipyretic. So it was reactive use and not prophylactic use. I don't know, Dr. Douoguih, if you want to add something?

DR. MACAYA DOUOGUIH: Yeah. Hello, can you hear me? Sorry, there's an incredible delay. Okay. Yeah. Because we didn't require prophylactic use, it's very difficult to assess. We encouraged people to take antipyretics symptomatically, so we really don't have a means to make that comparison officially. And as Johan said, I think the literature are conflicting in terms of what the impact potentially could be. Certainly, we will have some immunogenicity data. We can look to see if with the data that we have we can make some sort of assessment based on antipyretic use. But we have not yet done that.

DR. PAUL OFFIT: Yeah. I think the literature was all prophylactic where it did effect, not -- I don't know that there was a literature sort of post

developing fever. But thank you.

DR. ARNOLD MONTO: Dr. Chatterjee, you're still up there. Do you have -- are you still -- okay. Thank you. Dr. McInnes, you have another question?

DR. PAMELA MCINNES: No, I just took it down. Sorry.

DR. ARNOLD MONTO: Okay. Thank you. Dr. Fuller.

DR. OVETA FULLER: Yes. Thank you. This is for the sponsor as well as for FDA. Given that as my colleagues have said this is a very fluid situation where things are changing rapidly and we want to know some follow up that would be important to managing this pandemic and hopefully getting us out of it -- so to the sponsor, you enrolled 44,000 people around the world, which is wonderful. And you proposed a crossover study to retain them. I want to know if you have indications that that will work well for the people that you have enrolled.

And secondly -- and this is important for things like the response to the adenovector, to the

pregnancy, to the asymptomatic infections, to the duration of immunity, all those things we need to know. And then I'd like to address that question to the FDA in terms of the follow up with the Moderna and Janssen studies in terms of keeping the people in the trial.

DR. ARNOLD MONTO: No other vaccines, Oveta.

DR. OVETA FULLER: But that's to FDA. Excuse me?

DR. ARNOLD MONTO: No other vaccines. Off limits.

DR. OVETA FULLER: But it's about the whole vaccination process, Dr. Monto.

DR. ARNOLD MONTO: Okay. But --

DR. OVETA FULLER: They can answer if they want to or not. It's up to them. I just put the question out there because it's important.

DR. JOHAN VAN HOOF: We do hope that -- in the hypothesis that we have the Emergency Use application authorized, we do hope that offering the placebo the vaccine will also incentivize people to stay in the study because the reason to leave the study -- that's

what we have seen happening -- is to get access to the vaccine. Many of the people participated also because they want to contribute to the science and seem to understand indeed that by continuing to be in the study monitored for safety, monitored for immunogenicity will help science to progress and will help to address some of these critical questions.

Of course, we don't have a crystal ball, and it is not guaranteed, but we do think that by offering the vaccine we can really be and hope to be successful in retaining the people in the study. If we don't do this, we have seen that many people are already leaving the study and that by vaccines becoming more and more available this will become impossible. So that's why we have -- it's nice to go that route.

DR. OVETA FULLER: How long will it be before the crossover occurs? Have you determined that?

DR. JOHAN VAN HOOF: That is actually depends on the countries where it is happening, but we would like to make this happen within the next coming weeks to months.

DR. ARNOLD MONTO: Okay. I have a follow up for Dr. Van Hoof. Do you have any assurance if vaccination becomes -- is being given to hold people in the study that once they are vaccinated and know they are vaccinated -- because you're basically unblinding -- they won't leave the study at that point because they have achieved what they're after, getting vaccinated? And you'll have the worst of both worlds because you will now have an unblinded study of people -- you will basically have an open label study. Has that been considered at all?

DR. JOHAN VAN HOOF: It is certainly a risk that exists. We do think that that risk can be mitigated by community engagement with the participants. I think that apart from having the vaccine there's also the follow up that we do in terms of eventual workup of infections that would occur. So there is also the follow up that is important. We also follow up with regards the immune responses, so it's also part of the benefit that they have by participating to the study that they will know that

there will be follow up if COVID would occur but also that they will know if their antibody levels would drop extremely low or whatever. So I think there are some incentives which we hope can help to mitigate that risk.

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

DR. OFER LEVY: Hello. This is a question for Dr. Van Hoof. Can you hear me?

DR. JOHAN VAN HOOF: Yes.

DR. ARNOLD MONTO: We can.

DR. OFER LEVY: Wonderful. My question to the sponsor relates to the dose of the vaccine. In other words, you have certain efficacy with a single dose regimen with the current dose, and yet you feel compelled to start another study to look at a two-dose regimen in hopes of gaining more efficacy. Have you considered an intermediate dose for the phase 1 in between the current dose and the higher dose to see if that might give more efficacy in a single shot regimen and/or the addition of an adjuvant?

DR. JOHAN VAN HOOF: Yeah. These are very

good questions. Of course, we should not forget where this was a race against time. We obtained the sequence of the gene in mid-January. We evaluated 12 transgene candidates to see which one would give the most immunogenicity.

