

**FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
163rd Vaccines and Related Biological Products Advisory
Committee (VRBPAC) Meeting**

OPEN PUBLIC MEETING

**Web-Conference
Silver Spring, MD 20903**

December 17, 2020

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	
Arnold Monto, M.D.	University of Michigan
Hayley Gans, M.D.	Stanford University Medical Center
Archana Chatterjee, M.D., Ph.D.	Rosalind Franklin University
CAPT Amanda Cohn, M.D.	Centers for Disease Control and Prevention
Michael Kurilla, M.D., Ph.D.	National Institutes of Health
Steven Pergam, M.D., M.P.H	Seattle Cancer Care Alliance
H. Cody Meissner, M.D.	Tufts University School of Medicine
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Sheldon Toubman, J.D.	New Haven Legal Assistance Association
Gregg Sylvester, M.D., M.P.H.	Seqirus, Inc.
TEMPORARY VOTING MEMBERS	
A. Oveta Fuller, Ph.D.	University of Michigan
James Hildreth, Sr., Ph.D., M.D.	Meharry Medical College
David Kim, M.D., MA	U.S. Department of Health and Human Services
James Neaton, Ph.D.	University of Minnesota
Jeannette Lee, Ph.D.	University of Arkansas for Medical Sciences
Stanley Perlman, M.D., Ph.D.	University of Iowa
Pamela McInnes, DDS, MSc.	National Institutes of Health
Eric Rubin, M.D., Ph.D.	Harvard TH Chan School of Public Health
Patrick Moore, M.D., M.P.H	University of Pittsburgh Cancer Institute

Mark Sawyer, M.D., F.A.A.P	University of California San Diego
Robert Schooley, M.D.	University of California San Diego School of Medicine
Melinda Wharton, M.D. M.P.H.	Centers for Disease Control and Prevention
GUEST SPEAKERS	
Steven Goodman, M.D., Ph.D.	Stanford University
SPONSOR	
Tal Zaks, M.D., Ph.D. (Speaker)	ModernaTX, Inc.
Jacqueline Miller, M.D., FAAP (Speaker)	ModernaTX, Inc.
Melissa Moore, Ph.D. (Speaker)	ModernaTX, Inc.
David Martin, M.D., M.P.H. (Speaker)	ModernaTX, Inc.
Lindsey Baden, M.D. (Speaker)	Brigham and Women's Hospital/Dana-Farber Cancer Institute; Harvard Medical School
Darin Edwards, Ph.D. (Sponsor Attendee)	ModernaTX, Inc.
Nedim Altaras, Ph.D. (Sponsor Attendee)	ModernaTX, Inc.
Charles Lee, M.D., J.D., CCHP-P, FACCP (Sponsor Attendee)	American College of Correctional Physicians
FDA PARTICIPANTS/SPEAKERS	
Doran Fink, Ph.D.	Food and Drug Administration
Marion Gruber, Ph.D.	Food and Drug Administration
Philip Krause, M.D.	Food and Drug Administration
Celia M. Witten, Ph.D.	Food and Drug Administration
Peter W. Marks, M.D., Ph.D.	Food and Drug Administration

Rachel Zhang, M.D.	Food and Drug Administration
FDA ADMINISTRATIVE STAFF	
Prabhakara Atreya, Ph.D.	Food and Drug Administration
Kathleen Hayes, M.P.H	Food and Drug Administration
Michael Kawczynski	Food and Drug Administration
Monique Hill, M.H.A.	Food and Drug Administration

TABLE OF CONTENTS

OPENING REMARKS: CALL TO ORDER AND WELCOME.....	6
ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, INTRODUCTION OF COMMITTEE, CONFLICT OF INTEREST STATEMENT	8
FDA PRESENTATION ON EMERGENCY USE AUTHORIZATION	27
CONSIDERATIONS FOR PLACEBO-CONTROLLED TRIAL DESIGN IF AN UNLICENSED VACCINE BECOMES AVAILABLE	56
SPONSOR PRESENTATION: EMERGENCY USE AUTHORIZATION (EUA) APPLICATION FOR MRNA-1273.....	92
OPEN PUBLIC HEARING	144
ADDITIONAL Q&A FOR SPONSOR PRESENTERS	202
FDA PRESENTATION AND VOTING QUESTIONS	235
COMMITTEE DISCUSSION AND VOTING	269

1 **OPENING REMARKS: CALL TO ORDER AND WELCOME**

2

3 **MR. KAWCZYNSKI:** All right. Good morning and
4 welcome to the 163rd Meeting of Vaccines and Related
5 Biological Products Advisory Committee meeting. I'm
6 Mike Kawczynski, a project manager with FDA, and I will
7 be today's meeting facilitator. This is a live virtual
8 public meeting that is being broadcast in its entirety
9 through C-SPAN, YorkCast, Facebook Live, YouTube,
10 Twitter, and a variety of other live streams.

11 Today's event is also being recorded and will
12 be posted on FDA's VRBPAC webpage along with all
13 relevant meeting materials. Throughout today's
14 meeting, I'll be reminding our presenters, committee
15 members, sponsors, and OPH speakers as to when they are
16 close to their allotted time and assisting them when
17 needed. Just a reminder to everyone that once called
18 upon, please manage your mute and activate your webcam.

19 Note to all members and participants, we are
20 aware of the adverse weather conditions that we are

1 experiencing, and we've taken precautions. If we
2 encounter any issues, we may have to take an
3 unscheduled break. At this time, I'd like to now kick
4 off the meeting and introduce Dr. Arnold Monto, the
5 acting chair, who will now provide opening remarks.
6 Dr. Monto, please go ahead, activate your camera, and
7 take it away.

8 **DR. MONTO:** I'd like to add my good morning
9 greetings to Mike's. Again, this is a meeting, the
10 163rd Meeting of the Vaccines and Related Biological
11 Products Advisory Committee, affectionately called the
12 VRBPAC.

13 We have one topic for today, a topic to
14 discuss and vote on, the Emergency Use Authorization of
15 the Moderna COVID-19 vaccine for the prevention of
16 COVID-19 in individuals 18 years of age and older.

17 First, I'd like to turn the floor over to
18 Prabha Atreya, the designated financial -- federal
19 officer, excuse me -- of the VRBPAC who will give us
20 administrative announcements, the introduction of the

1 Committee, and Conflict of Interest statements.

2 Prabha.

3

4 **ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL,**

5 **INTRODUCTION OF COMMITTEE, CONFLICT OF INTEREST**

6 **STATEMENT**

7

8 **MR. KAWCZYNSKI:** Prabha, please unmute your
9 personal phone.

10 **DR. ATREYA:** Okay. I'll start again. Good
11 morning, everyone. This is Dr. Prabha Atreya, and it
12 is my honor and great pleasure to serve as the
13 Designated Federal Officer -- that is DFO -- for
14 today's 163rd Vaccines and Related Biological Products
15 Advisory Committee meeting. On behalf of the FDA, the
16 Center for Biologics Evaluation and Research and the
17 Committee, I would like to welcome everyone for today's
18 virtual meeting.

19 The topic for today's meeting is Emergency Use
20 Authorization, EUA, of Moderna COVID-19 vaccine for the

1 prevention of COVID-19 in individuals 18 years of age
2 and older. Today's meeting and the topic were
3 announced in the Federal Register Notice that was
4 published on December 12, 2020.

5 I would like to introduce and acknowledge the
6 excellent contributions of my team in preparing for the
7 meeting. Ms. Kathleen Hayes is my backup and co-DFO
8 providing support in all aspects of conducting this
9 meeting. Other staff are Christina Vert, Jeannette
10 Devine, and Monique Hill, who provided excellent
11 administrative support. Thank you, team, for your
12 support.

13 Please direct any press and media questions
14 for today's meeting to FDA's Office of Media Affairs or
15 fdaoma@fda.hss.gov. The transcriptionist for today's
16 meeting is Ms. Allegra Chilstrom.

17 We will begin today's meeting by taking a
18 formal role call for the Committee members and the
19 temporary members. When it is your turn, please turn
20 on your video camera, unmute your phone, and then state

1 your first name and last name. And when finished, you
2 can turn your camera off so we can proceed to the next
3 person. Please see the member roster slide in which we
4 will begin with the chair. Dr. Arnold Monto? Mike,
5 can you project the roster slide?

6 **DR. MONTO:** I'm Arnold Monto. I'm a professor
7 of epidemiology in the School of Public Health at the
8 University of Michigan.

9 **DR. ATREYA:** Dr. Amanda Cohn. You have to
10 unmute your speakerphone.

11 **DR. COHN:** Thank you. Good morning. I'm Dr.
12 Amanda Cohn. I'm Chief Medical Officer at the National
13 Center for Immunization and Respiratory Diseases at the
14 CDC.

15 **DR. ATREYA:** Thanks. Dr. Chatterjee. Archana
16 Chatterjee.

17 **DR. CHATTERJEE:** Good morning. I'm Dr.
18 Archana Chatterjee, Dean of the Chicago Medical School
19 and Vice President for Medical Affairs at Rosalind
20 Franklin University. I'm a pediatric infectious

1 diseases specialist by training and background, and my
2 interest is in the field of vaccines.

3 **DR. ATREYA:** Great. Dr. Cody Meissner.

4 **DR. MEISSNER:** Good morning. My name is Cody
5 Meissner. I am a professor of pediatrics at Tufts
6 University School of Medicine and Tufts Children's
7 Hospital. Thank you.

8 **DR. ATREYA:** Great. Dr. Sylvester. Gregg
9 Sylvester.

10 **DR. SYLVESTER:** Good morning. My name is
11 Gregg Sylvester, and I'm the non-voting industry
12 representative. I am the Chief Medical Officer at
13 Seqirus, and I'm a pediatrician and general
14 preventative medicine doc by training. Thank you very
15 much for having me.

16 **DR. ATREYA:** Okay. Thank you. Dr. Hayley
17 Gans. Dr. Gans?

18 **MR. KAWCZYNSKI:** She's relogging back in, so
19 let's go. We'll come back to her. Go ahead.

1 **DR. ATREYA:** Okay. We can move on Dr. Michael
2 Kurilla.

3 **DR. GANS:** Hi. This is Hayley Gans. Can you
4 hear me?

5 **DR. ATREYA:** Yes.

6 **MR. KAWCZYNSKI:** Yeah. Yeah. Go ahead,
7 Hayley.

8 **DR. GANS:** Hi. This is Dr. Hayley Gans, a
9 professor of pediatrics and pediatric infectious
10 disease from Stanford University. Good morning.

11 **DR. ATREYA:** Thank you. Dr. Kurilla, now.

12 **DR. KURILLA:** Good morning. Mike Kurilla. I
13 am a pathologist by training. I am the director of the
14 Division of Clinical Innovation within the National
15 Center for Advancing Translational Sciences within NIH.
16 Prior to that, I was at the National Institute of
17 Allergy and Infectious Disease, working on vaccine drug
18 and diagnostic development. Prior to that a stint in
19 industry doing drug development, and then past
20 experience in academia doing clinical microbiology.

1 **DR. ATREYA:** Thank you. Dr. Paul Offit.

2 **DR. OFFIT:** Yeah. Hi. Good morning. I'm
3 Paul Offit. I am a professor of pediatrics at
4 Children's Hospital of Philadelphia and at the Perelman
5 School of Medicine at the University of Pennsylvania.
6 Thank you.

7 **DR. ATREYA:** Great. Mr. Sheldon Toubman.

8 **MR. TOUBMAN:** Good morning. My name is
9 Sheldon Toubman. I'm an attorney at New Haven Legal
10 Assistance in New Haven, Connecticut. I represent low
11 income individuals mostly in the area of access to
12 healthcare. But I'm here today in my personal capacity
13 as a consumer representative.

14 **DR. ATREYA:** Okay. Thank you. Dr. Steven
15 Pergam.

16 **DR. PERGAM:** Hi. I'm Steve Pergam. I'm an
17 associate professor at the University of Washington and
18 Fred Hutchinson Cancer Research Center in Seattle,
19 Washington. And I'm an infectious disease clinician by
20 trade.

1 **DR. ATREYA:** Thank you. Next slide please.

2 Mike? Mike, can you present the next slide please.

3 Thank you. Dr. Fuller.

4 **DR. FULLER:** Good morning. I'm Oveta Fuller.

5 I'm an associate professor at the University of

6 Michigan in the medical school in microbiology and

7 immunology, and a member of the STEM Initiative at the

8 African Studies Center at the International Institute,

9 and I'm a virologist by training.

10 **DR. ATREYA:** Okay. Dr. David Kim.

11 **DR. KIM:** Good morning. David Kim. I'm the

12 division director at the Division of Vaccines in the

13 Office of Infectious Disease and HIV/AIDS Policy in the

14 Office of Assistant Secretary for Health, HHS. Thanks

15 for having me.

16 **DR. ATREYA:** Thank you. Dr. Eric Rubin.

17 **DR. RUBIN:** Good morning. I'm Eric Rubin.

18 Welcome from a very snowy Boston. I'm a microbiologist

19 at the Harvard TH Chan School of Public Health, an

20 infectious disease physician at the Brigham and Women's

1 Hospital, and editor-in-chief of the *New England*
2 *Journal of Medicine*.

3 **DR. ATREYA:** Excellent. Thank you. Dr. James
4 Hildreth.

5 **DR. HILDRETH:** Good morning. I'm James
6 Hildreth. I'm the President and Chief Executive
7 Officer of Meharry Medical College. I'm also a
8 professor of internal medicine and a viral immunologist
9 by training. Thank you.

10 **DR. ATREYA:** Thank you. Next, Dr. Jeannette
11 Lee.

12 **DR. LEE:** Good morning. I'm Jeannette Lee.
13 I'm a professor of biostatistics at the University of
14 Arkansas for medical sciences and happy to be here.
15 Thank you.

16 **DR. ATREYA:** Thank you. Dr. Mark Sawyer.

17 **DR. SAWYER:** Good morning. I'm Mark Sawyer.
18 I'm a professor of pediatrics at the University of
19 California San Diego and Rady Children's Hospital San
20 Diego. I am a pediatric infectious disease specialist.

1 **DR. ATREYA:** Thank you. Dr. Melinda Wharton.

2 **DR. WHARTON:** Good morning. I'm Melinda
3 Wharton. I'm director of the Immunization Services
4 Division at the Centers for Disease Control, and I'm an
5 adult infectious disease physician by training. Thank
6 you.

7 **DR. ATREYA:** Thank you. Dr. James Neaton.

8 **DR. NEATON:** Good morning. This is Jim
9 Neaton. I'm a professor of biostatistics in the School
10 of Public Health at the University of Minnesota.

11 **DR. ATREYA:** Great. Dr. McInnes. Pamela
12 McInnes.

13 **DR. MCINNES:** Good morning. My name is Pamela
14 McInnes. I'm retired as deputy director for the
15 National Center for Advancing Translational Sciences,
16 one of the NIH institutes.

17 **DR. ATREYA:** Thank you. Dr. Patrick Moore.

18 **DR. MOORE:** Good morning. I'm Patrick Moore -
19 - Pat Moore -- and I'm a professor at the University of

1 Pittsburgh Cancer Institute and also in the Department
2 of Microbiology and Molecular Genetics.

3 **DR. ATREYA:** Thank you. Dr. Robert Schooley.

4 **DR. SCHOOLEY:** Good morning. I'm Robert
5 Schooley, professor of medicine in the Division of
6 Infectious Diseases at the University of California,
7 San Diego.

8 **DR. ATREYA:** Thank you. Dr. Stanley Perlman.

9 **DR. PERLMAN:** Good morning. I'm Stanley
10 Perlman at the University of Iowa. I'm in pediatric
11 infectious diseases and microbiology, and I have a
12 long-standing interest in coronaviruses and immunology.

13 **DR. ATREYA:** Great. Thank you. Now, I will
14 do introductions for the FDA staff. I would like to
15 introduce Dr. Marion Gruber, Director, Office of
16 Vaccines, who will say a few welcome remarks. Dr.
17 Gruber, please turn on your camera and unmute your
18 phone so everyone can see and hear you. Thank you, Dr.
19 Gruber.

1 **DR. GRUBER:** Yeah, Good morning. My name is
2 Marion Gruber. I'm Director in the Office of Vaccines
3 Research and Review in the Center for Biologics
4 Evaluation Research at the FDA.

5 I would like to welcome the Committee members,
6 Moderna, and the public to today's meeting. I want to
7 thank the VRBPAC members who are convening again today.
8 We're looking forward to your thoughts and comments
9 regarding the scientific evidence that will be
10 presented by Moderna and the FDA. We also look forward
11 to your perspectives on whether the benefits of
12 Moderna's COVID-19 vaccine outweighs its risks to
13 support authorization of the vaccine and then EUA for
14 prevention of COVID-19 in individuals 18 years of age
15 and older. I look forward to the discussions and thank
16 you.

17 **DR. ATREYA:** Thank you, Dr. Gruber. I would
18 also like to acknowledge the presence of Dr. Celia
19 Witten, Deputy Director of CBER, and Dr. Philip Krause,
20 Deputy Director, Office of Vaccines at this meeting who

1 may chime in as needed later on in the meeting. Also
2 Dr. Peter Marks, our Center Director, will join us
3 shortly after I complete the reading of the Conflict of
4 Interest statement to make his remarks.

5 Now, I proceed with the reading the Conflict
6 of Interest statement. Thank you.

7 The Food and Drug Administration is convening
8 virtually today on December 17, 2020, the 163rd meeting
9 of the Vaccines and Related Biological Products
10 Advisory Committee, also known as VRBPAC, under the
11 authority of the Federal Advisory Committee Act, FACA,
12 of 1972. Dr. Arnold Monto is serving as the acting
13 voting chair for today's meeting.

14 Today, on December 17, 2020, the Committee is
15 meeting in open session to discuss the Emergency Use
16 Authorization, EUA, of the Moderna COVID-19 vaccine for
17 the prevention of COVID-19 in individuals 18 years and
18 older.

19 The topic is determined to be of particular
20 matter involving specific parties. With the exception

1 of industry representative members, all standing and
2 temporary voting members of the VRBPAC are appointed
3 Special Government Employees, SGEs, or Regular
4 Government Employees, RGEs, from other agencies, and
5 they're subjected to federal Conflicts of Interest laws
6 and regulations.

7 The following information on the status of
8 this Committee's compliance with federal ethics and
9 Conflict of Interest laws, including but not limited
10 to, 18 United States Code Section 208, is being
11 provided to participants in today's meeting and to the
12 public.

13 Related to the discussions today, all members,
14 RGE and SGE consultants of this Committee have been
15 screened for potential financial conflicts of their
16 own, as well as those imputed to them, including those
17 of their spouse or minor children and for the purpose
18 of 18 U.S. Code 208, their employer. These interests
19 may include investments, consulting, expert witness
20 testimony, contracts and grants, Corporate Research and

1 Development Agreements, CRADAS, teaching, speaking,
2 writing, patents, and royalties, and their primary
3 employment. These may include interests that are
4 either current or under negotiation.

5 FDA has determined that all members of this
6 Advisory Committee, both regular and temporary members,
7 are in compliance with federal ethics and Conflict of
8 Interest laws. Under 18 U.S.C. Section 208, Congress
9 has authorized the FDA to grant waivers to special
10 government employees, who have financial interest, when
11 it is determined that the Agency's need for the special
12 government employee's services outweighs the potential
13 for the conflict of interest. They also may be
14 authorized when the conflict of interest of the regular
15 government employee is not so substantial and deemed
16 not likely to affect the integrity of the services
17 which the government may expect from the employee.

18 Based on today's agenda, and all financial
19 interests reported by the Committee members and
20 consultants, there has been one conflict of interest

1 waiver issued under 18 U.S. Code 208 in connection with
2 this meeting.

3 We have the following consultants serving as
4 temporary voting members at this meeting today: Dr.
5 Oveta Fuller, James Hildreth, David Kim, Jeanette Lee,
6 Pamela McInnes, Patrick Moore, James Neaton, Stanley
7 Perlman, Eric Rubin, Mark Sawyer, Dr. Robert Schooley,
8 and Melinda Wharton. Among these consultants, Dr.
9 James Hildreth, a Special Government Employee, has been
10 issued a waiver for his participation today to
11 participate at the meeting. The waiver was posted on
12 the FDA website for public disclosure.