With regard to the dose or the platformed used, we actually do have quite experience with the platform, having tested it now in many of our other research programs. So as you know, in in vaccinology it is always the challenge to find the right balance between maximum immunogenicity and acceptable tolerability. We know historically with these vectors, with Adeno26, that there were two doses that we know were good.

We know the $5x10^{10}$ which is for most of our programs. We know the $1x10^{11}$ gives occasionally somewhat higher immune responses but also is more reactogenic. And that was the reason why we had selected these two doses. Then, based on the phase 1 results, we have seen that they give very similar immunogenicity while it was more reactogenic at least

certainly in younger people. And therefore, we decided to go for the $5x10^{10}$.

Now, in vaccinology very often it's not that much a matter of only giving the amount of antigen but also the schedules are important. And that is the other element. And you have study 2001 which is evaluating several schedules.

There is actually one element we are doing there is we want to test also the robustness of the immune response and immune memory by giving these people who have received a single dose -- giving them a very late boost of a small amount of antigen and then check whether within days you do see a rise in antibodies, which is a hallmark normally of a robust immune memory and an (inaudible) response. And that is work that is still ongoing.

DR. OFER LEVY: Thank you, Dr. Van Hoof. How about the older individuals who have comorbidities? Older people have less reactogenicity. Can you give a higher dose in that group and get better protection?

DR. JOHAN VAN HOOF: That is a theoretical

question, but again I would like to go back to the analysis we did. And we do see that we have there pretty high protection against hospitalization and also death, that was zero, too. But hospitalization was pretty high. So I'm not sure whether adding more would necessarily result in higher results.

We do think the antibody levels play an important role. We should not forget also that this vaccine has very strong cell (audio skip) immune responses. And when you look to the effect on severe disease, 16 as of day seven when there's hardly any antibodies present. So it is reasonable to assume that also some immune responses play a role here, and there we do know that it does not necessarily increase that much with increased dose.

DR. OFER LEVY: Thank you.

DR. ARNOLD MONTO: Okay. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you. Thank you. Yeah. This is a comment, I guess, for both the sponsor and the FDA. Ideally, it would be fantastic if your vaccine induced lifelong immunity. But while that's a

tremendous aspirational goal, I'm not sure any of us are really looking for that or have that expectation.

But that raises the issue you're talking about a one, now perhaps a two, dose for the primary vaccination, but then the expectation is that there may have to be ideally annual booster shots that people are talking about. And they're talking about boosters for the other vaccines. But we've also seen down the road where we may have to anticipate a strain change, that's being referred to as boosters. And I'm seeing quite a bit of confusion of what is meant by a booster.

So we have the initial primary vaccination with a two-dose regimen with you end up with calling that a prime boost. Then, we're talking about needing another boost. And then we're talking about a strain change that's a boost. It's going to become very confusing, and I think there needs to be some general agreement on the nomenclature here so that it is not -- it is not just another problem for the general public to understand what's going on as to why they need another vaccine at this time. Please give it some

thought.

DR. JOHAN VAN HOOF: Yeah. That's a fair point. Yeah.

DR. ARNOLD MONTO: Okay. Dr. Portnoy.

DR. JAY PORTNOY: Thank you. I've just turned on my microphone and my camera. Things are a little bit delayed. As an allergist, I'm concerned about allergic reactions to the vaccine, in particular anaphylaxis, which has been reported with other the vaccines. I was wondering if you had information about sensitization rates in terms of IgE to the adenovirus in people who receive your vaccine. I know anaphylactic reactions are likely to show up as more people receive it because it's a low frequency event, but what are the ingredients in the vaccine? And have you looked at them as possible sources of anaphylactic reactions?

DR. JOHAN VAN HOOF: For this, I'm going to refer to Dr. Douoguih if he can comment on that and also on the excipients that are present in the vaccine.

DR. MACAY DOUOGUIH: Hello. Can you hear me?

DR. JOHAN VAN HOOF: Yup.

DR. JAY PORTNOY: Yes.

DR. MACAY DOUOGUIH: Okay. Sorry. I think the camera's delayed. Yeah. So we have not seen a lot of hypersensitivity in our platform data, so just with respect to the IgE questions we have not had a trigger to explore that. In terms of the excipients that we have, yeah, I just would like to pull it up so I can read it to you if that would be helpful. We've used a lot of excipients that are basically considered common in terms of buffers. Yeah. So sodium chloride, citric acid monohydrate, bisodium citrate dihydrate, polysorbate 80, HBCD, ethanol sodium hydrochloric acid, and water for injection are our excipients.

DR. JAY PORTNOY: Okay. Yeah. And you've not found any evidence of IgE developed into the adenovirus. Have you looked at it, or have you thought about doing that?