13 Dr. Gregg Sylvester, of Seqirus Incorporation,
14 will serve as alternate industry representative for
15 today's meeting. Industry representatives are not
16 appointed as special government employees and serve
17 only as nonvoting members of the Committee. Industry
18 representatives on this Committee is not screened for
19 financial conflicts of interests and do not have voting
20 privileges. Also industry representatives act on

1 behalf of all the regulated industry and bring general
2 industry perspective to the Committee.

3 Mr. Sheldon Toubman is serving as the consumer
4 representative for this Committee. Consumer
5 representatives are appointed special government
6 employees and, therefore, are screened and cleared
7 prior to their participation in the meeting. They are
8 voting members of the Committee.

9 Today's meeting has one external speaker, Dr.
10 Steven Goodman, who will serve as the guest speaker.
11 He has been asked to disclose any financial interest he
12 may have related to the product before the Committee.
13 Disclosure of conflict of interests of guest speakers
14 follow applicable federal laws, regulations, and FDA
15 guidance.

16 FDA encourages all meeting participants,
17 including open public hearing speakers, to advise the
18 Committee of any financial relationships that they may
19 have with any affected firms, its products, and, if
20 known, its direct competitors. We would like to remind

1 standing and temporary members that if discussions
2 involve any of products and firms not already on the
3 agenda, for which an FDA participant has a personal or
4 imputed financial interest, the participant needs to
5 inform the DFO and exclude themselves from such
6 discussions and their exclusion will be noted for the
7 record. This concludes my reading of the Conflict of
8 Interest statement for the public record.

9 At this time, I would like to invite our
10 Center Director, Dr. Peter Marks, to make a few remarks
11 welcoming the Committee. Dr. Marks, please, could you
12 turn your camera on and the speakers unmute your
13 speakerphone, and the floor is yours now. Thank you.
14 Go ahead, Dr. Marks.

15 **DR. MARKS:** Well, good morning. Thanks,
16 thanks, Prabha. Good morning. I'd like to take a
17 moment, first of all, to welcome you all and also to
18 provide a brief overview of advisories committees and
19 the role they play in assuring transparency in FDA's
20 decision-making processes.

1 FDA uses advisory committees to obtain advice
2 from experts who work outside of the government. It
3 does so while working towards an open and transparent
4 government by presenting information under
5 consideration in a public forum and encouraging
6 patients, healthcare providers, and other interested
7 people to share their views during the open public
8 hearing or by submitting comments to the docket.

9 A key part of FDA's mission is to evaluate new
10 therapies and determine which are safe and effective
11 for their intended uses. This complex job often
12 involves many areas of expertise, and sometimes FDA
13 turns to outside experts for counsel such as for the
14 COVID-19 vaccine under consideration today.

15 Advisory committees weigh the available
16 evidence and provide scientific and medical advice to
17 the FDA on the safety, effectiveness, and appropriate
18 use of products that the Agency regulates. FDA
19 advisory committees are just that: advisory in nature.
20 It's important to note that the advice that the FDA

1 receives from the committee does not represent the
2 position of the FDA, rather the FDA weighs the advice
3 that it receives when taking actions on medical
4 products. FDA ultimately makes the final decisions on
5 all matters that come before the committee.

6 Also, to set expectations for today's meeting,
7 we've organized the agenda topics slightly differently
8 than last week's meeting to allow the Committee members
9 to have sufficient time for a robust discussion of the
10 questions before them. We invite the public and the
11 Committee to review the presentations and recording of
12 the December 10th meeting for more information on
13 COVID-19 epidemiology, vaccine safety and effectiveness
14 monitoring, and operational distribution plans as those
15 will not be covered in depth today as they were at the
16 last meeting.

17 As we begin today's proceedings, I want to
18 take the opportunity to thank you all, including all
19 the Advisory Committee members, for the insights that
20 they'll provide and also thank the FDA staff, the

1 sponsor, and those presenting at the open public
2 hearing today for participating. Your contributions
3 are very important in helping us at well-reasoned,
4 science-based decisions. Thanks very much, and we look
5 forward to the meeting today.

6 **DR. ATREYA:** Okay. Great. Thank you, Dr.
7 Marks. Now, I would like to hand over the meeting back
8 to our chair, Dr. Arnold Monto. Dr. Monto, take it
9 away.

10 **DR. MONTO:** Thank you very much, Prabha.
11 First, we're going to hear from Dr. Doran Fink, Deputy
12 Director of the Division of Vaccines and Related
13 Products Applications at FDA, who will give us a
14 presentation on Emergency Use Authorization. Dr. Fink.

15

16

FDA PRESENTATION ON EMERGENCY USE

17

AUTHORIZATION

18

1 **DR. FINK:** Hi. Good morning. If the AV staff
2 could please make me a presenter, then I will begin my
3 presentation.

4 In the meantime, I'll introduce myself. I'm
5 Doran Fink. I'm the deputy director for Clinical
6 Review in the Division of Vaccines and Related Products
7 Applications, Office of Vaccines, Research, and Review,
8 Center for Biologics Evaluation and Research at FDA.

9 The COVID-19 pandemic continues to worsen in
10 the U.S. and worldwide. As of the week ending December
11 15th, there have been a total of 16 million cases and
12 greater than 300 thousand deaths in the U.S. to date
13 and 1.5 million cases and greater than 17 thousand
14 deaths just in the past week.

15 On December 11th, just last week, FDA issued
16 an Emergency Use Authorization for the Pfizer-BioNTech
17 COVID-19 vaccine. This vaccine is authorized for
18 active immunization for prevention of COVID-19 due to
19 SARS-CoV-2 in individuals 16 years of age and older.
20 The EUA was issued after the December 10th VRBPAC

1 meeting to discuss the vaccine, data informing its
2 benefits and risks, and plans for its further
3 evaluation.

4 On November 30th, Moderna Therapeutics
5 submitted an EUA request for the Moderna COVID-19
6 vaccine, otherwise known as mRNA-1273. This, like the
7 Pfizer vaccine, is an mRNA/lipid nanoparticle vaccine,
8 and it is administered as a two-dose regimen, 28 days
9 apart. The requested use for this EUA is for active
10 immunization to prevent COVID-19 caused by SARS-CoV-2
11 in individuals 18 years of age and older. The
12 information submitted with the request include safety
13 and efficacy data from a large, randomized, blinded,
14 placebo-controlled Phase 3 trial.

15 FDA has been conducting a comprehensive review
16 of the Moderna COVID-19 vaccine EUA submission received
17 on November 30th. As with the Pfizer request, our
18 review has been comprehensive and conducted over a
19 short period of time. We have verified clinical data
20 integrity and integrity of Moderna's analyses and

1 conducted our own independent analyses from datasets
2 provided in the submission.

3 We have conducted ongoing review of
4 manufacturing, non-clinical and clinical assay
5 information, including information that has come in in
6 the last few days. We have reviewed and worked on
7 revisions of prescribing information on fact sheets
8 necessary to inform vaccine recipients and healthcare
9 providers. We have had multiple information requests
10 to Moderna to address our questions and need for
11 clarifications, and, of course, we have prepared for
12 today's VRBPAC meeting.

13 This will sound like a bit of broken record,
14 but I say it again because it's important. Today's
15 VRBPAC meeting continues FDA's commitment to an
16 expedited review process that is transparent,
17 scientifically sound, and data driven.

18 As a reminder from material presented last
19 week, the legal authority for Emergency Use
20 Authorization was established in Section 564 of the

1 Federal Food, Drug, and Cosmetic Act. It allows for
2 FDA authorization of unapproved medical products or
3 unapproved uses of approved medical products to address
4 public health emergencies related to biological,
5 chemical, radiological or nuclear agents.

6 HHS Secretary Azar issued a declaration on
7 March 27th justifying Emergency Use Authorization of
8 drugs and biological products to address the COVID-19
9 pandemic, which is a necessary prerequisite for
10 issuance of an EUA.

11 Here again are the criteria for FDA Issuance
12 of an EUA. The agent referred to in the EUA
13 declaration must cause a serious or life-threatening
14 disease or condition. Again, we know this to be true
15 for COVID-19. The medical product must be effective or
16 must be believed to be effective to prevent, diagnose,
17 or treat the serious or life-threatening disease or
18 condition caused by the agent. The known and potential
19 benefits of the product, it outweighs the known and
20 potential risks of the product. And also there must

1 not be any adequate, approved, and available
2 alternative to the product for diagnosing, preventing,
3 or treating the disease or condition.

4 As I explained last week, there is only one
5 FDA-approved product for COVID-19, which is remdesivir,
6 approved for treatment and not for prevention.

7 As I mentioned at the beginning of my talk,
8 the Pfizer-BioNTech COVID-19 vaccine is now available
9 under EUA for prevention of COVID-19. But it remains
10 unapproved, and its quantity is not sufficient for mass
11 vaccination needed to address the pandemic in the U.S.
12 Therefore, the fourth criterion is still met.

13 FDA explained in guidance, and in a VRBPAC
14 meeting on October 22nd, our expectations for data and
15 other information to support issuance of an Emergency
16 Use Authorization for a COVID-19 vaccine. This
17 information includes data to demonstrate manufacturing
18 quality and consistency. And similar to the case with
19 the Pfizer vaccine last week, FDA has reviewed the

1 manufacturing information provided by Moderna and found
2 it to be adequate to support issuance of an EUA.

3 We expect clear and compelling safety and
4 efficacy data to support a favorable benefit-risk of
5 the vaccine when rapidly deployed for administration to
6 millions of individuals, including healthy people. And
7 finally, we expect plans for further evaluation of
8 vaccine safety and effectiveness, including an ongoing
9 clinical trial, active and passive safety monitoring
10 during use under EUA, and observational studies.

11 Last week, I had a number of slides outlining
12 more details of these expectations. In the interest of
13 time, I'm going to skip those today.

14 If an EUA were to be issued for the Moderna
15 COVID-19 vaccine, it would specify the conditions of
16 use for which benefit-risk has been determined to be
17 favorable based on review of the available data. These
18 conditions include the populations to be included in
19 the EUA, conditions for vaccine distribution and

1 I want to pause here to address the issue of
2 anaphylactic reactions or serious allergic reactions
3 following vaccinations. While today's discussion is
4 about the Moderna vaccine, at last week's meeting we
5 reported on anaphylactic reactions that occurred in the
6 United Kingdom in two recipients of the Pfizer vaccine,
7 which is also an mRNA and lipid nanoparticle vaccine
8 and, therefore, relevant to today's discussion. Both
9 of these vaccine recipients had a medical history of
10 serious allergic reactions though not, as far as we
11 know, to any of the vaccine components.

12 Yesterday, as has been reported in the press,
13 two healthcare workers in Alaska experienced allergic
14 reactions minutes after receiving the Pfizer vaccine:
15 one of them an anaphylactic reaction resulting in
16 hospitalization. All of these individuals were treated
17 with appropriate medical interventions and, thankfully,
18 all are recovered or recovering.

19 We anticipate that there may be additional
20 reports, which we will rapidly investigate. We learned

1 of these cases through established safety surveillance
2 systems that worked exactly as designed. And FDA is
3 coordinating with CDC to further investigate the cases
4 in the U.S. and to communicate our findings in a timely
5 manner with vaccine providers and recipients.

6 FDA and CDC are also in close contact with
7 public health and regulatory authorities in the United
8 Kingdom as they continue their investigations. While
9 the totality of data at this time continue to support
10 vaccinations under the Pfizer EUA, without new
11 restrictions, these cases underscore the need to remain
12 vigilant during the early phase of the vaccination
13 campaign.

14 To this end, FDA is working with Pfizer to
15 further revise a fact sheet and prescribing information
16 for their vaccine, to draw attention to CDC guidelines
17 for post-vaccination monitoring, and management of
18 immediate allergic reactions. This revision will be in
19 addition to the information already included in the
20 contraindications and warnings, including that

1 facilities where vaccines are being administered should
2 ensure that medical treatment for managing serious
3 allergic reactions is immediately available. We will
4 do the same for the Moderna vaccine should it be
5 authorized for use under EUA.

6 Here is the agenda for today's VRBPAC. As Dr.
7 Marks mentioned, we have a lighter schedule than last
8 week to allow for more robust discussion. You will see
9 that some of the presentations from last week are
10 absent because the information has not materially
11 changed. We will have a repeat of Steven Goodman's
12 talk on considerations for placebo-controlled trial
13 design if an unlicensed vaccine becomes available. I
14 will explain the reasons why on my next slide.

15 Following Dr. Goodman's talk, we will hear a
16 sponsor presentation of the data for the Moderna COVID-
17 19 vaccine. You will then have an open public hearing
18 followed by a lunch break. And finally, an FDA
19 presentation of our EUA review, discussion items, and
20 questions for the committee to discuss and vote.

1 We have just one question today for discussion
2 without a vote. This question is similar to one we
3 asked last week, but we've rephrased it in a way that
4 we hope will focus the discussion.

5 The reason we are coming back to this question
6 is because it's important. The case-driven vaccine
7 trial conducted in the midst of a pandemic that very
8 quickly demonstrates clear evidence of efficacy, at
9 least in the short term, and allow the vaccine to be
10 made available under EUA. On one hand, this has a very
11 positive effect of helping to address the pandemic. On
12 the other hand, wide-spread vaccine availability can
13 interfere with conducting the trial to completion.

14 To be clear, FDA has never insisted that
15 placebo recipients enrolled in ongoing trials who want
16 the vaccine, be made to wait beyond when the vaccine
17 would otherwise be available to them under the
18 conditions of EUA, prioritization recommendations, and
19 available supply. Rather, we have been asking those
20 responsible for conducting COVID-19 vaccine trials to

1 think carefully and creatively about how to continue
2 trials after a vaccine becomes available under an EUA,
3 to preserve whatever societal value can be preserved,
4 and to ensure that sufficient data are ultimately
5 approved to support vaccine licensure.

6 This includes encouraging study participants
7 who are willing to remain in blinded follow up, for the
8 same altruistic reasons that prompted their enrollment
9 in the first place, to do so. Later today, you will
10 hear about Moderna's plans for their trial.

11 The question that we would like you to discuss
12 is in considering Moderna's plans for unblinding and
13 crossover of placebo recipients: Please discuss the
14 most critical data to further inform vaccine safety and
15 effectiveness to support licensure that should be
16 accrued in either ongoing clinical trials with the
17 Moderna COVID-19 vaccine or other studies, such as
18 additional clinical trials or observational studies
19 with that vaccine.

1 Following this discussion, which again will
2 not have any vote, we will have a single question for
3 VRBPAC discussion and vote. And that question is,
4 "Based on the totality of scientific evidence
5 available, do the benefits of the Moderna COVID-19
6 vaccine outweigh its risks for use in individuals 18
7 years of age and older? Thank you very much.

8 **DR. MONTO:** Thank you, Dr. Fink. We have a
9 full 20 minutes for discussion here. I think we should
10 restrict our discussion to the EUA process and its
11 characteristics.

12 Since we're going to be hearing from Dr.
13 Goodman about some of the other issues, we probably
14 should restrict questions or discussion about that
15 until after he presents. So raise your hands please if
16 you would like to make a comment. And Dr. Meissner.

17 **DR. MEISSNER:** Thank you, Dr. Monto. First, I
18 would like to express my gratitude to Dr. Fink, Dr.
19 Marks, Dr. Gruber, and their colleagues at the FDA for
20 the extraordinary amount of work that has been put into

1 this issue over the last few weeks and months. I think
2 that all the citizens of the United States should
3 recognize the enormous effort that has been put into
4 this. So thank you.

5 My question is as follows, and it's somewhat
6 similar to the question that I asked last week. It's
7 important that we move a vaccine from an EUA to a BLA
8 because there are a number of advantages to have a
9 vaccine licensed and recommended by the CDC. Is there
10 any way you can anticipate how soon that might happen?
11 And does the availability of a second messenger RNA --
12 a vaccine with a similar mechanism of action -- will
13 that facilitate the decision in any way for the FDA?

14 **DR. FINK:** Thank you for that question. As I
15 believe I responded last week, we are actively working
16 with the vaccine manufacturers, both Pfizer and
17 Moderna, to arrive at a data package that would support
18 vaccine licensure. This data package would include
19 some additional follow up from clinical trials as well
20 as data accrued from use under the EUA, as well as some

1 additional manufacturing information for vaccine that
2 is intended to be produced following licensure. So it
3 is our goal to arrive at a licensure application as
4 quickly as possible as the data allow.

5 And, in terms of your other question,
6 certainly new vaccines that are similar in platform,
7 although not exactly the same, will be considered
8 relevant to each other and will inform our assessment
9 of those respective vaccines.

10 **DR. MEISSNER:** Thank you.

11 **DR. MONTO:** Dr. Kurilla.

12 **DR. KURILLA:** Thank you. Doran, I want to
13 make sure that I understood what you said. You seemed
14 to imply that the issuance of a second EUA was partly
15 dependent on the fact that there was inadequate supply
16 of the initial EUA for mass vaccination. Is that a
17 criteria that would potentially impact the decision on
18 future EUA for other vaccines?

19 **DR. FINK:** So thanks for the opportunity to
20 clarify that question. So actually, the supply of

1 Pfizer vaccine is secondary at this time for
2 considering issuance of an EUA for a different vaccine.
3 And that's because the Pfizer vaccine is not approved.
4 So consideration of available alternatives requires
5 that those alternatives both be approved and adequate.
6 So the fact that the Pfizer vaccine is not approved
7 means that there is currently no approved available and
8 adequate preventive vaccine for COVID-19.

9 **DR. KURILLA:** Thank you.

10 **DR. MONTO:** Dr. Rubin.

11 **DR. RUBIN:** Thanks, Dr. Fink, for that very
12 clear presentation. I'm curious what FDA will do with
13 the discussion item on Dr. Goodman's proposal. Is it
14 likely to end up as an FDA requirement or a strong
15 recommendation to proceed to BLA for the manufacturers?

16 **DR. FINK:** As I explained before, we are
17 working actively with the vaccine manufacturers on
18 accruing data that would be necessary to support a
19 biologics license application. And this includes
20 discussions around the contours of their ongoing

1 clinical trials going forward. We are hoping that the
2 committee discussion will help to inform those
3 discussions with the manufacturers.

4 **DR. MONTO:** Dr. Perlman.

5 **DR. PERLMAN:** Yes, so I just have a question
6 about one of the last things you were talking about.
7 So the anaphylactic reactions have clearly been a big
8 deal in the press, and I and probably others get lots
9 of calls about what it means. I think the FDA
10 recommendations talk about allergies to components of
11 the vaccine, yet the components of the vaccine actually
12 are not obviously to me allergenic. Do you have any
13 sense for how the FDA's going to finally make
14 recommendations?

15 The U.K. has different recommendations than
16 the FDA came out with. So do you know this is going to
17 play out, and do you know what the components are in
18 the vaccine that could be inducing this?

19 **DR. FINK:** So, at this point, we and CDC are
20 continuing to investigate these cases and consider

1 data. At this point, we don't have enough information
2 to make definitive recommendations one way or another.
3 And, as we continue to investigate and evaluate the
4 data, we will consider whether additional
5 recommendations need to be made.

6 **DR. MONTA:** Dr. Pergam.

7 **DR. PERGAM:** Thanks, Dr. Fink, for that
8 clarity, again, and for a short presentation because I
9 know we have a lot to discuss today.

10 I had a question. You brought up the issues
11 of a couple of separate question in addition to the
12 main EUA question that we're going to be reviewing,
13 related to what other studies need to be done, et
14 cetera. I want to be clear. Is this for both
15 vaccines, since we did not get to review those and give
16 those recommendations to the Pfizer-BioNTech vaccine?
17 Those discussions for additional studies or additional
18 work that needs to be done, are those going to relevant
19 for both vaccine candidates?

1 **DR. FINK:** Well, they certainly will be
2 relevant for both vaccines. We'd like this discussion
3 today to focus specifically on Moderna's plans. But
4 clearly, the ideas discussed will be relevant to both
5 vaccines.

6 **DR. PERGAM:** Thank you.

7 **DR. MONTTO:** Dr. Moore.

8 **DR. MOORE:** For the long-term safety, meaning
9 beyond years, even decades-long safety, for this
10 vaccine and the other vaccines requires obtaining a
11 centralized resource that allows us to know who is
12 vaccinated and who is not. Is that being planned to be
13 collected for -- outside of the randomized control
14 trial? Is there a plan to collect that information to
15 securely store it so that you can do linkage analysis
16 with the cancer registries or autoimmune registries?

17 **DR. FINK:** So, as discussed last week, the
18 U.S. government is planning a number of studies
19 leveraging healthcare claims databases to evaluate
20 vaccine safety over the longer term with use under an

1 EUA. I'm not the expert on those studies, and so I
2 would have to defer comment on the details to those who
3 are spearheading them.

4 **DR. MONTO:** Dr. Fuller.

5 **DR. FULLER:** Thank you, Dr. Monto, and thank
6 you, Dr. Fink, for your explanations. The question,
7 which may be addressed later, but I'll ask you, how
8 will the FDA or CDC or other state health agencies
9 monitor the potential adverse events that happen, like
10 the allergies that you mentioned in Alaska? If it were
11 a continuing clinical study, those would be picked up
12 by the researchers. But, in this case, how will that
13 be done? Could you please share a little bit more?

14 **DR. FINK:** Sure. And this was also explained
15 last week in one of the presentations by CDC that we
16 don't have today, but I'll refer you and refer the
17 public back to the recording of that presentation.

18 We have robust safety surveillance and
19 reporting systems that have been in place for a long
20 time including VAERS, the Vaccine Adverse Event

1 Reporting System. Additionally, vaccine recipients
2 under the EUA will be asked to partake in a program
3 called V-safe, which is an electronic safety reporting
4 system that the government is using to track vaccine
5 safety with use under the EUA.

6 **DR. FULLER:** All right. Thank you.

7 **DR. MONTO:** Dr. Neaton.

8 **DR. NEATON:** Thanks, Dr. Fink. My question is
9 actually similar to Dr. Pergam's. Have you considered
10 aligning some of the future protocols for these two
11 vaccines in a manner, and also the current protocols
12 with the purpose of being able to combine the data from
13 each of those studies?

14 **DR. FINK:** Well, yeah. Combining or pulling
15 data involve complicated statistical considerations.
16 But what we have done -- and we discussed this at our
17 October 22nd VRBPAC meeting and also in our guidance
18 released in June of this year -- is we have recommended
19 standardized case definitions that will help to
20 evaluate efficacy results from trials of different

1 vaccines, not necessarily for comparing one vaccine to
2 another, although that is one possibility. We hope
3 that this standardized approach, which as we explained
4 in October, is not a requirement for the primary
5 endpoint but a recommendation that we've made for
6 inclusion in all of the Phase 3 trials.

7 We hope that this will facilitate the type of
8 broad and robust data analysis that you might be
9 thinking of.

10 **DR. NEATON:** Yeah.

11 **DR. MONTO:** Dr. Gans.

12 **DR. GANS:** Thank you very much. Thank you,
13 Dr. Fink. I had one question about -- I realized today
14 we're entertaining the Moderna vaccine. We've now
15 entertained the Pfizer one previously. And I'm
16 wondering in the context of other vaccines that are
17 coming to market -- all of which are going to have
18 different adverse events as well as different
19 populations in which they should be used.

1 I'm wondering in the context of equity in
2 terms of how we roll these out -- some are coming
3 obviously into use before others. I just worry a
4 little bit about how we should think about that in the
5 context of the broader field of different vaccines that
6 are coming that have different profiles. Have you had
7 any thoughts on that, or how the FDA and CDC are
8 thinking about those other vaccine models in the
9 context of this?

10 **DR. FINK:** Sure. So, to be clear, FDA's
11 responsibility is to evaluate data concerning the
12 benefits and risks of the vaccine in the context of the
13 Emergency Use Authorization request. And once FDA
14 issues an Emergency Use Authorization, then the
15 responsibility falls to CDC and the Advisory Committee
16 on Immunization Practices to set prioritization
17 recommendations and other recommendations for use of
18 the vaccine, considering its benefits and risks in the
19 populations included in the Emergency Use
20 Authorization.

1 **DR. GANS:** Thank you.

2 **DR. MONTO:** Dr. Chatterjee.

3 **DR. CHATTERJEE:** Good morning. I have a
4 question with regard to the BLA applications that may
5 be coming from the manufacturers. In the past from my
6 experience anyway, usually a BLA application comes in
7 after the clinical trials have been completed. For
8 these vaccines, is there a plan -- I couldn't quite
9 understand from your explanation, Dr. Fink -- whether
10 there will be interim data analyses, and we won't
11 actually have to wait until the trials are completed
12 before the BLA applications will be entertained by the
13 FDA?

14 **DR. FINK:** Yeah, thank you for that question
15 and the opportunity to provide clarification. Though
16 it's actually not unusual for a clinical trial to be
17 ongoing for longer term safety and/or effectiveness
18 follow up when a biologics licensed application is
19 submitted. At this point, we do have interim data for
20 two COVID-19 vaccines. One of which we have authorized

1 for emergency use, another of which we are considering
2 today. At this point, the data would not be considered
3 quite sufficient to support a biologics license
4 application. But as I mentioned before, we are working
5 with both manufacturers to accrue the data that would
6 be needed with the goal of getting these vaccines
7 licensed as soon as the data allow.

8 We heard from Pfizer last week that they are
9 anticipating potentially submitting a biologics license
10 application sometime in the spring of next year. And
11 that plan is certainly within the realm of what we
12 would consider possible.

13 **DR. CHATTERJEE:** Thank you very much.

14 **DR. MONTO:** Dr. McInnes.

15 **DR. McINNES:** Good morning, Dr. Fink. I have
16 a question regarding the status of inspection of
17 facilities. And the reason I think this becomes
18 important for us to have some sense of where you all
19 are in this, was this availability of information on
20 the news about unexpected volumes left in syringes.

1 So, while that may very well just be due to
2 residual volume in syringe and needle of a particular
3 type, verses what might be seen in another situation,
4 it does bring up the question of the confidence in the
5 manufacturing site, the manufacturer, the fill, the
6 consistency. And while I appreciate that a full
7 picture of that is not required under EUA, I would like
8 to have some sense of the sort of confidence of the FDA
9 in that particular state of data.

10 **DR. FINK:** So I can repeat that we have
11 reviewed extensive manufacturing information for this
12 EUA request and do feel confident that we have enough
13 information to justify issuing an EUA for this vaccine,
14 should everyone agree that the benefits outweigh the
15 risks based on the clinical data. I can't speak in
16 more detail about the facilities' inspections. I'd
17 invite other FDA colleagues who might be on the line to
18 chime in if they have something additional to say.

19 The other thing I'll mention about the volume
20 issue for the Pfizer vaccine, is that if you look at

1 the instructions, they are to add 1.8 mls of diluent to
2 0.45 mls of vaccine that's already in the multidose
3 vial. It gets you to a total of 2.25 mls. And so,
4 with a dose volume of 0.3 mls, it is actually not at
5 all unexpected that there would be more than five doses
6 in those vaccines -- or in those vials.

7 **DR. MONTTO:** Any further FDA comments? Okay.
8 Let's -- for the final question, Mr. Toubman.

9 **MR. TOUBMAN:** Thank you for the excellent
10 presentation, Dr. Fink. I have a question about the
11 FDA's review of the efficacy data. Your slide
12 indicated a November 30th mission for EUA. The
13 briefing documents indicate that Moderna submitted
14 another set of documents on 12/7 and that included --
15 so, instead of a close date of 11/7, it's a close date
16 of 11/21. And in the briefing document, you indicated
17 FDA has reviewed some -- and verified -- some of that
18 more recent data, but not all. You could just briefly
19 explain what that actually means?

1 And there's been reports in the press about
2 how the FDA's process is more rigorous than the British
3 review process, for example. But just briefly explain
4 what that really means. And second, to confirm that
5 you have been able to verify the efficacy data in the
6 second set according to primary endpoint as well as the
7 important secondary endpoint of any severe disease.

8 **DR. FINK:** Yes, we'll hear more about that in
9 our FDA presentation this afternoon. But I can verify,
10 I can confirm, that FDA has examined, verified the
11 integrity of, and confirmed the efficacy analyses from
12 the later timepoint, from the November 21st timepoint,
13 both for the primary efficacy analysis and for the
14 secondary analysis of severe cases.

15 What we have not done, due to time
16 constraints, is more in-depth probing of the data to do
17 our own independent analyses on some questions that we
18 look at that are maybe not so central but of interest.

19 So all this to say that we have verified and
20 confirmed Moderna's analyses for both the interim and

1 final efficacy analyses, those that we consider to be
2 most critical to inform the benefit-risk assessment.
3 We have not done quite as comprehensive a dive into
4 those data as we did for the interim analysis, but we
5 don't think that this should hinder in any way our
6 confidence in the data to support an assessment of
7 benefit and risk.

8 **DR. MONTTO:** Thank you. Okay. We're moving on
9 now to the presentation from Dr. Steven Goodman. And
10 he'll be telling us about the considerations for
11 placebo-controlled trial design if an unlicensed
12 vaccine becomes available. Dr. Goodman is Associate
13 Dean of Clinical and Translational Research at Stanford
14 University School of Medicine. Dr Goodman.

15

16 **CONSIDERATIONS FOR PLACEBO-CONTROLLED TRIAL**
17 **DESIGN IF AN UNLICENSED VACCINE BECOMES AVAILABLE**

18

19 **DR. GOODMAN:** Morning. Can you hear me fine?

20 **DR. MONTTO:** Yes.

1 **DR. GOODMAN:** Okay. Terrific. So thank you
2 so much for inviting me and, in fact, particularly for
3 inviting me back again. I think the reason for that
4 was presaged by the questions and talk just given,
5 which is that the issues we'll be considering here are
6 not just relevant for this vaccine, but for many trials
7 currently ongoing and those in the future. So this
8 arguably has potentially more long-lasting effect than
9 even the EUA today.

10 I don't want to scare you with this title,
11 which looks exactly the same as last week. I'm, in
12 fact, not going to be giving exactly the same talk.
13 I'll be picking up from where we left off last week and
14 taking a bit of a deeper dive to give you more material
15 for your discussion.

16 And this is the outline, I'll very briefly
17 remind you where we left off after last week, then go
18 into the Moderna consent and proposal. Then we'll take
19 a bit of a deeper dive into the deferred vaccination
20 design which we talked about last week. Then I'll

1 discuss the evidential and ethical effects of both
2 partial and complete unblinding of the placebo group,
3 which are both under consideration right now. Then
4 I'll have a final single slide on the evolution of
5 design, which is a perspective I hope you will consider
6 in your comments. And I already heard a suggestion of
7 this from Dr. Gans in her last question.

8 So let's go just to very briefly summarize
9 where we were after last week. We had an ethical
10 summary where we talked about the issue of ethical
11 dilemmas as being a choice between two "right" actions
12 or just justified in different ways which is certainly
13 what we're going to be facing today even more starkly;
14 the importance of trust in the whole vaccine
15 development process and prioritization, which enables
16 us to do these clinical trials and could be withdrawn
17 at any time; talk a bit about the issue of context
18 where the ethical calculus depends not only what we
19 know and what we don't but the availability of vaccine;
20 and we talked ethically relevant benefit in the sense

1 that whether the placebo group was taking on such a
2 risk relative to the vaccinated group that they were
3 owed something just by nature of that benefit. And the
4 argument was that they were not, even though there was
5 some very, very small deficit. But, of course, you
6 don't know that when you sign up for the trial. We
7 only know that in retrospect.

8 In terms of the epistemic or evidential
9 summary. I'm just going to use the word evidential
10 more today than epistemic, even though I'm really
11 talking about the same thing. Which is that all
12 designs can generate valid evidence albeit with
13 different efficiency and degrees of certainty, that's
14 randomized control trials, quasi-experimental and
15 observational designs and, in particular, knowledge of
16 mechanism and biology, which guides a lot of the
17 interpretation of the empirical design.

18 And finally, that RCTs are best to assess some
19 vaccine properties but not necessarily all. So they're

1 very good for some things, but we have to partition
2 between the things it's good for and not.

3 And finally, the idea that there shouldn't be
4 any bright lines drawn either on the ethics or the
5 epistemology fronts, and we shouldn't be declaring
6 anything particularly unethical. What we're really
7 saying when we use that word is we believe that one
8 principle outweighs another. And the word "unethical"
9 sort of disenfranchises people on the other side and
10 demonized them, and it doesn't lead to good
11 discussions, as well as strict adherence to
12 randomization when that's not necessary.

13 So let's go into the Moderna consent and
14 proposal. The consent is at the beginning exactly what
15 you expect. It mentions voluntariness. It is
16 particularly important that the participants may or may
17 not benefit from participating in the study, but it is
18 designed to help others in the future; that they can
19 leave at any time, this won't affect their future care.

1 Then we get into some of the questions which
2 state in very plain language what the participants
3 should expect, and it says what will happen at the end
4 of the study. Basically, you'll just be discharged
5 from the study by your doctor. Will you be informed if
6 new information becomes available? Yes. And
7 certainly, as with last week, the EUA is part of that.

8 But this is the most important clause here at
9 the bottom. "Can you continue getting the study
10 vaccine after the study?" And this is what was told in
11 the consent: "If you choose to withdraw from the study
12 or are taken out of the study, you will not continue
13 receiving the study vaccine. Also, if the study is
14 terminated early, or when the study is ended, the
15 Sponsor will not continue providing the study vaccine."
16 Now that will be highly relevant to the actual
17 proposal, which we will contrast here.

18 So, first of all, an observation was made that
19 there's going to be a large number of folks who are
20 eligible for early vaccine administration. This, in

1 particular, 25 percent of the enrollees are healthcare
2 workers. But here's the proposal: they will
3 proactively re-consent participants who received placebo
4 and then offer them the vaccination. And then they
5 will be observed unblinded for the rest of the entire
6 two years, and adverse events will be captured. But
7 basically, they are proposing to simply unblind and
8 immunize the placebo group.

9 This is importantly different from last week's
10 proposal, which was to wait until they were eligible
11 for receipt otherwise. And then, if they asked, they
12 would then be unblinded and immunized and that all
13 participants would be encouraged to stay in this
14 randomized trial as long as possible and that everybody
15 would be immunized at the end of six months.

16 So this is different in multiple ways. First,
17 that it's done immediately. Second of all, that they
18 be unblinded. That actually is common to both. But
19 that we don't wait for eligibility outside the trial.
20 So this is a very, very, very important difference and

1 something that will have, as I will argue, consequences
2 not just for this trial but for other trials of other
3 vaccines.

4 So this is exactly the same as what we talked
5 about before. What is owed to placebo participants.
6 And this really is, what is the obligation? And that's
7 something that can be asked of the investigators or the
8 company because it's owed to them. And the simple
9 answer is what's in the consent? That's what owed to
10 the placebo participants, that the conditions upon
11 which they enrolled. And of course, all the adherence
12 to the Belmont ethical principles.

13 They certainly would want to expect that they
14 wouldn't be denied the vaccine if it became available
15 to them, which could be done through an exclusion to
16 EUA, but I don't think that is actively being
17 considered. And potentially, reciprocity, which is
18 really a form of gratitude and not obligation, could be
19 operationalized through higher priority for vaccine
20 within their priority group when they become eligible.

1 But there's not an ethical obligation of
2 investigators to unblind on demand. It is if there's a
3 medical reason, but not for others. And not immediate
4 vaccination with trial before their turn is called
5 outside the trial. And that's actually reflected in
6 the consent. If this was an ethical obligation to
7 immediately vaccinate, once there was interim results
8 showing efficacy or even with an EUA, this would have
9 been in the consent, and it was.

10 So now let's take a little bit of a deeper
11 dive into the deferred vaccination design. We showed
12 this slide last week, there really are two alternative
13 designs at this point that might be considered for this
14 or future trials. One is this deferred immunization,
15 which is a blinded crossover design, and second is
16 active control designs.

17 I'm not going to focus on those, but I will
18 talk about the implications of the guidance on this
19 placebo group for the future of active control design.
20 That's very important. And of course, everything comes

1 with active and passive observational studies of almost
2 every aspect of the vac- -- not just safety of the
3 vaccine properties. So both approaches are going to
4 require some give on the evidential and ethical side.

5 So this is a picture you saw last week. This
6 is the deferred vaccination arm. On the top, you see
7 the arm that gets immediate vaccine, that's in blue.
8 That narrows, and the narrowing reflects a slow waning
9 of the vaccine efficacy. Of course, we don't know if
10 or when that happens, but this is just a schematic to
11 show you how they can be still compared if we crossover
12 blindly.

13 On the bottom, you see the placebo arm and the
14 point at which there's early efficacy established which
15 is roughly where we are today, is still in Period 1.
16 And then the proposal is that at some point, if
17 somebody is going to become eligible for vaccine, that,
18 if they are in the vaccine arm, that they get a placebo
19 injection. And that, if they're in the vaccine arm --
20 I'm sorry, the placebo arm, they get a placebo -- I'll

1 get this straight. If they're in the placebo arm, they
2 will get a vaccine injection.

3 So everybody ultimately gets immunized, but
4 they still don't know whether they were in the
5 immediate vaccination arm or in the deferred
6 vaccination arm. And this preservation of blinding,
7 even with the immunization of everybody in the trial,
8 allows a number of things that I'll talk about in a
9 minute, and I mentioned last week.

10 So this is another way to represent what's
11 going on, and here we're measuring efficacy, not as the
12 thickness of a bar, but in terms of attack rate. And
13 the attack rate is on the vertical axis. And what you
14 see is the attack rate you'd expect under placebo in
15 the early days -- and on the bottom is just time --
16 would be high. Here it's just nominally indexed at
17 one.

18 That would be the attack rate, and the red
19 line are the placebo group, and at the bottom would be
20 the attack rate in the vaccine group. In fact, in

1 practice this turned out to be much, much lower --
2 roughly 95 percent lower -- than the red line.

3 And then we watched them over time, and the
4 vaccinated arm, if vaccine efficacy starts to wane --
5 if and when -- what you would see is a slow rise in the
6 attack rate in the vaccinated group, and that the blue
7 line's starting to ramp up.

8 But, of course, there are other things going
9 on in the world that affect the attack rate, including
10 problems in the community, community restriction
11 measures. So there's a lot of things going on in
12 calendar time that need to be controlled for, which is
13 why we can't just observe what happens over time. We
14 won't know, if the attack rate starts to go in the
15 vaccine arm, exactly what it's due to.

16 So this is where the deferred vaccination can
17 still help us recover that information. And you see
18 that vaccination occur with a big drop, at the point of
19 deferred vaccination from the red line, down to a new

1 blue line. And we watched this attack rate for a
2 while.

3 And if there's a difference between the attack
4 rate in the early vaccinated group versus the late,
5 that is a sign that there's waning of efficacy. And,
6 of course, this can occur at every point. They could
7 be at the same level for a while, and then the early
8 vaccinees start to -- their efficacy starts to wane and
9 their attack rate goes up over time. It doesn't have
10 to be right at the point of crossover.

11 So this is what it looks like, and this is how
12 you can recover this really critical information about
13 how long this immunity lasts, which is going to be a
14 major question. And we will also see that there are a
15 few other things we can do with this design.

16 So I want to make the point that the crossover
17 can occur whenever an individual participant becomes
18 eligible for an available vaccine outside the trial.
19 So it's not occurring for everybody at the same time,
20 which those schematics suggested. It's occurring for

1 each individual potentially at a different time. I'll
2 talk more about that issue of design.

3 There's also some unexpected benefits: one is
4 that blinded crossover allows for more safety
5 assessment via self-controlled design. And you'll see
6 here on the bottom that for the placebo arm, we're
7 looking very, very carefully at adverse event incidents
8 in the post-placebo period. That serves as a control
9 for the AE seen in the vaccine arm, which I sort of
10 erased up here. I'm only looking at the placebo arm,
11 and you'll see why.

12 And then when they cross over blindly -- of
13 course, they don't know that they're crossing over --
14 we can then watch very closely adverse event incidents
15 post-vaccine. And we can compare the AEs after this
16 vaccination to before in a particularly powerful way,
17 which is with control within each individual.

18 This is not just comparing overall incidence
19 rate, which is like what's occurring in that first
20 period. It's a self-controlled design, which controls

1 for confounding in a particularly powerful way. So
2 this is a nice benefit of this design because they're
3 being watched carefully in that first period. So this
4 is very solid AE information.

5 We could ask people if they had a recent
6 stroke or heart attack or whatever, before entering the
7 trial, but they -- for certain AEs -- might not
8 remember it very well. And certain ones might prevent
9 somebody from enrolling. So this guarantees that
10 there's absolutely no bias about who's included.

11 There's another bonus, which is that as
12 vaccine efficacy wanes, if it does wane, the deferred
13 vaccination allowed the booster trial sort of right on
14 top of the trial infrastructure. And, in that sense,
15 it's an added benefit if we find that a second booster
16 -- that is a third shot -- is need. And this can be
17 piggy backed right on top of the deferred vaccination
18 structure. So this, again, is a very nice add-on if
19 needed.