DR. MACAY DOUOGUIH: To my knowledge, we have not looked at that. I mean, certainly from a clinical perspective we have not had the impetus to consider

that, so yeah, it's, I think, an open question. We don't have reason to expect that the adenovirus itself would cause that just based on what we know about natural infection. There doesn't appear to be IgE mediated manifestations associated with natural infection, so we wouldn't expect to see that with the adeno itself. So again, if there was any source, you know, the excipients would be more likely than the virus itself.

DR. JAY PORTNOY: Okay. Great. Thank you.

DR. ARNOLD MONTO: Dr. Kim.

DR. DAVID KIM: I'd like to follow up on what Dr. Gruber said earlier. When I mentioned -- brought up the discussion on case definition, I wasn't referring to changing any of the study protocols or retroactively modifying things to better suit the needs of the outcome. The Janssen protocol's first primary outcome as moderate to severe COVID disease, and the secondary outcome was symptomatic COVID. And symptomatic COVID is basically the same as moderate to severe COVID because altogether out of the entire study

population there were only six cases of mild COVID. So the FDA case definition and Janssen case definition for symptomatic COVID was essentially they are the same. So just to comment on that.

Nothing will be changed if Janssen proceeds with vaccine effectiveness against symptomatic COVID as opposed to moderate to severe COVID, and that would be consistent with all the other definitions that are out there. And that's not changing anything from Janssen's study protocol.

And the other thing I would like to bring up is I'd like to follow up on what Dr. Moore said this morning. It's a two-part question so please bear with me as I set up the question. The FDA briefing document stated this. "Regarding the benefit of the Ad26 for individuals with prior infection with SARS-CoV-2, there were limited cases of COVID-19 among study participants with positive SARS-CoV-2 infection status at baseline. The study was not designed to assess the benefit of individuals with prior SARS-CoV-2 infection."

So the first part of the question I have is

are there enough data to look into whether those who are present -- those who were COVID positive at baseline mounted a more robust immune response? So that's my first half of the question. And I want to bring up Dr. Moore's concern again -- or point again. He brought up possibly testing the subjects for evidence of infection in the placebo group at the time of unblinding before administering the vaccine. So this could help answer the second part of that question.

So the second part of the question is can the single dose of Ad26 serve as a de facto immunity booster for COVID? This will be relevant for the 19 million or so adults who've already tested positive and might be candidates for a one dose vaccine.

DR. JOHAN VAN HOOF: Can you hear me? Yeah.

DR. ARNOLD MONTO: Yes.

DR. JOHAN VAN HOOF: So with regard to the placebo's I can confirm to you that everyone will be swabbed, and a blood sample will be taken to look into seroconversion. So that is part of it. With regards

to the immune responses observed in the people who were seropositive, I would like to ask Professor Schuitemaker to comment. I think she has the information -- the details on that. Professor Schuitemaker?

DR. HANNEKE SCHUITEMAKER: Can you hear me?

DR. JOHAN VAN HOOF: Yes.

DR. HANNEKE SCHUITEMAKER: Because I don't think my camera's working, but I can do it off camera. So in our phase 1 2A study we had few individuals that were seropositive at baseline. And there we indeed saw the boosting effect of our vaccine resulting in some of the individuals in very high antibody titers. So it seems to have some beneficial vaccination in people who are seropositive at baseline. Over.

DR. DAVID KIM: Do you have enough data to conduct a robust analysis?

DR. HANNEKE SCHUITEMAKER: No. Well, we will do, of course, this analysis in our phase 3 study now that we have tests identified who were seropositive. We will look at the immune responses four weeks after

so that -- it's a work in progress. For the people in our phase 1 2A study where we have done this analysis there were too few to do a robust analysis but work in progress.

DR. ARNOLD MONTO: Thank you.

DR. HANNEKE SCHUITEMAKER: Over.

DR. ARNOLD MONTO: Dr. Meissner.

DR. CODY MEISSNER: Yes. I'd like to ask two brief questions if I may. The first question is you define asymptomatic serologically by antibodies -- the nucleocapsid protein. And is the nucleocapsid protein unique to SARS-CoV-2 so that there isn't cross reaction with seasonal coronaviruses for example? Is that really a reasonable way to determine if someone's been infected?

And then the second question is on the Janssen briefing document on page 73 out of 118 I think there's a typographic error, but it says that reactogenicity was evaluated in people under 18 years of age. And I think that was supposed to be greater than 18 years of age, but again, I'm interested in its use in

adolescents if that did occur.

DR. JOHAN VAN HOOF: With regard to the letter, it is indeed a typo. It should read over 18 years of age. With regard to your first question, I will go in a minute to Dr. Schuitemaker, but I do know that we asked ourselves the question to what extent can we validate the seroconversion against N protein as a hallmark for infection? And we did that by going to look through all the cases and validate and check all the cases we had detected by PCR, to what extent they were actually seroconverting, yes or no. And over to Professor Schuitemaker to give you the results of those and to comment also on the question about potential cross reaction.