1 Now, last week, that company was asked about
2 whether they were amenable to doing this. They pointed
3 to the logistics of maintaining the blind. They said
4 it was very difficult and maybe not worth it. I will
5 say that there are additional logistics, and it will be
6 up to you to explore the yield and to give FDA advice
7 on whether this is a determinant in whether it's worth
8 going, or worth instituting.

9 So there's mandatory crossover serology, plus
10 a dummy shot, and there's another dummy shot for both
11 arms. Because neither one can know which arm they were
12 in. There are possibly more blood draws, and these
13 have to be synchronized between the two groups. They
14 should be done and kept on the same schedule so
15 serology is comparable.

16 And finally, there is reconsent, but this is
17 necessary for any major design change, including
18 unblinding and administration of vaccine. So this is
19 not necessarily an additional logistical barrier. But
20 what's really critical is that, in theory, no one knows

1 their assignment. And all the parameters, all the
2 reasons we do the RCT, apply here in preventing bias
3 and ascertainment of a whole bunch of AEs, efficacy
4 endpoints, and even crowd participation as I will
5 mention.

6 So this is complicated, but I'm actually not
7 going to go through it in detail. I'm just going to
8 point out two things. This is a list of all the things
9 we still want to learn about the vaccine that is not
10 really captured very well at this interim point, which
11 includes duration of immunity after two months. This
12 actually under certain circumstances can be enhanced by
13 the deferred vaccination design even over continued
14 placebo control, even though I think that's off the
15 table.

16 And the other thing that's enhanced, which is
17 really critical, and this is the link for the future is
18 correlates of immunity, because we are now doubling the
19 vaccinated arm. We're doing so in this randomized way.
20 And we can enhance the finding of surrogate markers of

1 protection, which will be absolutely critical for
2 active control designs in the future. I mentioned a
3 variety of things here that are partly preserved; that
4 is we'll be able to get some information but not
5 necessarily definitive information.

6 Now finally, effects of complete or partial
7 placebo unblinding, both on the evidential and ethical
8 scale. In terms of partial unblinding, which would be
9 done if we gave the vaccine to those at the point they
10 became eligible. So we would never completely unblind
11 the group until maybe some timepoint in the future as
12 Pfizer recommended, but not as Moderna's proposing.

13 So it's important to mention the same fraction
14 of vaccine recipients would also be unblinded. Because
15 when they asked to be unblinded, or when they become
16 eligible, they don't know what group they're in. So
17 people in either group will be unblinded, and we'd lose
18 them both at least to the randomization.

19 The remaining cohort, therefore, will probably
20 be at lower risk, and the higher risk ones will be the

1 ones we will either potentially -- they will request
2 unblinding or we will offer the unblinding because they
3 become eligible.

4 Once a vaccinated person realizes they've been
5 vaccinated, they will probably engage in higher-risk
6 behavior, which will, for at least the one to two
7 months after the unblinding, will make them a more
8 difficult comparison group to the placebo group.

9 And finally -- not finally -- patient-reported
10 outcomes for the unblinded group can be biased in terms
11 of how people interpret various symptoms. They'll be
12 an impaired ability to evaluate waning vaccine efficacy
13 in the first six to eight weeks after crossover. After
14 eight weeks, everybody knows they've been vaccinated,
15 but, before this time, that vaccine efficacy is
16 uncertain.

17 And it has unpredictable effects on trial
18 retention, particularly safety assessment visits post-
19 crossover. Because once you do the unblinding, there's
20 a sense that, well, the experiment is over. You know,

1 you're coming back, you're giving information, but we
2 don't have the same sort of bonding to the trial in the
3 sense that adherence to the dictates are actually
4 critical for validity.

5 If we were going to completely unblind the
6 placebo group, then we lose a lot from the evidential
7 side. There's no comparison group to compare rates of
8 infection or safety. So the duration of protection and
9 long-term hazards will be much more poorly assessable:
10 very unpredictable effect on retention, again, in the
11 sense that the trial is over. Quality of evidence for
12 licensure will be only marginally different than that
13 for the EUA because of what we've giving up.

14 Actually, it weakens the scientific value of
15 the trial that is pledged to the participants on
16 enrollment. This can easily be done if there are good
17 reasons, but shouldn't be done if there are good
18 alternative, particularly ones that give them the
19 vaccine anyway.

1 Finally, this may make placebo-controlled
2 trials more difficult for other vaccines. We have a
3 very strong interest in developing good information for
4 those other vaccines because there will be a precedent,
5 that as soon as something has been shown to be
6 effective and it's available, that it's unethical to
7 ask people to wait any more time to be immunized in any
8 way. And this is a precedent you may not want to set.

9 I have a couple slides here on what the value
10 of having more vaccines is. I actually think this
11 committee knows it very, very well. They could have
12 different immunization properties. We might find that
13 they're better in combination, and they might have
14 different safety profiles and acceptance. It might
15 have different distribution and uptakes. But I'm not
16 going to go through this, but you have these slides
17 available.

18 So the last few slides, I just want to talk
19 about the ethical impact on the unblinding, which is
20 the trust in the whole trial system. Immediate

1 unblinding of vaccination could become a precedent and
2 a de facto expectation for others, perhaps undermining
3 either ongoing or new placebo-controlled trials. A
4 sense could take hold that even temporary withholding
5 of vaccination within a trial is "unethical" because it
6 was done in preceding trials.

7 I would suggest that the images of -- we have
8 to remember that what happens -- what we're doing here
9 if we do unblind, is we're disturbing the priority set.
10 That is we're going to be vaccinating young, low-risk
11 trial participants. And this will get out in the
12 community very different than the pictures we saw after
13 the authorization last week where it was healthcare
14 workers and others. So the images of young, low-risk
15 trial participants being knowingly vaccinated before
16 much higher-risk community members could adversely
17 affect trust in the fairness of the vaccine testing
18 system and the allocation system.

19 We'll then start looking very closely the
20 trial recruitment and enrollment procedures on all

1 trials, to see how we are choosing people who are in
2 the trials who then will jump the queue. And that is a
3 scrutiny we may or may not want to have done so
4 aggressively, that the enrollment in the trial is, in a
5 sense, a privileged position with regard to trial
6 vaccine administration.

7 And it may be dangerous to have different
8 ethical-evidential tradeoffs made in each trial, by
9 each company -- and there are a lot more coming as you
10 know -- thereby also bypassing societal priority
11 setting for vaccine access. These priorities are
12 generally regarded as fair, partly because the
13 processes that created them is perceived as fair. If
14 these are overridden in individual trials, there could
15 be very unpredictable effects on perceptions by groups
16 underrepresented in the trials and by the public.

17 If these trade-offs are trial and company
18 specific, then there'll be a rush by some current and
19 prospective participants to game the system in their
20 favor -- because everybody'll be looking for the trial

1 that does better by them -- thereby undermining an
2 ethos that we are all in this together, and that we
3 need to act collectively for the greater good.

4 So this trial-by-trial resetting of the
5 ethical prioritization system, I think, is something
6 that we have to think about from a large -- with a wide
7 lens. And here's the widest lens, which is the
8 evolution of designs that we're going to be
9 experiencing as EUAs are issued. And we're, right now,
10 at this very early point where there was no EUAs or
11 vaccine is unavailable to some folks.

12 And that's the only context in which we can do
13 these placebo-controlled trials. And we're getting the
14 benefit of those right now, but we're very rapidly --
15 in fact today and last week -- moving into this new era
16 where there's some EUA's available, some vaccines
17 available.

18 And then we might find that the deferred
19 vaccination RCT's planned from the inception, not this
20 conversion, will become the standard. That is we

1 believe that we can reasonably ask people to put off
2 vaccination for a few months, but, in the consent, it
3 will say, after a few months you will be vaccinated.

4 I believe we're going to very rapidly move
5 into that, and that asking for these trials to be in
6 that category would be a great precedent to allow that
7 transition so future studies can be designed with that.

8 Finally, once we get the BLAs issued -- the
9 approvals -- we're probably going to have to move into
10 an era -- and I don't know exactly when this will be,
11 but probably sooner rather than later -- where the only
12 RCTs we're able to do in populations that have the
13 vaccines available are active control RCTs. And, for
14 these, we really need good surrogate endpoints. We
15 really need good correlates of immunity, and that's
16 what we're getting -- we have the opportunity to get
17 right now. And if we undermine that, it's going to
18 weaken the interpretability of the later active control
19 RCTs.

1 So I'd like to strongly encourage you to look,
2 take the long view, look at this as a vaccine
3 development ecosystem. And then, if we can keep the
4 same standards for all of the trials, particularly the
5 priority setting for vaccine administration -- and, as
6 I mentioned, none of the current international priority
7 setting agreements include participation in a trial as
8 a priority, unless of course you fall in traditional
9 high-risk groups.

10 So, if we're consistent across all trials, I
11 think, they'll both be more comparable, we will enhance
12 trust in the system, and we'll be consistent across the
13 board. If we start making it company-by-company,
14 trial-by-trial exceptions, I think, we're going to run
15 into, rather quickly, problems with trust and
16 retention.

17 So, with that, I will thank you for listening,
18 yet again. And I want to, in particular, thank the
19 participants in the trial so far who've enabled us to
20 have this conversation today, whose contribution was

1 and will continue to be a tremendous gift to all of us.
2 Thank you very much.

3 **DR. MONTTO:** Thank you very much, Dr. Goodman.
4 You went over a bit, but this was a very important
5 presentation for our further thinking. I just want to
6 reiterate what you have said, and that is that the
7 crossover is not really just one design, it's a design
8 which will vary by when a crossover is done. Am I
9 correct in that?

10 **DR. GOODMAN:** Uh, yes. And one thing I'll
11 also add is that it doesn't necessarily have to be for
12 individuals. It could be that the stage -- that the
13 crossover is staged by priority group. That if it's
14 preplanned every two weeks or every month, the next
15 priority group will come in. But, yes, it does depend
16 on when it's done, and you want to maintain it as long
17 as you can, as long as it's practical.

18 **DR. MONTTO:** And this could be part of future
19 consent forms. So you don't have the logistic
20 challenge now of reconsenting individuals.

1 **DR. GOODMAN:** Yes, absolutely. This could be
2 prespecified, and I think as the design of the trial,
3 that the trial from inception is designed this way.
4 And it seems inevitable, honestly. If we're talking
5 about converting these placebo-control trials into
6 this, it's hard to imagine doing a complete placebo
7 trial going forward. So I do think that is what we
8 will evolve to, but that's something you can discuss.

9 **DR. MONTO:** Okay. We have about ten minutes
10 now for discussion, but we're going to circle back and
11 rediscuss all of this after we hear the sponsor
12 presentations. Okay. Dr. Chatterjee, please. And I
13 think some people have unmuted their phones.

14 **DR. CHATTERJEE:** Dr. Goodman, thank you for
15 your presentation. I wanted to ask this question last
16 week actually, which is, is it not going to be
17 difficult to maintain the blind in any of these
18 crossover trial designs that you're talking about.
19 Because of the difference in the adverse events, the
20 vaccines are clearly much more reactogenic than the

1 placebo. But at least the recipient, and presumably
2 the people conducting the trial, would become aware of,
3 or could guess, which product they received.

4 **DR. GOODMAN:** Absolutely. I do think for a
5 certain subset of folks, they will be able to guess
6 more often. But remember there's a fair overlapping in
7 symptoms. That is, even things like chills, which you
8 would think would be vaccine specific, are occurring in
9 the placebo group as well. So it is true that that
10 symptom and others occur more often, absolutely, in the
11 vaccine group. But the occurrence of any of these
12 symptoms won't necessarily unblind.

13 And still it won't be as complete an
14 unblinding. It's really all relative, obviously, as
15 that you tell people, this is what you got. People may
16 well suspect that. I don't think they necessarily act
17 in ways that assume that they were vaccinated. For
18 example, if that happened, you would imagine that
19 people in the current trials or in future trials, when
20 they got those reactions would go out with very high-

1 risk behavior. That's really what we're trying to
2 avoid, but absolutely.

3 All I can say is it will occur more with the
4 unblinding than it will with a continued blind. And
5 we're trying to preserve as much as we can for valid
6 inferences. But you're absolutely right, this is not -
7 - and it's true in also in therapeutic trials as well.
8 So it's a relative issue. It's not that this
9 completely unblinded with the blinding -- I'm sorry --
10 that blinding is perfect, but it's much better.

11 And also there's this other sense of sort of
12 staying within the experimental framework and not
13 leaving the trial and making it impossible. We haven't
14 even talked about, you know, further follow up,
15 whatever, and retention for all the other endpoints.

16 So you're right about that, but I still think
17 it's preferential from both an evidential point of view
18 than basically just telling everybody which arm they
19 were in.

20 **DR. CHATTERJEE:** Thank you.

1 **DR. MONTO:** Dr. Meissner.

2 **DR. MEISSNER:** Dr. Goodman, I would like to
3 thank you again for another very thoughtful and clear
4 presentation on this really difficult issue.

5 I'd like to make a comment and a question. As
6 a former chair of the Vaccine Injury Compensation
7 Program, it's important to have as careful in
8 understanding as we can reasonably acquire from longer-
9 term follow up of vaccinees. I think the Vaccine
10 Injury Compensation Program has had an enormously
11 favorable impact on the uptake of vaccines in the
12 United States, and has resulted in the highest uptake
13 of vaccines in history.

14 I would certainly encourage the blinded
15 crossover design that you have proposed, because that
16 may give us some opportunity to evaluate long-term
17 complications between a vaccinated group and an
18 unvaccinated group. So I would just like to support
19 that.

1 And then the second question I have, and it
2 may not be answerable, but has Pfizer made any decision
3 as to how they're going to follow subjects based on
4 your first presentation? Thank you. Over.

5 **DR. GOODMAN:** Actually, that will have to be
6 your last question about what Pfizer will do, and
7 obviously today is not about that. But you could ask
8 the same question about what the consequences will be
9 in the decisions for Moderna as well. I don't know.
10 That's going to be a question for the FDA. I don't
11 know what the nature of their conversations with either
12 of these companies about the requirements in the BLA.

13 I think that's where this will play out, not
14 necessarily in the EUA but in the subsequent request
15 for the kind of information they would like for the
16 BLA. And I don't know what is happening as a
17 consequence of after last week's meeting, just as I
18 probably will not know after this week's meeting. But
19 that is something for you to ask the FDA, and ask the

1 FDA representatives what they're working for or what
2 they think they can ask.

3 **DR. MONTTO:** Dr. Kurilla.

4 **DR. KURILLA:** Thank you. Dr. Goodman, this
5 has to be one of the most insightful, ethical
6 discussions I've been privileged to listen to, so thank
7 you for that.

8 The question I have concerned the ongoing
9 trials. If we were to do a blinded crossover, I'm
10 wondering how two populations would be handled. The
11 first is people who actually develop COVID, what do we
12 do with them? Are they done? Do we just -- they just
13 fall out or? And the other population, because of the
14 unreliability of serology in this regard, that unless
15 you catch it in the very post-acute phase, you may not
16 necessarily be able to recognize someone, there's going
17 to be an increasing percentage within both arms from
18 asymptomatic infection, and they may be contributing to
19 immunity and that's going to complicate. I'm just

1 wondering how you think going forward that can be
2 handled appropriately with those populations?

3 **DR. GOODMAN:** Yeah, fantastic question. So
4 there was a line in my slide of what we could learn
5 that said, for the ability to prevent infection --
6 which is really catching the asymptomatic -- and
7 infectiousness, other designs may be needed. So this
8 won't necessarily capture that well unless you did very
9 frequent serology. And even then, as you say, the
10 serology's not perfect.

11 So this means we can capture a little bit of
12 that, particularly if we increase the number of
13 serologies. We almost certainly can't do that if
14 they're not retained in a semi-randomized study. And
15 that's all I will say.

16 I think that's something for the FDA to think
17 about for both the observational designs going forward,
18 but it is something that could be done better within a
19 blinded crossover, and I think more successfully than
20 if it's not blinded. But it is an incredibly important

1 question. We can get partial information out of it
2 here better blinded, but not perfect. I think we're
3 going to have to lean heavily on other designs as well.

4 **DR. KURILLA:** Thank you.

5 **DR. MONTO:** Final question. The other people
6 who've got their raised, please circle back. We're
7 going to have more discussion later. Dr. Rubin.

8 **DR. RUBIN:** Thanks. I'll echo what everyone
9 else said, Dr. Goodman. Thank you for coming and
10 speaking with us twice.

11 Of course, what you're arguing about is very
12 compelling, particularly, I think, for the adverse
13 events. I think we will learn something about that
14 waning immunity from observational trials, but this
15 really does preserve the ability to look AEs. And
16 clearly, I think it's the way that they should have
17 been designed.

18 But let me ask about the logistics of
19 implementing it now, right now, for the Pfizer vaccine
20 or Moderna, should it receive an EUA, people are

1 already getting a vaccine. And they're getting vaccine
2 in specific groups, so that high-risk groups are
3 getting it first. And we may already be losing those
4 people. So is it, do you think, going to be practical
5 to implement this design at this point?

6 **DR. GOODMAN:** So, as I mentioned, what this
7 does is it keeps the groups equal. So, yes, you might
8 lose preferentially, for example, all the healthcare
9 workers at the beginning. You'll lose them from both
10 the placebo arm and the vaccine arm in terms of the
11 blinded part. But then you have a period of time
12 before maybe the folks in the older risk groups, I
13 mean, there's a sequencing.

14 So you lose them sort of slice by slice. And
15 in terms of logistics, whether you do that on an
16 individual basis, or whether you plan it into the
17 trial. And you simply say, this strata will be crossed
18 over, you know, at 2.5 months after the two months of
19 observation of the placebo groups, the next one three
20 weeks later, the next one three weeks later.

1 So yes, you sequentially lose from the blinded
2 part, not from follow up, the highest risk patients.
3 But you can still learn a lot from those who are left.
4 But the cohorts do change, but they stay comparable in
5 the two arms.

6 **DR. MONTO:** Thank you, Dr. Goodman, and please
7 stick around for -- what will be late morning for you -
8 - for the discussion later on.

9 **DR. GOODMAN:** Okay.

10 **DR. MONTO:** Now, it's my pleasure to introduce
11 representatives of the sponsor. We're going to hear
12 from Dr. Tal Zaks and Jacqueline Miller from Moderna.
13 Please.

14

15 **SPONSOR PRESENTATION: EMERGENCY USE**

16 **AUTHORIZATION (EUA) APPLICATION FOR MRNA-1273**

17

18 **DR. ZAKS:** Good morning. Can everyone hear me
19 okay?

20 **MR. KAWCZYNSKI:** Yes, sir. Go ahead.

1 **DR. ZAKS:** Okay. Thank you. Good morning.
2 My name is Tal Zaks, and I'm the Chief Medical Officer
3 at Moderna. On behalf of myself and my colleagues, I'd
4 like to thank the committee and FDA for the opportunity
5 to present our data today.

6 We've carefully watched and listened to the
7 meeting last week and, in preparing our presentation
8 for today, we've attempted to proactively address many
9 of the topics raised at that meeting and in the days
10 that have followed. We have been developing our mRNA-
11 1273 vaccine with a goal to seek global licensure for
12 the prevention of the COVID-19 disease. And are here
13 today seeking Emergency Use Authorization based on
14 Phase 3 safety and efficacy data.

15 I don't need to belabor the damage this virus
16 continues to wreck directly on our health and
17 indirectly on our society and our way of life. Since
18 the pandemic began, we at Moderna have moved rapidly to
19 leverage the advantages of our mRNA platform. And
20 we've been working closely with colleagues from the

1 National Institutes of Health to develop our vaccine.
2 We've done so in a very transparent manner, sharing our
3 Phase 3 clinical trial protocol as well as recruitment
4 metrics with the public.

5 Let me briefly explain the merits of our
6 vaccine. mRNA-1273 is based on messenger RNA, a
7 molecule that is fundamental to the biology of every
8 living cell and serves as the blueprint for all protein
9 syntheses. Our vaccine uses our body's own cells to
10 activate the immune system. It enables these cells to
11 make only the part of the virus that is critical for
12 the immune system to recognize: in this case, the spike
13 protein.

14 Importantly, our vaccine platform has some
15 inherent safety features: the mRNA does not self-
16 replicate, does not enter the nucleus, and does not
17 integrate into our DNA. The manufacturing process is
18 cell free. It does not use products of animal or human
19 origin, and it does not contain preservatives or

1 adjuvants, thus avoiding some of the potential concerns
2 of older vaccine technologies.

3 Now mRNA-1273 is not our first infectious
4 disease vaccine. In fact, we've been in early phase
5 clinical trials for the past five years conducting 12
6 clinical trials that have enrolled over 17 hundred
7 healthy volunteers. SARS-CoV-2 is the ninth virus
8 against which our mRNA vaccines have elicited
9 neutralizing antibodies. And we have not seen a
10 significant safety concern in any of our trials to
11 date.

12 Since the company's inception, we've been
13 investing heavily in understanding the critical quality
14 attributes of our mRNA medicines. And we have been
15 using these insights to continuously improve our
16 process and manufacturing capability. We've leveraged
17 this progress, at the start of the pandemic, to develop
18 a product that remains potent and stable in cold chain
19 shipping and storage conditions, that are widely
20 available in hospitals, pharmacies, and assisted living

1 and skilled nursing facilities. At the point of care,
2 mRNA-1273 can be deployed in a multiuse vial with no
3 further mixing or dilution, while remaining stable for
4 up to 12 hours at room temperature.

5 Our Phase 3 study, which is the basis of our
6 presentation today, was conducted in collaboration with
7 the NIH and in accordance with clear FDA guidance. It
8 enrolled over 30 thousand participants, and we believe
9 the results support Emergency Use Authorization. mRNA-
10 1273 efficacy clearly exceed the recommendations for an
11 EUA and eventual licensure.

12 The vaccine efficacy rate for symptomatic
13 COVID-19 infection was 94.1 percent with a 95 percent
14 confidence interval lower bound of 89.3 percent. These
15 results are clinically meaningful and highly
16 statistically significant. The efficacy observed is
17 broadly consistent across all evaluated subgroups.

18 Importantly, we also observed a dramatic
19 reduction in severe cases. All of the 30 severe cases
20 observed at the time of primary analysis occurred in

1 people given placebo. A reduction in total symptomatic
2 cases predicts a reduction in cases leading to
3 hospitalization, intensive care, and death.

4 Finally, data from nine weeks of median
5 exposure in more than 15 thousand people vaccinated
6 with mRNA-1273 have well characterized the short-term
7 safety profile. We see generally good tolerability.
8 Most solicited injection site reactions and systemic
9 adverse events were reported as mild to moderate and
10 resolved quickly.

11 It is important to note, and to educate
12 people, that we see an increased rate of severity of
13 expected systemic symptoms like headache and myalgia
14 after the second dose. We view these as consistent
15 with a potent activation of a specific immune response.
16 They are transient and self-limited, and we do not see
17 a significant safety risk. These results support
18 acceptable benefit risks for broad population
19 vaccination to help prevent COVID-19 infections.

1 We acknowledge the need for longer term safety
2 and effectiveness data. We will continue to
3 transparently share our data, and the independent DSMB
4 will continue to monitor safety as well as monitoring
5 the duration of immunity and effectiveness. And we
6 will continue to leverage the Phase 3 trial, even as we
7 amend it to enable access to participants who received
8 placebo.

9 Now, in this regard, we face some unique
10 circumstances. First, as it relates to vaccine
11 supplies, none of our trial participants would be
12 quote/unquote jumping the line ahead of others, because
13 we have clinical trial supplies available that, in
14 fact, would expire and go to waste if we don't use
15 them.

16 Second, all of our participants are at
17 increased risk of infection, and many have risk factors
18 for severe disease. One of the participants on our
19 placebo arm died from COVID-19 during this trial. He

1 was a 54-year-old male whose sole risk factor was
2 diabetes.

3 I'll defer to Dr. Baden to describe our
4 proposed next steps on the trial, which will continue
5 to be overseen by the DSMD and should provide
6 significant additional data on both safety and
7 effectiveness.

8 Now beyond the Phase 3 trial, Moderna will
9 conduct additional studies in active pharmacovigilance
10 to gain a more comprehensive understanding of the
11 vaccine risk profile over time. We are initiating
12 pediatric clinical trials, collaborating with the
13 National Cancer Institute to evaluate the vaccine's
14 safety and immunogenicity in people with cancer, and
15 will continue to collaborate with FDA and other
16 agencies to gather additional long-term safety data.

17 Here now is the agenda for the rest of our
18 presentation. Let me now turn it over to Dr. Melissa
19 Moore.

1 **DR. MOORE:** Hello. Good morning. My name is
2 Melissa Moore, and I am the Chief Scientific Officer of
3 Platform Research at Moderna. I'm also a professor in
4 the RNA Therapeutics Institute at the University of
5 Massachusetts Medical School.

6 Over the next few minutes, I will walk you
7 through a description of Moderna's vaccine platform
8 and, specifically, our COVID-19 vaccine mRNA-1273.

9 As the basis of our vaccine, we created a
10 messenger RNA, or mRNA, that only contains the
11 instructions to make the SARS-CoV-2 spike protein in a
12 pre-fusion confirmation. We manufacture this mRNA in
13 large quantities in a cell-free process that utilizes
14 no ingredients of human or animal origin. We then
15 formulate this mRNA with lipids to form lipid
16 nanoparticles, or LNPs. As can be seen in the electron
17 micrograph at the bottom right, our GMP manufacturing
18 process yields a highly consistent product about a
19 hundred nanometers in diameter.

1 In addition to the mRNA and lipids, the only
2 other ingredients in the vial are water, sucrose, and
3 two FDA-approved pharmaceutical buffers. Importantly,
4 our vaccine contains no preservatives, no antibiotics,
5 no adjuvants, and all components are rapidly cleared
6 from the body. When our vaccine is entered
7 intramuscularly, it is primarily taken up in the
8 draining lymph nodes by specialized immune cells known
9 as antigen presenting cells, or APCs. Once inside the
10 antigen presenting cell, mRNA instructs the cells
11 protein synthesis machinery to make the spike protein,
12 which is then displayed on the cell's surface.

13 In the lymph node, this allows B cells and T
14 cells to interact with the spike protein and develop an
15 adaptive immune response. This adaptive immune
16 response includes production of antibodies and the
17 development of T cell responses against the spike
18 protein, resulting in both humoral and cell mediated
19 immune memory. Once the mRNA has done its job, it is
20 degraded.

1 Importantly, our mRNA vaccine has no capacity
2 to alter DNA. First, our externally delivered mRNA
3 constitutes only a tiny fraction of all mRNA molecules
4 in the cell. Second, our mRNA is transient and remains
5 in the cytoplasm until eliminated by the natural mRNA
6 decay process. To alter DNA, our mRNA would have to
7 both gain access to the nucleus and be reverse
8 transcribed. Our mRNA contains no signals for nuclear
9 access and no known signals for reverse transcription.

10 Though in summary, mRNA-1273 directly educates
11 the immune system by instructing antigen presenting
12 cells to synthesize the SARS-CoV-2 spike protein. In
13 this way, it efficiently drives an adaptive immune
14 response by protein expression in situ. Finally, our
15 mRNA can neither interact nor can it integrate into
16 DNA. Thank you. I'll now pause and hand the
17 presentation over to Dr. Jacqueline Miller to discuss
18 mRNA-1273 efficacy.

19 **DR. MILLER:** Morning. My name is Dr.
20 Jaqueline Miller, and I am the senior vice president

1 and therapeutic area head of Infectious Diseases at
2 Moderna. I'm please to share with you today some of
3 the details of our clinical development program in our
4 key immunogenicity and efficacy results. Before moving
5 to our clinical program, I would like to review our key
6 non-clinical results.

7 We generated an extensive non-clinical data
8 package in three different animal models including non-
9 human primates, or NHPs. Our data demonstrate that
10 mRNA-1273 induces humeral and cellular immunity,
11 including memory B cells in vaccinated animals. We
12 also challenged these animals with SARS-CoV-2 virus and
13 found that the vaccine could fully protect animals at
14 sub-therapeutic doses. No evidence of vaccine-
15 associated enhanced respiratory disease. We have
16 recently completed our developmental and reproductive
17 toxicology study which indicated no safety concerns.

18 Development of mRNA-1273 has been accelerated
19 given the COVID-19 pandemic. Nonetheless, a full
20 development program including Phase 1, 2 and 3 studies

1 have been executed. Study 101 was our Phase 1 dose-
2 ranging safety and immunogenicity study conducted
3 across three age strata: 18 to 55, 56 to 70, and over
4 71 years of age. Study 201 was a Phase 2 safety and
5 immunogenicity study.

6 The primary focus of our presentation will be
7 the Phase 3 COVID-19 efficacy and safety study, or 301,
8 as it enrolled over 30 thousand participants,
9 approximately 15 thousand of whom received mRNA-1273.
10 Study 301 generated the vast majority of safety in all
11 of the efficacy data.

12 So let's begin with the study 101. This slide
13 summarizes the neutralizing antibodies induced by 100
14 micrograms of mRNA-1273 across three age strata. The
15 shaded area represents a range of titers, from a panel
16 of convalescent sera, taken from individuals recovering
17 from COVID-19 disease. It serves as the clinical
18 benchmark to compare immunogenicity between the doses
19 and the (audio skip). Samples were collected from 23
20 to 54 days after diagnosis. Neutralizing antibodies

1 were induced in all participants by Day 36 for one week
2 after Dose 2. GMTs were comparable across the three
3 age strata including participants in the older age
4 strata and persisted until day 119.

5 Now, let's discuss the T cell immunity
6 evaluated in Study 101. CD4 T cells were further
7 evaluated for Th-1 and Th-2 phenotypes since T cells
8 are thought to be associated with enhanced disease. The
9 top panel of this slide represents the Th-1 phenotype,
10 and the bottom panel is the Th-2. Th-1 dominant CD4 T
11 cells are induced by Day 43 across age strata, minimal
12 detection of the Th-2 phenotype. This analysis showed
13 no evidence of enhanced disease.

14 I'd now like to present the immunogenicity
15 results for the 100 microgram in placebo groups in
16 Study 201. The dark blue bars represent the hundred
17 microgram dose, and the gray bars represent placebos.
18 By Day 43, there was more than a 50-fold increase in
19 geometric mean titers in the vaccine group. And in the

1 placebo group, GMTs remained below the level of
2 quantitation.

3 So, in summary, our Phase 1 and 2 studies
4 showed the induction of neutralizing antibody titers in
5 all participants by one week following the second dose.
6 GMTs were observed to be higher than those of a panel
7 of convalescent sera, and neutralizing antibodies
8 persisted for three months after the second dose across
9 all three age strata. Th-1 dominant CD4 T cell
10 response was also observed across age strata and was
11 consistent with our findings in animal models.

12 So now, let's look at the efficacy data from
13 Study 301. Study 301 was designed to evaluate the
14 efficacy, safety, and immunogenicity of mRNA-1273
15 compared to placebo in adults at least 18 years of age
16 who are at risk for COVID-19. Thirty thousand four
17 hundred twenty participants were randomized one to one
18 and received two doses: vaccine or placebo.
19 Participants received the first dose on Day 1 and the
20 second dose one month later on Day 29. Participants

1 have been monitored for efficacy, immunogenicity, and
2 safety endpoints throughout the study.

3 Immunogenicity endpoints include the measure
4 of binding and neutralizing antibodies at the indicated
5 timepoints. These immunogenicity samples will also be
6 used to assess for asymptomatic zero conversion non-
7 vaccine antigen. These data were not available for the
8 emergency use submission and will not be discussed for
9 today.

10 Efficacy surveillance occurred throughout the
11 study. Once diagnosed with COVID-19, participants
12 underwent daily telemedicine visits to ensure close
13 medical follow up. Participants were also given pulse
14 oximeters to manage their oxygen saturation daily.

15 Study 301 primary efficacy objectives were
16 based on COVID-19 cases that occurred in SARS-CoV-2
17 sera negative participants that demonstrated success.
18 The lower limit of the 95 percent confidence interval
19 for vaccine efficacy had to be greater than 30 percent.

1 Secondary endpoints for vaccine efficacy
2 include the evaluation of efficacy against severe
3 disease and death, COVID-19 using the CDC case
4 definition, and COVID-19 cases occurring after the
5 first dose. There was also a secondary objective to
6 evaluate asymptomatic SARS-CoV-2 infections, but the
7 results are not yet available.

8 Please let me review the case definition for
9 COVID-19 and severe COVID-19 disease. Primary efficacy
10 endpoint were symptomatic, adjudicated COVID-19
11 diseases that occurred at least 14 days after dose 2.
12 To be considered a case of COVID-19, a study
13 participant had to have experienced at least two
14 systemic symptoms, or at least one respiratory sign or
15 symptom or clinical or radiographical evidence of
16 pneumonia and confirmed SARS-CoV-2 infection from at
17 least one naso- -- (audio skipped).

18 Study 301 also analyzed efficacy against
19 severe COVID-19. Severe cases had to meet all criteria
20 for the primary endpoint and have at least one of the

1 four following criteria: severe systemic illness; or
2 respiratory failure, acute respiratory distress
3 syndrome or evidence of shock; or significant acute
4 organ disfunction; or admission to an ICU or death.

5 To ensure adequate safety monitoring and to
6 enable the interim efficacy analyses to (audio skip)
7 this study has been monitored by a data and safety
8 monitoring board or DSMB. DSMB was chartered and
9 convened by the National Institutes of Health and is
10 completely independent from the company.

11 In addition, an independent efficacy endpoint
12 adjudication committee was assembled to determine if
13 the case definitions for COVID-19 and severe COVID-19
14 were met. This committee has adjudicated all cases for
15 the primary efficacy endpoints and continues to
16 adjudicate cases as they accrue and will ultimately
17 adjudicate all COVID-19 cases reported.

18 Thirty thousand four hundred twenty
19 participants were randomized in Study 301 including
20 15,210 subjects to each group. The full analysis set

1 includes 15,181 participants who have received at least
2 one dose of mRNA-1273. A modified intent to treat
3 population includes participants who had no evidence of
4 infection prior to receiving their first dose of study
5 vaccine or placebo.

6 Per-protocol population was redefined for the
7 primary efficacy analysis. It includes participants in
8 the MITT who received both planned doses and had no
9 major protocol deviations. More than 92 percent of
10 participants vaccinated in both treatment groups are
11 part of this population.

12 Now, let's return to the efficacy results.
13 Enrollment was stratified to ensure that we studied
14 participants most at risk for COVID-19. We pre-
15 specified that at least 25 percent of our study
16 population would include participants over 65 years of
17 age or subjects between 18 and 65 with comorbid medical
18 conditions. We were successful and enrolled a total of
19 42 percent of the study population in these two
20 categories.

1 Let's review the study demography by gender
2 and age. Approximately equal proportions of males and
3 females participated, and the mean age was 51, the
4 range of 18 to 95 years. Twenty five percent of the
5 study population was over 65 years of age, and half of
6 those individuals were over 70. Age and gender
7 distribution were well balanced between (audio skip).
8 This trial included approximately 10 percent African
9 Americans, 5 percent Asian Americans, ad 21 percent of
10 participants who identified as being Hispanic.

11 This is the breakdown of the comorbid
12 conditions reported in the study: 23 percent of
13 participants overall reported at least one pre-existing
14 condition. That included nine percent with diabetes
15 mellitus, seven percent with severe obesity, five
16 percent each with significant cardiac disease or
17 chronic lung disease. A specific inclusion criterion
18 was that participants had to be at increased risk for
19 COVID-19.

1 Overall, 25 percent of our study participants
2 are healthcare providers, and a substantial proportion
3 of the remaining subjects meet the definition for
4 essential workers, making together the participants
5 depicted on this table represent more than 50 percent
6 of our study population.

7 So here are the numbers of COVID-19 cases
8 contributing to the primary endpoint by demographic
9 subgroups. Thirty-three cases occurred in the elderly,
10 including ten of the severe cases. Forty-two cases
11 occurred in people from communities of color that have
12 been disproportionately impacted by COVID-19.

13 This slide displays the primary efficacy
14 results for the prespecified interim analysis. Primary
15 efficacy hypothesis was met. Vaccine efficacy after
16 the second dose was 94.5 percent with the lower limit
17 of 86.5 percent. The difference between groups was
18 statistically significant. The p-value less than
19 0.0001. The incidence rate in the vaccine group was
20 1.8 as compared to the 33.4 1000 person-years in the

1 placebo group. This interim analysis was submitted as
2 part of Moderna's EUA application currently under
3 review by the EUA.

4 A second analysis was performed when the full
5 pre-specified cohort of 151 cases of COVID-19 had
6 accrued, and the 2-months median follow up timepoint
7 had passed. This analysis was predefined in the
8 protocol as the primary efficacy analysis. There were
9 196 cases: 11 of which occurred in the vaccine group
10 and 185 occurred in the placebo group. Vaccine
11 efficacy was 94.1 percent with the lower limit of 89.3
12 percent. The difference between the groups was also
13 statistically (audio skip). Incidence rate was 3.3 in
14 the vaccine group compared to 56.5 in the placebo
15 group.

16 Now, I would like to show you a forest plot of
17 various subgroup analyses we performed on the primary
18 endpoint stratifying the population by age, gender,
19 race, and risk factors. All subgroup analyses were

1 consistent with the primary analyses, finding
2 confidence to the generalized ability of the efficacy.

3 We also evaluated the efficacy of mRNA-1273
4 against severe COVID-19 disease, the secondary
5 objective. Thirty severe cases have been adjudicated
6 at the time of the primary efficacy analysis and all
7 occurred in the placebo group resulting in a point
8 estimate of vaccine efficacy of 100 percent. There's
9 also a single death due to COVID-19 reported in the
10 placebo group.

11 We have also evaluated efficacy according to
12 the CDC's case definition, which required only one
13 clinical symptom from an expanded list and a swab
14 positive for SARS-CoV-2 virus. Point estimate of
15 efficacy with this definition, 95.1 percent, which is
16 highly consistent with the primary efficacy hypothesis.

17 We have also investigated that the efficacy
18 against cases of COVID-19 which occurred 14 days after
19 dose one as a secondary objective. There were 11 cases
20 in the vaccine group compared to 225 cases in the

1 placebo group for an overall estimate of vaccine
2 efficacy of 95.2 percent. The result is limited by
3 fact that not all cases are adjudicated. More than 96
4 percent of participants received their second dose.
5 The analysis included cases which occurred after the
6 second dose. Nonetheless, the fact that the efficacy
7 estimate is so consistent with the primary analysis is
8 (audio skip).

9 The Kaplan-Meier curve, the cases that
10 occurred in the modified intent to treat cohort since
11 randomization are shown on this slide supporting the
12 secondary efficacy analysis -- for efficacy after the
13 first vaccination. Based on this, we also evaluated
14 the percentage of subjects in the modified intent to
15 treat cohort according to the CDC case definition which
16 occurred after randomization. We'll see on the next
17 slide.

18 So these are all the cases reported in each
19 group stratified by two-week intervals up to the second
20 dose. Overall, prior to 14 days Post-Dose 2, there

1 were 62 cases in the placebo group as compared to 8
2 cases in the vaccine group. Most of the cases in the
3 vaccine group were reported in the first two weeks
4 after vaccination. Taken together, these analyses
5 suggest that protection may begin prior to Dose 2, but,
6 for maximum protection, both doses should be given.

7 Our protocol specified analysis on the
8 efficacy against asymptomatic infection was not
9 available at the time of the EUA submission. However,
10 it did collect Pre-Dose 1 and Pre-Dose 2 swabs for
11 SARS-CoV-2 virus and has performed a descriptive
12 summary comparing the number of positive swabs as a way
13 to estimate asymptomatic infection.

14 Among baseline negative participants -- 14 in
15 the vaccine group and 38 in the placebo group -- had
16 evidence of SARS-CoV-2 infection at the second dose
17 without reporting symptoms. There were nearly two-
18 thirds fewer positive swabs in the vaccine group as
19 compared to the placebo group at the Pre-Dose 2

1 timepoint suggesting the possibility for prevention of
2 asymptomatic infection.

3 So, in conclusion, mRNA-1273 has demonstrated
4 clear and compelling evidence of vaccine efficacy
5 against symptomatic COVID-19 disease. Vaccine efficacy
6 was 94.1 percent, the lower limit of the 95 percent
7 confidence interval of 89.3 percent successfully
8 meeting the primary efficacy hypothesis and exceeding
9 the FDA guidance for COVID-19 vaccine.