DR. HANNEKE SCHUITEMAKER: Yes. There's delay, so maybe my camera will turn on when I finish my answer. We validated indeed the IgG seroconversion or N antibody seroconversion by test -- by looking back in seropositive cases whether they also had a PCR, so whether the cases that we had the PCR positive cases had seroconverted based off the first analysis for N

seroconversion on day 29. And there we observed that 90 percent of the PCR positive cases had seroconverted, and it was interesting to see that people who were PCR positive too close to day 29 had not yet seroconverted. So there is a slight delay there. But there was overall very good concordance between people who had a PCR positive result and a seroconversion for N antibodies. I missed your second question. Johan, can you repeat?

DR. JOHAN VAN HOOF: It was a typo in the briefing book. So no problem. It was okay. Just solved.

DR. HANNEKE SCHUITEMAKER: Okay. Thank you.

DR. ARNOLD MONTO: Cody, I can tell you from a paper we have under review right now there are cross reactions between seasonal coronavirus infections low level and the full N protein of SARS-CoV-2. But the other thing that's going on now is that we have -- are practically not seeing seasonal coronaviruses, just like we're not seeing influenza viruses right now. But it is something we will have to watch for going

forward.

DR. CODY MEISSNER: Yes. And do you think -- is that true everywhere, Arnold, in the world, for example, and in Africa that the coronavirus is --

DR. ARNOLD MONTO: I have no idea outside our area, but it is something that needs to be checked on. Thank you. Next is Dr. Sawyer.

DR. MARK SAWYER: I'm good. Somebody already asked my question. I'm good. Thank you.

DR. ARNOLD MONTO: Okay. Dr. Pergam. We're moving along quite nicely.

DR. STEVEN PERGAM: Thank you. Thanks. Dr. Van Hoof, I have a question. In relationship to the new variants, we have a couple of variants of interest at the moment. Since there has been evidence that may be a little less response to the vaccine in the South African strain as an example, is there efforts by the company to start working on additional updates to the vaccine that might include these new variants? And what would the timeframe be to make that change if you needed to?

DR. JOHAN VAN HOOF: That's a very good question. First, I would like to come back to what we have observed in South Africa where, observing the efficacy against the severe endpoints, the efficacy was quite high as we have said. And also, even for the moderate and severe, we did see that the efficacy gradually increased. So I think the judge is still out on whether there's a new generation vaccine needed.

This being said, we are not complacent, and we are in the making of a new variant vaccine that should end the phase 1 trials before summer. Also depending why we will monitor in parallel in how the situation is evolving, but again, I would like to say that what we observe is that also against moderate and severe there was efficacy. But efficacy increased over time and was substantially higher by day 56 than it was earlier. So I think the judge is still out there on some elements, and we have not -- these are data that are fresh from the laboratories that you also do see that we have central activities that are related to the (inaudible) fragment of the antibody.

And Professor Schuitemaker referred to that. And we are evaluating to what extent these functions are impacted by the variants, yes or no, because we do hypothesis that these mutations should not impact those. And we have preliminary data that suggest indeed that those functionalities are preserved. This being said, we don't want to take risks, and that's why we are preparing also, if need be, a second-generation vaccine. And that could be in phase 1 before summer.

DR. ARNOLD MONTO: Okay. Dr. Moore.

DR. PATRICK MOORE: Dr. Pergam just asked the question I was going to ask, but following up on his question -- and it's more of a question to FDA -- is how much change -- or is there any change genetically that can be made to the vaccine without triggering a full re-examination through the EUA, meaning that you have to do full phase 3 trials? Is there any change that can be done, or do we -- how much clinical or wiggle room do we have on something like that?

DR. ARNOLD MONTO: Dr. Gruber.

DR. MARION GRUBER: Yeah. This is Marion

Gruber. I'm trying to start my webcam here. So well, I think you know what I look like. So the --

DR. ARNOLD MONTO: We hear you.

DR. MARION GRUBER: You can hear me, right? Yeah.

DR. ARNOLD MONTO: Yes, we can.

DR. MARION GRUBER: Okay. So, you know, on the question about making adjustments to the original vaccines to really, you know, get protection against emerging variants, we have actually just recently -- was it last week -- amended our EUA guidance document to really discuss the type of data that we would need to see to authorize a modified vaccine against some of these variants of concern. And we basically would address it by way of immunogenicity bridging studies. We would not request clinical disease endpoint efficacy studies. Does that answer your question?

DR. ARNOLD MONTO: I guess it does because he signed off. Okay. Dr. Marasco.

DR. WAYNE MARASCO: Yes. I'd like to address this to the sponsor. So you have a lot of experience

with adenoviral vectors, and can you give a sense to what extent they're activating the innate immune system? I mean, do you have cytokine levels or any other quantitative parameter which may allow this adenoviral vector to act as an adjuvant without adjuvating it? I mean, do you have science on that?

DR. JOHAN VAN HOOF: For that one, I'm going to refer again to Dr. Zahn who is our clinical expert. Dr. Zahn?