10 At the time of the data cutoff, 30 cases of
11 severe COVID-19 had occurred in the placebo group, and
12 no cases had occurred in the mRNA-1273 group. Efficacy
13 against severe disease is reassuring about the lack of
14 enhanced disease, and participants in this trial will
15 continue to be followed for breakthrough disease.

16 All key secondary sensitivity and subgroup
17 analyses were consistent with primary analysis
18 underscoring the performance of the vaccine across
19 high-risk populations. Given this high and consistent

1 efficacy, mRNA-1273 offers the potential to address the
2 public health crisis of COVID-19.

3 Thank you. I'd like to invite Dr. David
4 Martin, the head of Pharmacovigilance at Moderna, to
5 discuss the safety data.

6 **DR. MARTIN:** Good morning. My name is David
7 Martin, and I'm the vice president of Pharmacovigilance
8 at Moderna. I will review our safety results from
9 Study 301 whose vast study represents 97 percent of
10 total mRNA-1273 vaccine exposures.

11 I will present the nine-week median exposure
12 follow up data using the same November 25th data cutoff
13 as the primary efficacy analysis. This provides 6,579
14 person-years of safety data. It represents 20 percent
15 more follow-up time than previously available in our
16 EUA submission, which was based on a seven-week median.
17 Let's take a look at the Study 301 safety data.

18 More than 30 thousand participants were
19 enrolled and received at least one dose. In both
20 groups, compliance with getting a second dose was high.

1 About 97 percent of participants received the second
2 dose. As of the data cutoff, more than 60 percent had
3 complete two-months follow up.

4 Now moving to the data. Beginning with
5 solicited adverse reactions captured for the entire
6 population. Overall, there were more solicited
7 reactions reported in the mRNA-1273 group than in
8 placebo with a consistently higher occurrence after the
9 second injection.

10 Here are the data for solicited local adverse
11 reactions after the first injection. As you can see,
12 the most commonly reported was pain. Eighty-seven
13 percent of participants in the mRNA-1273 group aged 18
14 to under 65 and 19 percent of the same age range in the
15 placebo group experienced pain. In participants 65 and
16 older, 74 percent of the mRNA-1273 group and 13 percent
17 of the placebo group had pain.

18 Similar patterns but much lower rates were
19 seen for erythema, swelling, and axillary swelling or
20 tenderness. Overall, these reactions were mostly mild

1 to moderate in severity represented by the dark green
2 shading, Grade 1, and the lighter green shading, Grade
3 2. Grade 3 reactions shown here in orange occurred at
4 lower rates. There were no Grade 4 events reported.
5 Overall, solicited local reactions were short lived
6 with a median duration of one to three days.

7 A similar pattern was seen for solicited local
8 adverse reactions after the second injection, and,
9 again, the most commonly reported was pain. A higher
10 percentage of participants in the mRNA-1273 groups
11 experienced these symptoms with an increase after the
12 second injection compared to the first. Again, Grade 3
13 reactions occurred at low rates, and no Grade 4 events
14 were reported.

15 Here, we're looking at solicited systemic
16 adverse reactions after the first injection. Fatigue,
17 headache, myalgia, and arthralgia were the most
18 commonly reported, and they were mostly mild to
19 moderate. Grade 3 reactions occurred at a low rate,
20 and Grade 4 were even lower. The Grade 4 reactions

1 aren't visible because they were reported in 0.1
2 percent or less in both groups. These reactions were
3 also short-lived lasting a median of one to two days.

4 Here are the data for solicited systemic
5 adverse reactions after the second injection. As you
6 can see, there is an increase in Grade 3 reactions
7 after the second injection in the mRNA-1273 groups.
8 Again, the Grade 4 reactions occurred at very low
9 rates. Overall, most reactions were still mild to
10 moderate and resolved within one to two days.

11 I'll now review the unsolicited adverse
12 events. Unsolicited adverse events reported in the
13 overall stage of the trial were comparable between
14 groups. Six deaths occurred in the mRNA-1273 group,
15 and there were seven deaths in the placebo group.

16 This figure depicts medically attended adverse
17 events by system organ class. These too were
18 comparable between groups and the rates were low.

19 Here we see serious adverse events by system
20 organ class. These were comparable and infrequent with

1 no terms reported in more than 0.25 percent of
2 participants.

3 Deaths were balanced between groups and were
4 assessed by investigators as not related to mRNA-1273.

5 This slide shows solicited adverse reaction
6 rates after any dose by baseline SARS-CoV-2 status
7 subgroup. Rates are shown for local adverse reactions
8 on the left and systemic adverse reactions on the
9 right. These data indicate that individuals who were
10 positive at baseline for SARS-CoV-2 did not experience
11 higher rates of solicited adverse reactions and
12 baseline serum negatives.

13 We have actively scrutinized our safety data
14 to identify and analyze possible cases of anaphylaxis.
15 We found no cases suggestive of anaphylaxis to mRNA-
16 1273. It's important to note that participants with a
17 history of anaphylaxis, urticaria, or other significant
18 hypersensitivity were not excluded from Study 301.

19 There were two anaphylactic reactions reported
20 as unsolicited adverse events: one in placebo and one

1 in the mRNA-1273 arm. The placebo event occurred ten
2 days after the first dose. That was attributed to co-
3 administration of radiocontrast dye, and the
4 participant received the second dose of placebo.

5 The mRNA-1273 event occurred 63 days after the
6 second dose in a person with a history of asthma and
7 allergy to shellfish. We also ran the anaphylaxis
8 Standardized MedDRA Query and reviewed events that
9 occurred within 48 hours of vaccination. None met
10 Brighton Collaboration Anaphylaxis Case Definition
11 criteria. Of course, we will continue to actively
12 monitor for these events.

13 I'll now review our safety monitoring
14 activities for the post-authorization period. Moderna
15 works hard to develop an integrated vaccine monitoring
16 system that complements U.S. government and other
17 established programs and is focused on identifying
18 safety signals as rapidly as possible.

19 This system has three goals. One, to monitor
20 for adverse events of special interest and other

1 concerns associated with vaccines in general. We will
2 of course, look for AESI patterns in VAERS, but we will
3 also actively monitor AESI in real-world healthcare
4 data as I'll explain in a moment.

5 With respect to safety in the event of vaccine
6 exposure during pregnancy, a developmental and
7 reproductive study was completed in December 2020 with
8 no adverse findings. Given the limited human exposure
9 to date in the Phase 3 trial, we will establish a
10 pregnancy registry that includes a cohort recruited
11 from the general population.

12 Our second broad goal is to monitor long-term
13 vaccine effectiveness through a study in an integrated
14 healthcare delivery system.

15 Third, we will identify and assess
16 unanticipated safety signals as rapidly as possible.
17 Again, by monitoring adverse event reports from the
18 U.S. and from other countries. But, in addition using
19 real-world healthcare data, we can add any

1 unanticipated safety signals to the vaccine monitoring
2 system as I will describe.

3 Given the recent events in the United Kingdom,
4 we know that an active surveillance system using a
5 large data source is critical to capture rare adverse
6 events. We will identify expected rates of AESIs prior
7 to vaccination using a cohort of 45 million adults from
8 a large, linked healthcare claims data source. In this
9 scaled visual, you can see how the sample, with women
10 in red on the left and men in blue on the right,
11 closely matches the U.S. population. This cohort
12 complements but does not duplicate the large electronic
13 health data surveillance systems operated by the FDA
14 and the CDC.

15 Next, to capture observed rates of adverse
16 events post-vaccination, we will follow new vaccine
17 administrations providing data updates every two weeks.
18 This is will enable analyses comparing observed to
19 expected rates. We will also include linked open
20 claims data for early visibility on vaccination that

1 can be connected to subsequent adverse events. In
2 addition to AESI, we can rapidly add new safety signals
3 to this monitoring program for assessment.

4 In conclusion, I'd like to point out that
5 collaboration is key to a successful global vaccine
6 safety monitoring program in a world-wide pandemic.
7 Moderna's global pharmacovigilance and risk management
8 plans are currently being reviewed by the FDA as well
9 as by international regulatory agencies. We will
10 interface with vaccine safety stakeholders to learn
11 from their safety signal detection programs and to
12 share their information. These will include the U.S.
13 FDA and CDC, as well as international regulatory and
14 public health agencies. Working together, we can
15 enhance public confidence in the vaccine through robust
16 collaborative safety monitoring.

17 I will now turn the lectern over to Dr.
18 Lindsey Baden who treats COVID-19 patients and will
19 share his clinical perspective on the ongoing Phase 3
20 trial.

1 **DR. BADEN:** Can you hear me?

2 **DR. MARTIN:** Yes, we can, sir.

3 **DR. BADEN:** Thank you. So I'm Dr. Lindsey
4 Baden. I'm a physician and investigator at Brigham and
5 Women's Hospital in the Dana-Farber Cancer Institute.
6 I'm an associate professor of medicine at Harvard
7 Medical School, a medical journal editor, and one of
8 the three co-principal investigators of this trial.

9 As co-principal investigator of this study, I
10 am funded by the NIH for this work. I have received no
11 funding from Moderna. I share my views, but they are
12 informed by many discussions with colleagues at NIH
13 NIAID, CoVPN, Moderna, study PIs, site staff, and study
14 participants, among others.

15 The efficacy data from the two large, well-
16 done Phase 3 trials are compelling and are not lost on
17 many of our study participants. How many more severe
18 illnesses in the placebo group will we have -- and we
19 have about two to three per week -- do we need to
20 convince ourselves of the short-term efficacy? It's

1 important that we carefully consider the volunteer's
2 viewpoint as we navigate fairness, equity, trust,
3 transparency, as well as the larger societal interests.
4 Without them, clinical research cannot function.

5 We have a unique obligation to handle this
6 study properly as these are likely the last large-scale
7 data from a high-quality, randomized allocation
8 process. Future observational work will be invaluable
9 but will have methodologic issues that require
10 challenging analytics to get correct.

11 There are many ethical challenges in trial
12 conduct, and a quarrel one is that study volunteers
13 should not be disadvantaged. Principles of research
14 require our informing participants of new information,
15 such as a clinically available 95 percent effective
16 vaccine, especially one that can prevent severe
17 illness. By doing this, we build trust in research
18 broadly. We need to communicate with our study
19 participants in a clear and understandable manner.
20 They are intelligent and informed.

1 They will vote with their feet. We are
2 currently -- since the EUA authorized last week --
3 having substantial dropout from study participation
4 given the increasing availability of vaccines. This
5 dropout undermines the data integrity and what can be
6 learned. We must be proactive to ensure that the best
7 choice is for our participants to remain in the study.

8 They will continue to make sacrifices for us
9 to gain knowledge as they have done, but we must ensure
10 our ask of them is reasonable and respectful. This
11 requires moving with haste and ensuring that are
12 treated fairly.

13 Should those who are more health and health
14 system savvy and vocal be treated differently than
15 those who are more passive in the process? The study
16 enrolled rapidly, especially in Caucasian and
17 healthcare provider communities. Given efforts to
18 enhance diversity, participants enrolled later in the
19 study were from more diverse communities.

1 Should the communities earlier in the study be
2 treated differently than those communities enrolled
3 later in the study? A majority of those in this trial,
4 as already mentioned, would fall into CDC priority
5 Groups 1a through c. These numbers on this image need
6 to be interpreted carefully as Groups 1a and b are
7 mutually exclusive, but they are not with Group 1c. In
8 any case, this reminds us that the majority of our
9 volunteers have substantial risk for suffering
10 significant health consequences from COVID-19.

11 Maintaining the volunteers in the research
12 trial, not just for the next few months but for the
13 next 18 months, is of value. To this end, my Moderna
14 colleagues, as Dr. Zaks mentioned earlier, have
15 informed me -- us -- that they have residual research-
16 labeled vaccine product due to expire soon which could
17 be used for an open-label crossover redesign of this
18 study. This vaccine product is unlikely to be
19 available for any other purpose given timing and
20 regulation.

1 This next image shows -- well, there are many
2 possible paths forward including maintaining the
3 original double-blind design for at least six months,
4 unlikely to be successful due to volunteer dropout; a
5 double-blind crossover; and an open-labeled crossover
6 as seen in this image.

7 I want to comment a moment on the double-blind
8 crossover. As Dr. Goodman raised at in some detail --
9 and that is my favored design, and I am a co-author on
10 that paper and have discussed it extensively with Dr.
11 Follmann and others, as we have thought about
12 redesigning the path forward since efficacy data emerge
13 from the DSMV meetings a month ago. The problem is
14 it's impractical at this point in time in my view.
15 And, if we lose our volunteers, then the ability to
16 learn anything further will be substantially impaired.
17 So we must carefully consider the merits and risks of
18 the different paths forward, but we do have to choose a
19 path forward, one that, hopefully, builds participants

1 and trust and enables us to gain more knowledge as to
2 how these vaccines work.

3 So, in this image, as a pragmatic path
4 forward, what one sees is reconsenting of all
5 volunteers, informing them of the new EUA associated
6 information, obtaining a serology -- this exit serology
7 -- from the double-blind RCT component of the study
8 will allow us to make an assessment of the vaccine on
9 asymptomatic and subclinical infection. We need high
10 compliance with this data point.

11 At this time, the volunteer can choose to stay
12 in the study as designed: double-blind placebo
13 controlled or crossover to an open-label format with
14 placebo recipients being now being vaccinated. All
15 will be followed as per the original study design
16 including assessments of safety, immunogenicity, and
17 efficacy.

18 All will continue in a randomized research
19 study, so research continues. This is not clinical
20 application. This is a continued research study

1 evolving to an open-label format from a double-blind
2 format in the volunteers in our early versus late
3 vaccine recipients which will allow systematic
4 knowledge to being gained, including a potential
5 identification of a correlate of protection. By using
6 vaccine research supply, there was no impact on
7 clinical EUA vaccine deployment.

8 Of note, about two-thirds of volunteers would
9 make it to the six months of double-blind, placebo-
10 controlled follow up in March. Crossing over to an
11 open label format in the next month or so would lose
12 about two months of volunteer blinded follow up. We
13 must carefully balance the value of collecting data
14 from a double-blind format with the ethics and
15 participant interests which will translate into study
16 retention or loss to follow up and the impact on data
17 and knowledge that can be gained.

18 In the proposal on this slide, all volunteers
19 are treated fairly and equally. The research
20 enterprise continues to build and maintain the trust of

1 our community, and society gains knowledge. The
2 proposed design balances obligation to both the
3 volunteer and society. Next image please.

4 We must continue to learn from those who are
5 in this RCT and are four to six months ahead of the
6 rest of us. There are many more questions over the
7 next months to years that these volunteers can help us
8 answer but only if they stay in the study. If the
9 volunteers leave the study, particularly for non-random
10 reasons, then future knowledge will be fundamentally
11 undermined. I would like to now turn the lectern back
12 to Dr. Zaks.

13 **DR. ZAKS:** Thank you, Dr. Baden.

14 **DR. MONTO:** I just wanted to let you know
15 you're already over time.

16 **DR. ZAKS:** I will briefly conclude. Thank
17 you. In conclusion, the data from Study 301 supports
18 the Emergency Use Authorization, and we expect the data
19 to support sure licensure. The safety and
20 reactogenicity have been well characterized and will

1 continue to be characterized as these occurred both on
2 trial and using passive and active surveillance during
3 real-world deployment.

4 I am grateful for the ongoing collaboration
5 with the NIH and the clear and timely guidance of FDA,
6 and we look forward to the opportunity to prevent
7 COVID-19 with mRNA-1273. We also appreciate the
8 efforts of this Committee for reviewing our data, and
9 we look forward to answering your questions. Thank you
10 for your attention, and I will turn it to Dr. Miller to
11 moderate the Q and A session.

12 **DR. MONTO:** I think -- Dr. Miller, I think I'm
13 the one who's supposed to be moderating the Q and A
14 session.

15 **DR. MILLER:** No, absolutely. I'm just helping
16 out with coordinating on our side.

17 **DR. MONTO:** Okay. Thank you. It won't be
18 very much time to do it right now. We have just a few
19 minutes for the start of the Q and A.

1 I just want to remind everybody that the open
2 public comments is a fixed part of this meeting. We'll
3 start at noon Eastern time and go on for an hour. We
4 also need to have a short break before that time
5 especially for technical reasons. So we can only have
6 a couple of questions now. We'll circle back.

7 I'm sure you will all remember the questions
8 that you have stored and have the question session
9 starting at 1:00 Eastern. So a couple of question now.
10 I see many hands raised. I'll just do the first few
11 right now, and we'll put the rest of them off until
12 1:00. Dr. Offit.

13 **DR. OFFIT:** In the 11 breakthrough cases, you
14 showed data that you clearly have sera that were
15 collected following Dose 2. So what I'm trying to
16 understand is the characteristics of those 11 cases. I
17 mean, it may be that there's immunological correlate
18 infection, which Dr. Baden correctly said. It would be
19 really important to know, so it would be great to have

1 those data. But it sounds like you don't have them
2 yet. Is that true?

3 **DR. MILLER:** That is correct although we
4 expect them in January.

5 **DR. OFFIT:** Okay. And then was there anything
6 else about those 11 patients, any characteristics of
7 them that distinguish them from those who were
8 protected by the vaccine?

9 **DR. MILLER:** Nothing in particular, Dr. Offit.

10 **DR. OFFIT:** Okay.

11 **DR. MILLER:** These were cases that were split
12 relatively evenly given the small sample size between
13 males and females: three were Hispanic, eight were
14 white and non-Hispanic; and they ranged in age from 29
15 to 72.

16 **DR. OFFIT:** Okay. Thank you very much.

17 **DR. MONTO:** Dr. Gans.

18 **DR. GANS:** Thank you very much. Thank you for
19 all of those illuminating presentations. I had a

1 couple of questions, and one was a continuation of the
2 breakthrough cases that Dr. Offit had raised.

3 Not only humoral immunity or our trying to
4 understand the correlates of protection as he
5 suggested, I noticed one of my questions -- and it all
6 moves to the breakthrough -- is that T cell immunity
7 was only evaluated. Actually, it looks like not in the
8 Phase 3, and I don't know if those samples are also
9 being included and particularly relevant to the
10 breakthrough disease.

11 My other question, which you can either handle
12 now or later, is what about other adverse events like
13 Bell's palsy, which we did note of interest because
14 that seems to be a signal not only with this vaccine
15 but the other one.

16 **DR. MILLER:** Thank you, Dr. Gans, for those
17 two questions. And maybe I'll address your second
18 question first. So, given the review of last week, we
19 have looked carefully into the data. We have four
20 cases of Bell's palsy that have been reported: three of

1 them occurred in the vaccine group, one of them
2 occurred in the placebo group. And this will be part
3 of our post-marketing safety surveillance.

4 So, in addition to continuing to monitoring
5 through the Phase 3 trial, as the vaccine is,
6 hopefully, authorized for EUA and expanded, this will
7 be one of the key safety endpoints that we will be
8 looking for in our signal detection.

9 And then your question about the T cell
10 immunity, so indeed our T cell work was done in
11 collaboration with the NIH in our Phase 1 clinical
12 trial. And, in terms of looking for a correlate of
13 protection, so our search for a correlate has focused
14 up until now on the neutralizing and binding antibody
15 responses. So you mentioned the breakthrough cases
16 that we've observed will go towards that analysis, and,
17 as we continue to accrue data in the trial, additional
18 breakthrough cases will be added to that analysis.

19 The samples in the Phase 3 trial, as they
20 require very special handling for T cell immunity and

1 as we were implementing across a hundred U.S. sites,
2 the T cell immunity was not part of what we instituted
3 in Phase 3. So the correlate work that we're
4 collaborating with the NIH on we're really focused on
5 the binding and (audio skip).

6 **DR. MONTO:** Dr. Moore.

7 **DR. MOORE:** Thank you. So also I want to
8 really thank you for presenting the data even though it
9 was interim data on the asymptomatic infections because
10 I just feel that's so strongly important for control of
11 this epidemic, and it could determine wide-spread use
12 of one vaccine versus another vaccine. Although
13 asymptomatic infection is a surrogate measure for
14 transmissibility, it's a commonsense measure of
15 transmissibility or shedding at least.

16 So, if you break blinding, do you anticipate
17 re-swabbing all the participants beforehand, and do you
18 -- what are your plans for a second swab? I know that
19 you measured them right before your second dose. Is

1 there plans for having another nasopharyngeal swab from
2 these patients -- from these participants?

3 **DR. MILLER:** Thank you for that question. So
4 you're correct that it was the predefined swabs at both
5 Pre-Dose 1 and Pre-Dose 2 that enabled us to be able to
6 do that analysis. And a pretransition swab could
7 certainly be implemented into the Phase 3 study.

8 The way we predefined our surveillance for
9 asymptomatic infection was actually through serology
10 against the anti-nucleocapsid protein, so it's a
11 serologic evidence of immunity to non-vaccine antigen.
12 But, to your point, swabs really add a lot of important
13 additional data.

14 Some further data that were not available at
15 the time of the EUA also include swabs we obtained
16 frequently from subjects who were found to be COVID-19
17 positive. So the intent there is really to look at the
18 viral shedding and the burden of shedding comparatively
19 between groups, so we should have some additional data
20 on some of that.

1 **DR. MONTO:** Thank you. Dr. Hildreth.

2 **DR. MOORE:** Can I just a question? If you
3 sequence that virus, do we have any idea of whether
4 there's virus escape antigen that escape from when you
5 vaccinated?

6 **DR. MILLER:** So we are deep sequencing the
7 virus as part of the surveillance of the breakthrough
8 cases, and I am going to ask Dr. Darin Edwards from our
9 --

10 **DR. MONTO:** Can we -- have time for exactly
11 one more question. We'll circle back to -- I'll call
12 on you again to answer the sequencing and the
13 breakthrough question, which is a very big one. Dr.
14 Hildreth, your final question.

15 **DR. HILDRETH:** Yes, I was concerned about the
16 lower efficacy in the older age group, and I wondered
17 if you had some thoughts about addressing that either
18 with a higher dose or an additional injection? Any
19 comments about -- thoughts about that?

1 **DR. MILLER:** Yes, to speak about the older age
2 group, I want to mention -- and let me bring up this
3 slide -- that that efficacy was really based on the
4 relatively small sample size with a wide 95 percent
5 confidence interval. So the confidence interval
6 completely overlaps with the confidence interval for
7 the overall efficacy.

8 You can see that that was based on 33 cases.
9 If you were to evaluate efficacy in the those above 75
10 years of age -- so at even greater risk -- there were 7
11 cases, all of which were reported in the placebo group,
12 and I think it highlights -- I mean, it certainly is
13 very helpful to look at all of these subgroup analyses
14 to ensure that we're not seeing dramatic differences.
15 I think we do have to keep in mind that there weren't
16 multiplicity adjustments for the multiple endpoints.
17 And so our view is actually that the efficacy in the
18 elderly is indeed consistent with the efficacy in the
19 overall population.

20 **DR. HILDRETH:** Thank you.

1 **DR. MONTO:** Thank you all. Thanks to Moderna,
2 and don't forget you have to come back to answer our
3 questions at 1:00. Now, we have a break until the open
4 public hearing which starts at exactly noon Eastern
5 time.

6 **[BREAK]**

7

8 **OPEN PUBLIC HEARING**

9

10 **MR. KAWCZYNSKI:** Alright. Good afternoon and
11 welcome back to our meeting. We will now get started
12 with our OPH session. Now, I'll pass it back off to
13 our chair, Arnold. Dr. Monto, do you want to take it
14 away?

15 **DR. MONTO:** Okay. Welcome to the open public
16 hearing session. Please note that both the FDA and the
17 public believe in a transparent process for information
18 gathering and decision making. To ensure such
19 transparency at the open public hearing session of the
20 Advisory Committee, FDA believes that it is important

1 to understand the context of an individual's
2 presentation.

3 For this reason, FDA encourages you, the open
4 public hearing speaker, at the beginning of your
5 written or oral statement, to advise the committee of
6 any financial relationship that you may have with a
7 sponsor, its product, and if known its direct
8 competitors. For example, this financial information
9 may include the sponsor's payment of your travel,
10 lodging, or other expenses in connection with your
11 attendance at the meeting.

12 Likewise, FDA encourages you, at the beginning
13 of your statement, to advise the committee if you do
14 not have any such financial relationships. If you
15 choose not to address the issue of financial
16 relationships, at the beginning of your statement, it
17 will not preclude you from speaking. Over to you
18 Prabha for leading the open public discussion.

19 **DR. ATREYA:** Good afternoon everyone. Thank
20 you for joining us today. I'm going to read out your

1 name one after another. When I call your name, please
2 start speaking. And when you finish, please mute your
3 phone so that we can call the next person. Thank you
4 so much.

5 Speakers you have only three minutes and there
6 is a timer that indicates three minutes for your
7 remarks. Thank you. Okay. The first name is Dr.
8 Winston Wong. Go ahead, please.

9 **DR. WONG:** Thank you, Madam Chair, for the
10 opportunity to provide public comment. My name is
11 Winston Wong, and I am the Chairperson and acting CEO
12 of the National Council of Asian Pacific Islander
13 Physicians. I have no relevant financial disclosures
14 to share.

15 I speak on behalf of our national council,
16 that was formed 10 years ago to provide an advocacy
17 voice for physicians who are actively committed to the
18 healthcare needs and public health needs of vulnerable
19 Asian Pacific Islander and Native Hawaiian communities.
20 Technical assistant, could you please go to the next

1 slide which shows the logo of the National Council of
2 Asian Pacific Islander Physicians?

3 In this context, the impact of COVID-19 on the
4 AANHPI community has been underreported. Its impact on
5 our community mirrors that of other communities of
6 color. And could you go to the next slide which talks
7 about the under-reported story of COVID-19 burden on
8 Asian Americans?

9 For example, according to a recent report from
10 the Kaiser Family Foundation, derived from electronic
11 health records from 52 million patients across 32
12 states, Asian Americans were less likely to get tested
13 for COVID, more likely to have a positive test result,
14 and require a higher level of care at diagnosis.
15 Moreover, they were more likely to be hospitalized and
16 die compared to all other racial, ethnic groups
17 according to the EPIC data that I referenced. Against
18 this sobering backdrop, NCAPIP greets the news of the
19 Moderna vaccine with cautious optimism.

20 Our communities need the protection offered by

1 the promise of our vaccine. It's provision to the
2 AANHPI community must incorporate critical components
3 that are both relevant and unique to our population.
4 I'd like to go to the next slide, which starts with the
5 title critical issues in vaccine deployment for our
6 community.

7 Therefore, our organization recommends, number
8 one; this aggregating data for the broad category of
9 the AANHPI in efficacy and potential adverse vaccine
10 effects, in recognition that this category is comprised
11 of dozens of subgroups and important differences can be
12 lost when data is not broken down. Can I have the next
13 slide which has the numeration of Asian Americans?

14 As the vaccine is deployed, the immigration
15 status of Asian American individuals should not be a
16 barrier for access. Although the vaccine itself may be
17 free of charge to U.S. residents, the special status of
18 individuals from the Pacific jurisdictions such as
19 Micronesia should be accounted for. Can I go to the
20 next slide?

1 As the Moderna vaccine is deployed, every
2 effort should be made to provide information about its
3 background in a culturally competent and linguistically
4 accessible manner. Since many AANHPI individuals
5 travel to and from Asian countries, and also obtain
6 information about COVID-19 from sources other than
7 those that originate in the mainstream and or American
8 press, efforts should be made so that there is no
9 confusion or misinformation about an individual's
10 vaccine status.

11 Number four, physicians and other clinicians
12 from Asian American, Native Hawaiian, Pacific Islander
13 communities like those at community health centers
14 should be supported as critical ambassadors that
15 advocate for the Moderna --

16 **MR. KAWCZYNSKI:** Time.

17 **DR. WONG:** -- and other COVID-19 vaccines.
18 Thank you for allowing me this opportunity to comment
19 on the important issues relative to the Asian American,
20 Native Hawaiian community as we look forward to the

1 approval of the Moderna vaccine.

2 **DR. ATREYA:** Thank you. The next speaker is
3 Ms. Lisa Butler.

4 **MS. BUTLER:** Hello. My name is Lisa Butler,
5 Executive director of the GBS/CIDO Foundation. At this
6 time I have no financial interest or conflicts of
7 interest to disclose. Thank you to the FDA for this
8 opportunity.

9 Guillain-Barré Syndrome is an acute
10 inflammatory disorder of the peripheral nerves. GBS is
11 characterized by the rapid onset of numbness, weakness,
12 and often paralysis of the legs, arms, breathing
13 muscles, and feet. The paralysis is ascending. The
14 cause is unknown. We do know that about 50 percent of
15 cases occur shortly after a microbial infection, viral
16 or bacterial, some as simple and common as the flu or
17 food poisoning. Many theories suggest an autoimmune
18 trigger.

19 The COVID-19 pandemic sparked a flurry of
20 anxiety for healthcare professionals and former GBS

1 patients. Our community waited eagerly for the news of
2 an increase of GBS cases being triggered by COVID-19
3 infection. Fortunately, despite a handful of GBS cases
4 happening around the time of COVID-19 infection, there
5 has not been any indication of an increased risk of GBS
6 from a COVID-19 infection.

7 A recent study out of the U.K., published in
8 the Brain Journal of Neurology this week, confirmed
9 that there is no epidemiological association between
10 the COVID-19 and GBS in the U.K. The resulting
11 commentary from the published article highlighted the
12 opinion of leading peripheral nerve experts, that there
13 should not be any increased risk of GBS from the COVID
14 vaccine. Please see the chart on the slide.

15 In 1976, there was an apparent association
16 between the influenza vaccine and GBS. However, since
17 then several studies have researched the risk of GBS
18 after influenza vaccinations and have no, or a very
19 small, increase in the risk of someone contracting GBS
20 after influenza vaccine. And this finding was recently

1 highlighted by an article from CBER, CMS, and the
2 Immunization Safety Office of the CDC.

3 Additionally, leading peripheral nerve experts
4 remain confident that any GBS cases resulting from mass
5 COVID-19 vaccination of the global community are
6 coincidental and likely in line with the expected rate
7 of GBS. Regardless of the science though, the GBS
8 community expresses understandable skepticism towards
9 vaccinations. A safe and effective vaccine against
10 COVID-19 served as a beacon of hope for many Americans,
11 but the Guillain-Barré Syndrome community feels a
12 renewed sense of worry and panic at the news of this
13 expedited scientific miracle.

14 Though the data is still quite limited, the
15 Foundation's Global Medical Advisory Board and the
16 Peripheral Nerve Society are hopeful that the relative
17 risks of GBS after a COVID-19 infection is not
18 significant, and that there is no reason to suspect
19 that the vaccine would cause it. The Foundation
20 urgently hopes for a partnership with the FDA to

1 collaboratively and truthfully instill necessary and
2 earned trust in the GBS community regarding
3 vaccinations, especially the COVID-19 vaccinations.

4 We will continue to rely on experts who serve
5 the Global Medical Advisory Board at the Foundation for
6 their assessment of science and safety. So in
7 conclusion, we are a very nervous patient community,
8 yet we are very optimistic for the future. Thank you
9 for your interest.

10 **DR. ATREYA:** Thank you, Ms. Butler. Next
11 speaker is Dr. Diana Zuckerman.

12 **DR. ZUCKERMAN:** Hi. I'm Dr. Diana Zuckerman,
13 President of the National Center for Health Research.
14 Next slide, please. We scrutinize the safety and
15 effectiveness of medical products and we don't accept
16 funding from companies that make those products. My
17 expertise is based on post-doctoral training in
18 epidemiology, as a former faculty member and researcher
19 at Vassar, Yale, and Harvard, and a former Fellow in
20 Bioethics at Penn. I've also worked at HHS and

1 Congress. Next slide, please.

2 I'll focus on three concerns. Number one, the
3 two-month median follow-up is too short so Moderna's
4 proposal to immediately unblind and offer to vaccinate
5 the entire placebo group should be rejected. Number
6 two, Moderna recruited a diverse group of participants,
7 but only four COVID cases were Black, and even fewer
8 were in other racial groups. We can't assume that the
9 vaccine was highly effective in demographic groups with
10 so few cases. And there were 25 cases among
11 participants with comorbidities, which is slightly more
12 substantial.

13 Number three. I'm glad to see that, unlike
14 Pfizer, Moderna provided a total number of participants
15 who reported one or more adverse events. That's
16 important. Unfortunately, the total of severe,
17 systemic adverse events, after the second dose, was
18 over 17 percent for the vaccine group compared to 2
19 percent for placebo. Next slide.

20 There were 30 severe COVID cases after the

1 second dose, none in the vaccine group. This is a
2 strong finding. Nine required hospitalization but 12
3 were based on the questionable criteria of at least
4 slightly low blood oxygen saturation. Next slide.

5 Long-term care patients were not included in
6 the study. And 1,300 people over 75 were in the study
7 but only three were cases. We want to save their
8 lives, but with no data it's not possible to provide
9 useful, informed consent to nursing home patients.
10 That puts a tremendous burden on those patients and
11 their family members. Next slide.

12 We need longer-term data on benefits and
13 risks. The vaccine is clearly effective but does it
14 last two months, or four months, or a year? To learn
15 that, the FDA needs to ensure the blinded RCT is
16 continued. Last slide, please.

17 In conclusion, FDA should initially target
18 authorization to priority populations. If the EUA is
19 given for all adults, celebrities and others who are
20 well connected will cut in line. We've already seen

1 that. (audio interruption).

2 -- other people could apply for the vaccine
3 under FDA's expanded access program. We need at least
4 one year of blinded, randomized control data. I agree
5 with Dr. Goodman's proposal that FDA should delay
6 access to vaccines, by placebo group members, unless
7 they are in priority populations. Blinded crossover is
8 better than not continuing a blinded controlled study
9 if that's the only alternative. Thanks so much for the
10 opportunity to speak today.

11 **DR. ATREYA:** Thank you. Next speaker is Dr.
12 Charles Lee.

13 **DR. LEE:** Good morning. I am Dr. Charles Lee.
14 Next slide, please. I represent the American College
15 of Correctional Physicians and I am speaking on behalf
16 of correctional workers and those who are incarcerated.
17 There are no conflicts.

18 Just look at the numbers. There are 2 million
19 people incarcerated in the United States and 500,000
20 workers working within correctional facilities. The

1 infection rate amongst those incarcerated is six times
2 that of the general population. 1,700 folks have died.

3 Why so many? There's an inability of inmates
4 to follow the CDC guidelines. Why? They cannot
5 socially distance. They are unable to get proper hand
6 sanitizers because of the alcohol content. They live
7 in close-dorm quarters or cells. There's an inability
8 to get frequently tested. There's poor ventilation.
9 Many of these facilities are 18th, 19th century, and
10 they may not get masks. I realize that this varies
11 from facility to facility.

12 There are increased inmate vulnerabilities.
13 An inmate has a physiologic and medical age of 20 years
14 younger than that of the general population. Someone
15 50 incarcerated, his body equates to that of someone 65
16 on the outside. There are increased percent of
17 minorities within correctional facilities. There's a
18 significant increase of patients who have
19 comorbidities, diabetes, asthma, cardiovascular
20 disease.

1 There's also increased vulnerabilities of
2 workers. Out of necessity, they have close contact
3 with inmates. They have extremely demanding working
4 conditions. Unfortunately, too many officers may get
5 sick, thereby unable to properly manage the facility,
6 increasing the danger within a correctional facility.

7 What are the consequences of this? Increased
8 deaths, suicidality. There have been fears of patients
9 that they may die of Coronavirus committing suicide.
10 As a result of this, there's increased community
11 infections. Ninety percent of inmates are released at
12 some point in time, workers go home daily. There's
13 increased use of community resources, clinics,
14 emergency rooms, hospitals. When patients who are
15 incarcerated become sick, they are referred to the
16 community resources.

17 The Moderna vaccine has certain advantages
18 that may be extremely applicable to correctional
19 populations. As a result, the American College of
20 Correctional Physicians recommends approval of the EUA

1 for Moderna's vaccine. Thank you very much.

2 **DR. ATREYA:** Okay. Thank you, Dr. Lee. The
3 next speaker is Dr. Bisola Ojikutu.

4 **DR. OJIKUTU:** Thank you for this opportunity
5 to speak. My name is Dr. Bisola Ojikutu and I have no
6 financial disclosures. I am an infectious disease
7 specialist and a frontline provider based in
8 Massachusetts, which has one of the highest death rates
9 from COVID-19 in this country. I work at Brigham and
10 Women's Hospital and Massachusetts General Hospital,
11 and I've been working directly with Black community
12 members for the last few months to promote acceptance
13 of the COVID-19 vaccine, as many of us have.

14 Many of the community members that I've worked
15 with have suffered personal losses secondary to COVID-
16 19, so this is a particularly important issue to them.
17 Next slide. In this process of working with the Black
18 community, I have attended numerous town halls and had
19 many meetings and discussions, and I think it's really
20 important to emphasize that mistrust of government and

1 of the pharmaceutical industry runs deep. And though
2 the recent polls show that willingness and acceptance
3 may be increasing, we still believe that the mistrust
4 will delay and even completely inhibit uptake of these
5 vaccines.

6 While it's highly unlikely that we will make
7 our institutions more trustworthy over the course of
8 the next few weeks as vaccines are rolled out, I and
9 others believe that the same amount of effort and
10 funding that was placed in the development of this, and
11 other successful vaccine candidates, needs to be
12 directed toward ensuring uptake and promoting vaccine
13 confidence, specifically within Black, Latinx, and
14 indigenous communities who are most disproportionately
15 affected.

16 What do we need to do? First, we need better
17 messaging articulated by trusted messengers that will
18 resonate with racially and ethnically diverse
19 individuals. Second, we need more intensive community
20 engagement. Though I'm well aware of several

1 initiatives that, quite frankly, recently just got
2 started, what has been done thus far is nowhere near
3 enough. Next slide.

4 In terms of messages, first, we need complete
5 transparency, in lay language, regarding potential side
6 effects, and we need to be honest and emphasize that
7 there are many unknowns, and much work remains to be
8 done. Secondly, our government institutions and
9 industry need to consistently acknowledge that systemic
10 inequity and structural racism have led to this deeply
11 rooted mistrust. Thirdly, we need to reframe
12 vaccination as a form of empowering our communities in
13 fighting back against COVID-19 related inequity.

14 And lastly, we need to explain this process,
15 this process that we're part of today, to our
16 communities. People want to know who was looking out
17 for them and their best interest and the interest of
18 people who look like them, and who was really at the
19 table. Next slide.

20 And in regard to the table, quite frankly,

1 communities of color have not been at the table
2 throughout the entire vaccine development process.
3 They were not engaged early enough, and that is a
4 problem. Going forward, we must change that dynamic.

5 People of color will begin to trust this
6 process, and the process of other vaccine development,
7 if they feel that they're truly part of it. Therefore,
8 community engagement and community investment must be
9 enhanced, amplified, and fully supported. I believe
10 that this is necessary or we will continue to see
11 racial and ethnic disparities and we will not end this
12 epidemic. I'll stop there. Thank you.

13 **DR. ATREYA:** Thank you. The next speaker is
14 Dr. David Berger.

15 **DR. BERGER:** Thank you. Hi, my name is David
16 Berger. Thank you for the opportunity to address this
17 committee again. I have no conflicts of interest.
18 Slide two.

19 I'm a board certified pediatrician and senior
20 medical advisor for the Vaccine Considerations Project.

1 Slide three. From the available data, it appears the
2 Moderna and Pfizer vaccines are quite effective in
3 minimizing the incidence of serious COVID disease.
4 This is an amazing scientific accomplishment that will
5 hopefully aid in our defeat of the virus. Slide four.

6 Vaccine hesitancy is prevalent in the
7 healthcare community and public at large. Full
8 transparency can reduce this hesitancy. As more
9 manufacturers apply for authorizations, I urge the FDA
10 to provide timely information for review. Meaningful
11 input is not possible when we are given only two days
12 to review manufacturer's data before addressing the
13 committee, or when data is released after deadlines
14 pass for submission. Slide five.

15 Seniors are one of the first targeted
16 populations to receive COVID vaccine, yet only 860
17 subjects over 75 years old were included in the
18 reported Pfizer data. Moderna's data mentions subjects
19 over 55 years old but made no distinction of
20 participants over 75 years old. Our team found minimal

1 data on pregnant women or those with preexisting
2 allergic, hyperinflammatory and autoimmune conditions.

3 If this data's not available, it will be very
4 difficult for individuals to weigh the risk and
5 benefits, which is fundamental to making an informed
6 decision. As with the Pfizer vaccine, Moderna's report
7 reveals incidents of Bell's Palsy. While the number of
8 cases was a small fraction of participants, we should
9 closely monitor this to see if the trend develops for
10 this and other inflammatory conditions. Slide six.