DR. ROLAND ZAHN: I'm back on. Yes. This is Roland Zahn. So indeed we have done studies with Ad26 vectors, not for this specific Ad26.CoV.2 to a vector but other adenoviral vectors coding for HIV or vaccine inserts. And there we have seen indeed that multiple cytokines are used -- measured systemically after administration to humans or in vitro by stimulating (inaudible) when given the Ad26 vector. So we think (audio skip) viral vaccine vector itself, also, for this vector.

DR. WAYNE MARASCO: So are you suggesting that that is adequate to explain its immunogenicity or

potentially enhanced immunogenicity? For example, the aminopurine activation.

DR. ROLAND ZAHN: Yes, it's certainly one of the factors which drives the immune response and which activates adaptive gene response to a vaccine insert of this vector.

DR. WAYNE MARASCO: Thank you.

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

DR. HAYLEY GANS: Hi, all. Thank you. I want to follow up on a question that I asked previously because it wasn't really answered, and it was really to just get some more details on the study 2001 and 3006 that are planned for hopefully enrollment this year. And particularly I understand starting next week with the 12- and 18-year-olds, there's some indication in the table that those will be done in the same geographic locations that were done just as an extension down in those populations. But I just wanted to ensure that we're actually going to get good demographic representation within our pediatric populations for those two studies. So that's my first

part of the question. My second part is people are starting to have issues enrolling children into these studies, and I'm wondering what is the backup plan for that for your particular vaccine?

DR. JOHAN VAN HOOF: Yes. As mentioned in earlier we do have a trial that will start recording adolescents very soon. Actually, we hope this week -- which will be next week. With regard to the pediatric plan and to speech to which we will recruit, I'm going over to Dr. Douoguih who is closer to the details of those studies. But indeed we do also plan to recruit in several countries, including the U.S. but also other countries. Dr. Douoguih?

DR. MACAYA DOUOGUIH: Yes. And thank you for the question. Yeah. So we are going to be running these trials in multiple countries. Some will be different than the ones where we were conducting the efficacy studies, but there's a lot of overlap. And from the operations team, you know, they've done an extensive feasibility to look at where there might be interest in vaccinating certain age groups. And as you

can imagine, depending on the age of the child there is more or less interest in enrolling. So our plan -- and of course, I don't have a crystal ball -- is to really diversify and make sure that we're in a number of different locations and partner with investigators that really have good experience and track record in recruiting all age groups such that we can conduct these as expeditiously as possible.

And so from a demographic point of view, I think we should have quite a mix. And again, we'll have to see how things start up, but we were hoping that we can recruit very quickly. Of course, the first dataset that would come forward is in the oldest adolescents, the 16- and 17-year-old and then move down in age range over the course of this year. But the aim is really to generate as much data as we can this year. And one last point, the totality of the dataset from the two trials that we intend to generate will be over 3,000 children.

DR. HAYLEY GANS: Thank you.

DR. ARNOLD MONTO: Dr. Kurilla. You seem to

be the last. If anybody -- to my great surprise we have come to the end of the list. Some more people who may want to make -- so we have some extra time for comments if necessary. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. We've seen recently some in vitro studies of neutralization of virus by serum from patients who have -- from subjects who have been vaccinated, but we've also seen quite a bit of variability between neutralization of variants based on whether there're point mutations or whether they are actual clinical isolates. But we don't have any direct correlation with the clinical efficacy of those studies that have been done. You're in a unique situation where you can actually do that, and I'm wondering do you have those in vitro studies going on. And do you have any results to share at this point?

DR. JOHAN VAN HOOF: Indeed we do have -- can you hear me because my camera is frozen.

DR. MICHAEL KURILLA: Yes.

DR. JOHAN VAN HOOF: We do indeed. This is an

important question. We actually are looking at using sera from our phase 1 studies and later on probably also phase 3, and in collaboration with academic labs both in South Africa and UK we are conducting these studies. We do have data that look to the neutralization of the UK variant. That actually -- like for the other vaccines, we observed indeed a drop in neutralization.

But what was interesting as an observation is that by day 71 that drop had substantially decreased. So it looks like over time there's some qualitative improvement -- for lack of a better term, let's call it maturation or affinity -- that shows that the drop in neutralization went from about an eight-fold drop to a threefold drop, so it was an interesting observation.

At the same time, it's also interesting to see that even in presence of such a drop -- of course, this was for the UK variant, but we have also some preliminary data from South Africa that's going in the same direction. But even the presence of that drop, it still seems to work. So it looks like it is a

biomarker but perhaps not the only one that correlates with protection.

DR. MICHAEL KURILLA: Oh, good. Thank you.

DR. ARNOLD MONTO: Dr. Marks.

DR. PETER MARKS: Thanks very much, Dr. Monto. I was hoping that the Committee could potentially make some comments -- I want to follow up on something that Dr. Perlman brought up. I think there was an explanation given by the company about the fact that there is this difference between 72 percent and 42 percent between people over 60 with and without medical comorbidities -- 42 percent in those with, 72 without in this group for -- that were seen. And there's also the issue that the two medically attended cases in people over 60 were also in those with medical comorbidities.

Now, granted I'm going to be the first one to say that that's a group that we're dealing with very small numbers. But I think it would be nice to hear some comments about the comfort there because, particularly in that group, there may be people looking

at that with a lot of scrutiny vis a vis other things that have been done in the past, not to bring in other vaccines from previously. But I think it would be good to hear some comments about that based on what Dr. Perlman brought up.

DR. ARNOLD MONTO: And I also noticed in some of the earlier immunologic studies older people seem to get an antibody response slower than younger individuals. Could that have any effect on this finding based on the time they have been under study? So I'd welcome -- we'd welcome comments from the Committee. Dr. Sawyer.

DR. MARK SAWYER: Thank you. Sorry, I've been having audio issues. I was going to ask with regard to Dr. Marks' question whether we are going to get data from the two-dose study in adults over 60 with comorbidities after their first dose. Is there a sufficient space between the doses that we could get some additional information from that study? And I guess that's a sponsor question.

DR. ARNOLD MONTO: Let's go on to Dr. Wharton

and gather our questions together about this topic. Dr. Wharton.

DR. MELINDA WHARTON: Thank you. Because of the way the staged recruitment, the follow up period for that group -- the people over age 60 with comorbidities -- was less. And so I wonder if there's been any additional accrual of events in that group since the dataset was closed out that would help narrow -- that would have a larger number of events and perhaps narrow the confidence interval.

DR. ARNOLD MONTO: Dr. Van Hoof, do you have any reply?

DR. JOHAN VAN HOOF: Yeah. Indeed, as Dr. Wharton just said, the point is indeed that this study's still ongoing, and additional cases are accumulating. But of course, we are completely blinded. I cannot comment on any results there. But so we do have roughly close to 400 cases that are accumulating. I didn't have the breakdown in that particular cohort, so we would have to look into that. I would like to come back, though, to the observation

that we shared. When we looked to hospitalizations in that group, that was statistically significant with the difference between the placebo and active group despite the low numbers, and that was very encouraging.

With regard to the schedule, the current protocol doesn't allow us to go and look, so it could only be when we have sufficient cases accumulated after the second dose that we would do an interim analysis. At which timepoint we could look at the difference between the single and two dose and also the efficacy of two doses. Again, it remains to be seen whether there is benefit from the second dose. That's something the data would have to tell us.

DR. ARNOLD MONTO: Thank you. Dr. Marks, have we satisfied your concern, and what are the options in our voting which is going to be coming up very shortly if we do continue to have concerns about this?

MR. MICHAEL KAWCZYNSKI: Sorry, who was that for, Arnold? I just want to make sure that -- who were you calling out?

DR. ARNOLD MONTO: Dr. Marks or Dr. Gruber.

DR. PETER MARKS: Sorry.

MR. MICHAEL KAWCZYNSKI: There we go.

DR. PETER MARKS: This is Peter Marks. Sorry. I must have disconnected myself. Sorry about that. You know, I think you've -- it sounds like the Committee -- other Committee members don't seem to have a concern with it. I think it's been asked and answered. If it comes up, I think we can handle it after you take a vote if there are issues.

DR. ARNOLD MONTO: With anything in these fluid situations there's no right or wrong answer to a lot of these questions. Dr. Gruber.

DR. MARION GRUBER: No, I actually wanted to make a comment, but it has been -- I'll take it back. I'm going to be quiet right now.

DR. ARNOLD MONTO: Okay. Are we ready to vote? Anybody from the group want to make any further comments? The procedure we're going to do is we are now going to vote, and after the vote anyone -- you don't have to -- is going to be able to go on and explain their vote. So we are voting on the question:

based on the totality -- it went away. Based on the totality of scientific evidence available, do the benefits of the Janssen COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older? Dr. Hayes.

KATHLEEN HAYES: Thank you, Dr. Monto. Can everybody hear me fine?

DR. ARNOLD MONTO: Yes.

KATHLEEN HAYES: Great. Okay. So we're going to pull up the slide that has all of our members and temporary voting members on it. There we go. Thank you. So all members and temporary voting members that you see on this slide, excluding the industry representative, will be voting in today's meeting. And in regard to the process, Dr. Monto just read the question for the record, but you may have to restate it. And then afterwards, all members and temporary voting members will cast their vote by selecting one of the voting options, which include yes, no, or abstain.

And you'll have two minutes to cast your vote after the question is read. Once all the votes have

been placed, we will broadcast the results and read the individual votes aloud for the record. Please note that once you cast your vote you may change your vote within a two-minute timeframe. However, once the poll has closed, all votes will be considered final. Does anyone have any questions related to the voting process before we get started?

DR. WAYNE MARASCO: This is Wayne Marasco. My screen's frozen, so I can't see what you're displaying.

MR. MICHAEL KAWCZYNSKI: If your screen froze, go ahead and take a moment to just log out/log back in. We will hold until you're in, so just don't hang up your phone. In the meantime, Dr. Monto, there is a question -- or Kathleen there is a question as well.

DR. ARNOLD MONTO: My screen just went blank.

MR. MICHAEL KAWCZYNSKI: That's all right. So while those people are resetting, go ahead, Dr. Rubin.

DR. ERIC RUBIN: If I add, I think a lot of us are delayed by probably two minutes on the video. So if we vote, by the time it comes up we won't have been able to vote.

KATHLEEN HAYES: So if you log out and then log back in --

MR. MICHAEL KAWCZYNSKI: We will make sure everyone can see -- hold on, Kathleen. We will make sure everyone can see the vote up on screen before we start the timer and all that. We will confirm it. Okay? So it's not in the video. It's just what you can see on the screen. So let's just make sure everybody is seeing a live feed of -- what should be up right now is you should all see the temporary voting members' names all listed.

DR. WAYNE MARASCO: Oh, yes.

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

KATHLEEN HAYES: Okay. Is everyone on? Everyone can see?

DR. ARNOLD MONTO: Not yet.

DR. ERIC RUBIN: Yeah. I can't see. I don't see the flags. Mike, would you like us to raise our hands if we can see the voting? Would that make the most sense?

MR. MICHAEL KAWCZYNSKI: I got it. Yes. We haven't pulled the voting stuff up yet. So right now, do you see a slide with all your names on it?

DR. WAYNE MARASCO: Yes.

DR. ARNOLD MONTO: I just did. I just see it. I see it now.

MR. MICHAEL KAWCZYNSKI: We will make sure -- and plus, we know when everybody casts -- we will make sure we know when everybody casts their vote. So those of you -- and I'm double-checking. Dr. Wayne Marasco, if that's you, you are not logged in at all. That's because you're on a frozen screen. So you need to log in. That's way.

DR. WAYNE MARASCO: I have a live screen.

MR. MICHAEL KAWCZYNSKI: Okay. You're good now? All right. So go ahead, Kathleen, while we go forward.

KATHLEEN HAYES: Okay. Does anyone else have any questions just about the voting process or procedure while you're getting logged back in? Okay. So --

DR. ERIC RUBIN: I'm sorry, Kathleen.

KATHLEEN HAYES: Go ahead.

DR. ERIC RUBIN: Just this second I'm still several minutes behind the YouTube feed here, so should I log out and log back on. Will that get me back into sync?

KATHLEEN HAYES: I would recommend --

MR. MICHAEL KAWCZYNSKI: You shouldn't be watching this on YouTube. You should be watching this here, in the meeting room.

DR. ERIC RUBIN: I am, but this screen is many minutes behind the -- I just went to look at the YouTube. So I'm still behind everybody.

KATHLEEN HAYES: There's going to be a delay in the YouTube.

MR. MICHAEL KAWCZYNSKI: There's a delay in YouTube. There's like a 30 second or so delay for feed in YouTube.

DR. ERIC RUBIN: No, no. YouTube is way ahead of me -- way ahead of me.

UNIDENTIFIED FEMALE: I think we're all having

issues with our screens because I'm having it too. It's just delayed, so just make sure, please, that our votes get in.

KATHLEEN HAYES: We'll make sure that everybody's vote has been submitted.

MR. MICHAEL KAWCZYNSKI: Yes. Again, let us go ahead and, one, Kathleen, go ahead. As she'll mention, she will not close the vote until we make sure all of you have had the opportunity.

KATHLEEN HAYES: Correct. So, Mike, if you could call up the voting slide, and then, Dr. Monto, if you could just please read the voting question aloud for the record.

DR. ARNOLD MONTO: For the record, based on the totality of scientific evidence available, do the benefits of the Janssen COVID-19 vaccine outweigh its risks for use in individuals 18 years of age and older?

KATHLEEN HAYES: Thank you. So you should be able to see the voting pod. If everyone could submit their vote. You have two minutes or longer if I don't see your vote in.

DR. ARNOLD MONTO: I see, yes, 100 percent on my end. Is everybody seeing --

MR. MICHAEL KAWCZYNSKI: Arnold, Arnold?

DR. ARNOLD MONTO: Yup? Okay. I gotcha.

MR. MICHAEL KAWCZYNSKI: Yes. So…

KATHLEEN HAYES: We've got about 30 seconds left. Okay. So it looks like all the votes are in. If we could close the poll at this time and broadcast the results, and then I'll read the votes for the record. Dr. Meissner, yes; Dr. Lee, yes; Dr. Perlman, yes; Dr. Monto, yes; Dr. Chatterjee, yes; Dr. Fuller, yes; Dr. Portnoy, yes; Dr. Marasco, yes -- sorry, we had a couple people here that accidentally voted. Dr. Pergam, yes; Dr. Levy, yes; Dr. Offit, yes; Dr. Moore, yes; Dr. Kurilla, yes; Dr. Cohn, yes; Dr. Kim, yes; Dr. Rubin, yes; Dr. McInnes, yes; Dr. Gans, yes; Dr. Wharton, yes; Dr. Hildreth, yes; Dr. Sawyer, yes. And that concludes the votes.

Since the majority voted yes, we do have a favorable vote. And I will now hand the meeting back over to Dr. Monto for the voting explanation, so thank

you, everybody.

DR. ARNOLD MONTO: Thank you, all. Now, if anybody wants to explain their vote, please raise your hands, and I'll call on you. This is not a requirement. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thank you, Dr. Monto. Just wanted to say that despite the concerns that were raised during the discussion, I think what we have to keep in mind is that we're still in the midst of this deadly pandemic. There is a shortage of vaccines that are currently authorized, and I think authorization of this vaccine will help meet the need at the moment.

DR. ARNOLD MONTO: Thank you, Dr. Chatterjee. Anybody -- oh, Dr. Perlman?

DR. STANLEY PERLMAN: Yeah. The only thing I would -- I just want to agree with that and also add that I hope we keep getting new information about the vaccine efficacy and safety. In some ways we have information that's supportive, but it'd be nice to have even more in the future.

DR. ARNOLD MONTO: Thank you, Dr. Perlman.

Dr. Rubin?

DR. ERIC RUBIN: I agree as well. I think it's a relatively easy call. It clearly gets way over the bar, and it's nice to have a single dose vaccine. It is a bit challenging to know how to use it clinically right now, but the demand is so large that it clearly has a place. It is a very changing environment, though, so I think having new information coming out constantly will really help us understand how best to apply this.

DR. ARNOLD MONTO: Dr. Portnoy.

DR. JAY PORTNOY: Great. Thank you. Yes, I agree that the vaccine is as safe and as effective as other vaccines that are currently approved, such as influenza. The main thing to keep in mind is that we're dealing with a pandemic right now, and this is like a very urgent thing as opposed to an endemic virus that most of the vaccines that we use treat. And so there's an urgency to get this done. We're in a race between the virus mutating, new variants coming out that can cause further disease, and stopping it.

So the fewer people who are infected with the virus the less opportunity it has to emerge as a more virulent strain. So we're in a hurry. We need to get this vaccine out. I do believe that the evidence supports its safety and effectiveness, and therefore, I think it's great that we're able to have this vaccine.

DR. ARNOLD MONTO: Dr. Moore.

DR. PATRICK MOORE: This is a comment not so much to the Committee but to the public and to reporters who may be watching this on YouTube or whatever. But the point is if you go back to December -- the early days of December when we first went through this process, those trials involved about 45,000 people. Now, 55 million people, which is a thousand-fold more people, have been vaccinated in just the last two months. At that time, we had comparable amounts of time to look at safety and efficacy of the vaccine as we do today.

As of February 26th, things are looking good. That could change tomorrow, but this whole -- my whole point is this process -- the EUA process does seem to

have worked despite my own personal concerns about it, say, six months ago. It does seem to have worked. And listening to particularly Dr. Shimabukuro's talk today it was quite clear that there was nothing surprising in terms of the safety and efficacy of the previously approved vaccines that occurred. And they're being monitored. So in terms of vaccine hesitancy, one should be at least aware that experts are trying to take a look at this and trying to give the best possible answers in this emergency.

DR. ARNOLD MONTO: Thank you, Dr. Moore. And I would add that the increased confidence with the process can be measured the changing votes that we have had in subsequent reviews. We are very comfortable now with the procedure as well as the vaccines we are approving. Dr. Meissner.

DR. CODY MEISSNER: Thank you. I agree with everything that has been said. I would also add the comment, Dr. Monto, that there is no -- I think it's important that people do not think that one vaccine is better than another. And this falls under the purview

of the CDC -- the ACIP obviously, but hopefully they will emphasis that there's no preference for one vaccine over another. And all vaccines work with what appears to be equal efficacy and equal safety as of this time.

DR. ARNOLD MONTO: And in this environment, whatever you can get, get is the conclusion. Dr. Levy, final remarks.

DR. OFER LEVY: Yes. Can you hear me?

DR. ARNOLD MONTO: Yes.

DR. OFER LEVY: Okay. In addition to the safety and efficacy that we were impressed with as a Committee is the storage at four degrees, which is very practical for rural areas in these United States and around the world. This is a global challenge -- the single dose and also not to be forgotten is the experience with the Ad26 platform in other vaccine programs, including in children and the pediatric -- potential pediatric indications. So I just wanted to end with those comments. Thank you.

DR. ARNOLD MONTO: Always good to end with

positive comments. I'd like to turn the meeting over to Dr. Atreya for formal closing now. Thank you all. Thanks to the Committee and thanks to all the participants. It's been a very smooth -- with a few technical glitches -- and positive meeting. Prabha.

DR. ERIC RUBIN: Thank you, Dr. Monto.

DR. PRABHA ATREYA: -- in preparing for this meeting. Thank you. I hope you heard my final comments. Thank you all for your time and effort that you put into this process and giving your recommendations. Greatly appreciated. The meeting is adjourned now.

DR. ARNOLD MONTO: Thank you. Bye until next time.

[MEETING ADJOURNED]