11 Please provide long term data and outcome for
12 patients with or who may develop autoimmune and
13 hyperinflammatory conditions. Significant symptoms may
14 take longer than two months to become evident. Please
15 provide quantitative standards for COVID IgG
16 antibodies, so people can determine if they have
17 immunity and if their immunity is persisting. Slide
18 seven.

19 Our team have not discovered significant
20 differences in efficacy or adverse events between the

1 Pfizer and Moderna vaccines. We will continue
2 analyzing and commenting on other manufacturers as they
3 apply for emergency authorization. It will be helpful
4 to have comparative data to guide the decision making
5 process between brands. Slide eight.

6 The Vaccine Considerations Project is building
7 a central repository of COVID vaccine health and safety
8 concerns. Our national network of medical and graduate
9 students are compiling and analyzing science, data, and
10 evidence-based information to help address these
11 concerns. We are inviting all interested students,
12 professionals, and others to join this important effort
13 by connecting with us at vaccineconsiderations.com.
14 Slide nine.

15 It is critical that rigorous safety mechanisms
16 are maintained and we are given complete transparency
17 with data. We should closely monitor and report on
18 unique subpopulations, such as different minority and
19 racial communities, the elderly, and those with
20 allergies, autoimmune, and hyperinflammatory

1 conditions. With such actions, the FDA and vaccine
2 manufacturers have the opportunity to provide Americans
3 the information they need to make the most informed
4 decision possible for themselves and their loved ones.
5 Thank you.

6 **DR. ATREYA:** Thank you, Dr. Berger. The next
7 speaker is Dr. Renu Dhanasekaran.

8 **DR. DHANASEKARAN:** Thank you very much. Thank
9 you very much for the opportunity to speak at this
10 public hearing. My name is Renu Dhanasekaran. I'm a
11 board certified gastroenterologist and hepatologist at
12 Stanford University, California. I am here as a
13 physician to advocate for vaccine access for my
14 patients and also as a scientist conducting COVID-19
15 research. I have no conflicts of interest to disclose.
16 Next slide.

17 COVID-19 is a global public health crisis. It
18 has led to more than 1.5 million deaths in the world
19 with more than 290,000, unfortunately, occurring in the
20 United States alone. Next slide. Patients with

1 chronic medical conditions like cancer, heart disease,
2 and obesity experience worse outcomes with COVID-19.

3 As a physician taking care of some of the
4 sickest patients with chronic liver diseases and
5 immuno-compromised patients with liver transplantation,
6 I have personally seen the devastation COVID-19 has
7 caused for our patients both directly and indirectly.
8 Hence, clearly, the vaccine is a welcome relief for our
9 elderly patients and those with chronic medical
10 conditions. Next slide.

11 As discussed by the earlier speakers, the
12 Moderna vaccine has been shown to be effective in
13 preventing COVID-19. When I looked at the data, I was
14 happy to see that among the 30,000 participants in the
15 Phase 3 COVE study, around 7,000 were older than 65
16 years, around 5,000 who were younger than 65 years had
17 underlying medical disorders like diabetes, obesity,
18 and cardiac disease. Overall, around 42 percent of the
19 cohort consisted of medically high-risk groups. This
20 is reassuring to me. These are the very patients who

1 are in dire need for this vaccine. Next slide.

2 Moving on, I would like to acknowledge a sad
3 reality that communities of color have been
4 disproportionately affected during COVID-19. The CDC
5 reports that American Indians, Blacks, and Hispanics
6 are at more than 2.5 times the risk for death with
7 COVID-19 than white Americans. Several investigators,
8 including us, have shown that socioeconomic factors and
9 medical comorbidities play a huge role in this. Next
10 slide.

11 I'm happy to see that the COVE study cohort
12 overall included 11,000 people from communities of
13 color with more than 6,000 Hispanic and more than 3,000
14 Black. I believe these vulnerable communities will
15 benefit greatly with the Moderna vaccine approval.
16 Next slide. I have reviewed the safety profile of the
17 Moderna vaccine, the vaccine was generally well
18 tolerated as can be seen from the Grade 3 events listed
19 here. In my opinion, the benefits far outweigh the
20 risks with the vaccine, especially in patients with

1 comorbidities. Next slide.

2 I would like to end with these two take-home
3 points. Number one, a safe and effective vaccine is
4 the need of the hour. Number two, vulnerable
5 populations will be especially well served with vaccine
6 approval. Next slide. Thank you very much for the
7 opportunity to speak.

8 **DR. ATREYA:** Okay. Thank you Dr.
9 Dhanasekaran. The next speaker is Dr. Marie Garlock.

10 **DR. GARLOCK:** Warm greetings. I am Dr. Marie
11 Garlock. I'm a board member of the U.S.A. Patient
12 Network. We're a grassroots patient advocacy group and
13 we're not funded by or beholden to industry in any way.
14 We're completely independent. Hundreds of members
15 across the nation, like me, were patient caregivers of
16 leading health justice advocates for drug and device
17 safety, efficacy, and affordability.

18 Our letter submitted to the federal docket
19 today has references for all four of our main concerns
20 and action items. And I'd like to say before we move

1 to the next slide titled, "EUA is Stopgap not a Stand
2 In," given recent project on government oversight
3 reporting I want to start with a note. Unlike at last
4 week's EUA hearing, today's deliberation must take time
5 to transparently include all expert members' questions,
6 voting amendments, and explanations. Today is not
7 about PR, it's to take public health seriously, a
8 commitment on which the FDA leadership must make good.
9 So the next slide titled, "EUA is Stopgap not a Stand
10 In."

11 Clinical trial must continue. Here is the
12 basic part of it, do we want to control COVID-19, then
13 we have to keep the control groups going. Anything
14 less skirts accountability for industry and FDA. We
15 need public trust in COVID-19 vaccines that will only
16 come from transparent public knowledge about how they
17 work long terms, when, and for whom.

18 What does that mean? Placebo groups much
19 continue alongside Phase 4 trials. We need metrics
20 that matter. Does the vaccine prevent transmission?

1 Does it mitigate severity of disease that results in
2 hospitalizations and death?

3 Next, we need to incorporate the National
4 Vaccine Injury Compensation Program. Folks can go to
5 [hrsa.gov/vaccinecompensation](https://www.hrsa.gov/vaccinecompensation). And then we need for
6 health-focused media, elected officials, FDA and
7 Moderna, and its peer industries to know that EUAs are
8 not standard FDA approvals and authorizations. We need
9 transparency on that. And an EUA should not ever be
10 precedent for future similar, or unrelated drugs and
11 devices, to be rushed through on loopholes. And next
12 slide.

13 We need transparency on diversity. So this
14 means for age and comorbidities. Because this
15 population is so vulnerable, how many are at or near 75
16 years old? How many are frail elderly, i.e. older and
17 with comorbidities? On sex and reproductive health
18 status, we need to understand that females should know
19 they should not get pregnant for a specified time after
20 getting the vaccine, given lack of data on both

1 developing fetuses and pregnant parents. And most of
2 all, we need to understand for ethnic and racial
3 difference.

4 Given systemic racism as the root of COVID-19
5 health disparities, we need precise numbers for Black,
6 Indigenous, Pacific Islander, Latino, and Hispanic
7 folks. And in order, those folks in comparison to
8 their white counterparts, Indigenous, Black, Pacific
9 Islander, Latino and Hispanic people are three times as
10 likely to die from COVID-19, and four times as likely
11 to be hospitalized with severe COVID-19.

12 In a framework called structural competency,
13 we know systemic racism influences these upstream
14 inequities in employment, housing, transportation,
15 parallel health challenges, and healthcare insurance
16 coverage. And that is directly reflected in COVID-19
17 severity, hospitalizations, and deaths. So we need
18 nuance on the numbers and we need retainment of these
19 specific groups in placebo groups for Phase 4.

20 Most of all, FDA needs clinical trial

1 diversity standards that have a systemic fix. We
2 commend Moderna for showing its trial recruitment, but
3 it should not be only optional for companies. And our
4 next slide.

5 **MR. KAWCZYNSKI:** Time.

6 **DR. GARLOCK:** Okay. Thank you so much. And I
7 would like to ask the FDA to focus on needing nuance on
8 the numbers, keeping the control groups going, knowing
9 that integrity requires adverse event reporting
10 infrastructure, and that action means action. The FDA
11 must ensure safety in these protection practices.
12 Thank you.

13 **DR. ATREYA:** Okay. Thank you. The next
14 speaker is Ms. Gwen Schell.

15 **MR. KAWCZYNSKI:** Gwen, do you have your
16 personal phone muted?

17 **MS. SCHELL:** Sorry about that. My name is
18 Gwen Schell. I represent a community of rural
19 population. I'm a nurse and I work for a public health
20 district. I want to describe the impact that COVID-19

1 has had on the rural population and touch on the value
2 of a vaccine.

3 We have very limited nursing staff in this
4 part of the United States. And in a rural population,
5 that nursing staff is covering an area of about 500
6 miles. We have noticed an uptick in people being sent
7 home from the hospital who are not meant to be home.
8 All of the local assisted living and skilled nursing
9 facilities are very particular about who they take. A
10 vaccine would not only benefit those who are at risk
11 for contracting COVID-19, but would also benefit the
12 health population at large.

13 I wish to express our excitement and gratitude
14 for treatments that are coming. And I forgot to
15 mention, I don't have any financial ties. But I just
16 wanted to bring to light the impact that a vaccine will
17 have on rural populations. Thank you.

18 **DR. ATREYA:** Thank you, Ms. Schell. Next
19 speaker is Dr. Douglas Dieterich.

20 **DR. DIETERICH:** Thank you. I'm Dr. Douglas

1 Dieterich. I'm the Director of the Institute for Liver
2 Medicine at Mount Sinai Health System and a Professor
3 of Medicine at the Icahn School of Medicine at Mount
4 Sinai.

5 I'm here as a patient actually, not as a
6 professor, even though COVID-19 causes significant
7 liver disease and significant mortality in patients
8 with preexisting liver disease. I think it's important
9 to recognize that there is a space between life and
10 death. We see the deaths which are extraordinary,
11 3,600 yesterday, and the number of people infected.

12 I was infected in mid-March as was about two-
13 thirds of my clinical team. I was hospitalized for
14 about a month and sent home on six liters of oxygen.
15 Subsequently, I discovered that I had severe peripheral
16 neuropathy in my feet and severe fibrosis, pulmonary
17 fibrosis, which I'm still getting treated for actually
18 both of them. And of course my sense of smell is
19 completely gone. So I think it's important to
20 recognize that as good as our treatment is now,

1 prevention is clearly much better. There's a lot of
2 long-term effects of COVID.

3 After I was at home for a few months I
4 developed some severe atrial arrhythmias. When they
5 subsided, I've developed severe hypertension which I'm
6 still battling. And of course, I'm still taking
7 medicine so that I can feel my feet and hopefully
8 recover some of my sense of smell.

9 So I think the important thing is that there's
10 a real price to be paid for getting COVID, whether it's
11 severe or not. There are long-term side effects. And
12 I think that the vaccine is the answer to prevent
13 COVID-19 and not to get it, and get treated, as good as
14 treatment is nowadays.

15 In addition actually, even though my antibody
16 levels remain extremely high, I will get vaccinated
17 when my time comes. I think that's an important thing
18 to recognize as well.

19 I wanted to thank the Moderna people and the
20 other vaccine makers for helping us prevent this

1 disease so other people don't suffer like I have.

2 Thank you for the opportunity to speak.

3 **DR. ATREYA:** Thank you. The next speaker is
4 Dr. Jasmine Marcelin.

5 **DR. MARCELIN:** Yes. Thank you very much. My
6 name is Dr. Jasmin Marcelin and I'm an infectious
7 diseases physician in Nebraska. I am employed by the
8 University of Nebraska Medical Center, but my comments
9 do not represent my employer and I have no conflicts or
10 disclosures to report.

11 After reviewing the available information
12 about the mRNA vaccine, developed by Moderna, I am
13 encouraged by the 94 percent effectiveness demonstrated
14 and review of expected adverse effects. I would
15 advocate for continued long-term monitoring of clinical
16 trial participants to evaluate for the long-term
17 effectiveness and safety. However, I am encouraged for
18 this vaccine to receive EUA status with prioritization
19 of those at highest risk.

20 We still do need data regarding pregnant

1 people and children, and hope that there will be more
2 sharing of outcomes of people who become pregnant
3 during the trial period. I know that there were 36
4 percent of participants in the trial from communities
5 of color, and few reported cases from these
6 participants. Considering how and what we know about
7 the disproportionate rates of COVID-19 in Black and
8 Brown communities, I urge vaccine discussions to avoid
9 centering mistrust of the Black and Brown communities
10 as originating within those communities, and instead
11 acknowledge the fact that the healthcare profession has
12 previously betrayed these communities through centuries
13 of structural racism, including grievances that are
14 happening today.

15 So, therefore, we need to have open listening
16 and understanding of the concerns of these communities.
17 And trusted healthcare professionals from communities
18 of color need to be engaged to ensure that the approach
19 continues through a lens of equity and cultural
20 congruence.

1 I would also comment on the importance of
2 funding campaigns with appropriate messaging and
3 community engagement in the rollout, to emphasize
4 safety and efficacy for laypeople to encourage vaccine
5 confidence, and appropriate messaging about expected
6 side effects so as not to alarm people when they occur.

7 And then finally, hoping for an equitable
8 distribution plan that ensures that people in rural,
9 low income and communities of color have adequate
10 access to the vaccine, including follow up for second
11 injections. Thank you for the opportunity to
12 participate in this open comment and I'm looking
13 forward to seeing what the vaccine has to do for the
14 community in the future. Thank you.

15 **DR. ATREYA:** Thank you. The next speaker is
16 Dr. Robert Wong.

17 **DR. WONG:** Hi. Good afternoon. I have no
18 conflicts or disclosures. Dear committee members,
19 thank you for giving me an opportunity to speak today
20 and share my thoughts on the importance of timely and

1 equitable implementation of this COVID-19 vaccine. My
2 name is Robert Wong. I'm a Clinical Associate
3 Professor of Medicine at Stanford and a practicing
4 gastroenterologist and hepatologist serving our U.S.
5 Veterans at the VA Palo Alto Healthcare System in
6 Northern California.

7 In addition to my clinical practice, which
8 focuses on management of patients with complex liver
9 diseases, my clinical research is focused on healthcare
10 disparities, particularly among ethnic minorities,
11 vulnerable populations, and underserved safety net
12 health systems. Even prior to the COVID pandemic,
13 ethnic minorities and vulnerable populations suffer
14 significant healthcare disparities. From receiving
15 timely screening and surveillance exams to delays in
16 access to life-saving treatments.

17 Specifically, for patients that I serve, my
18 research has demonstrated disparities in timely receipt
19 of high-quality liver disease care, including access to
20 viral hepatitis treatments for patients with chronic

1 Hepatitis B and Hepatitis C, as well as timely
2 screening for liver cancer among cirrhosis patients.
3 In the past nine months, since the pandemic began in
4 the U.S., we have seen these disparities exacerbated as
5 our chance to deliver high quality care has been
6 disrupted by this pandemic. Patients avoiding care due
7 to fear of venturing out to medical visits for labs or
8 imaging for cancer screening, also healthcare systems
9 transitioning to telehealth delaying non-urgent
10 procedures. And trying to balance the risks of
11 delaying diagnostic and treatment procedures with the
12 risk of our vulnerable patients being exposed and
13 infected with SARS-CoV-2.

14 These vaccines that are now before us present
15 some hope at the end of this deadly year, where many of
16 us have lost not only patients but close friends.
17 While these vaccines will not be the magic bullet, that
18 miraculously reverses all the damage this pandemic has
19 caused, it gives us hope that one day in the not too
20 distant future some semblance of normalcy will be

1 within our reach.

2 While I have no doubt in the eventual approval
3 and dissemination of these vaccines, I would like to
4 encourage all of us to be particularly cognizant of
5 ensuring equitable access, particularly among those
6 underserved and vulnerable populations whose existing
7 healthcare disparities have been disproportionately
8 exacerbated by this pandemic. Thank you all very much
9 for taking time to hear my comments.

10 **DR. ATREYA:** Thank you, Dr. Wong. The next
11 speaker is Dr. Joseph Bick.

12 **DR. BICK:** Good morning. My name is Joseph
13 Bick and I'm an infectious diseases specialist serving
14 as statewide director of healthcare services for the
15 California Department of Corrections and
16 Rehabilitation. I have no financial disclosures to
17 report.

18 I appreciate the opportunity to speak to the
19 committee regarding the importance of including those
20 who work and reside in our jails, prisons, and

1 detention centers in the first phase of COVID
2 vaccination. Over 2 million people are incarcerated in
3 this country. Over 500,000 individuals interact with
4 them on a daily basis as correctional officers, nurses,
5 cooks, respiratory therapists, physicians, teachers,
6 and others.

7 More than 260,000 inmates and 58,000
8 correctional employees have been diagnosed with COVID
9 resulting in at least 85 employee and 1,700 inmate
10 COVID-related deaths. The age-adjusted death rate due
11 to COVID among the incarcerated is several folds higher
12 than what is seen in the outside community. And case
13 rates among both inmates and employees are
14 significantly greater than those seen outside
15 incarcerated settings. Many of the largest COVID
16 outbreaks in this country have occurred in correctional
17 facilities.

18 Many facilities do not routinely test for
19 COVID, and therefore these numbers underestimate the
20 true burden of COVID in these settings. Most inmates

1 are housed in large, overcrowded congregant living
2 environments in which consistent physical distancing is
3 not possible. Many of these settings suffer from
4 insufficient ventilation and hygiene, contributing to
5 the likelihood of widespread COVID outbreaks. Inmates
6 are disproportionately people of color, and often they
7 have multiple comorbidities that increase their risk
8 for serious illness, hospitalization, and death if they
9 become infected with COVID.

10 Delaying vaccine distribution to inmates will
11 exacerbate the disparate racial impact of COVID-19.
12 Advanced age is one of the greatest predictors of poor
13 outcome of COVID, and age-associated risk for prisoners
14 begins to rise in their 50s. The average age of
15 inmates in this country has risen significantly over
16 the years. Currently, over 10 percent of prisoners are
17 55 years of age or older. Many of our prisons are
18 essentially nursing homes, long term care facilities,
19 and skilled nursing facilities with bars.

20 Jails, prisons, and detention centers are

1 often a major employer in some rural settings. When
2 employees unknowingly introduce COVID, the disease can
3 be rapidly amplified and subsequently fuel large
4 outbreaks in the outside communities. Inmates who
5 require hospitalization can quickly overwhelm bed
6 capacity in surrounding community healthcare
7 facilities.

8 Cases among staff and inmates are currently
9 surging to unprecedented numbers threatening to
10 overwhelm local resources. Not including correctional
11 staff and high-risk inmates in vaccination Phase 1 will
12 result in preventable illness and deaths, burdens upon
13 local economies, unsafe jails and prisons, and
14 increased pressure upon over-stressed community
15 hospitals. In closing, I urge you to include high risk
16 inmates and front-line correctional workers in phase 1a
17 for this and all future COVID vaccines. Thank you.

18 **DR. ATREYA:** Thank you, Dr. Bick. The next
19 speaker is Dr. Donald Middleton.

20 **DR. MIDDLETON:** Hi. I'm Don Middleton, a

1 professor of family medicine at the University of
2 Pittsburg School of Medicine. I am unofficially
3 speaking to support EUA approval of the Moderna mRNA
4 vaccine, which has shown its worth in rigorous blinded
5 clinical trials. I do serve on a Moderna mRNA vaccine
6 advisory board. My background is in vaccine education
7 and I am one of the developers of a free vaccine app
8 for iPhones and Androids called "Shots," by AAFP/STFM.

9 COVID-19 is ubiquitous. It's in the air, on
10 doorknobs, on computers, in the trash. Even when
11 social separation policies are followed to the fullest,
12 infection still occurs. The number of infected persons
13 is staggering, the number of deaths more so. In the
14 U.S., 300,000, a number that is difficult to grasp.
15 Basically, the city of Pittsburg wiped out.

16 As we have already heard, recovery from COVID
17 often takes months or is incomplete. Most days when I
18 walk into UPMC Saint Margaret, my true home, a
19 community hospital with about 200 beds, I wonder how
20 many COVID patients do we have. Is this the day, is

1 this the one when I will become infected?

2 Others who work here share that fear, but it
3 does not stop thousands of our hospital employees from
4 doing their jobs. Our hospital staff always keeps in
5 the forefront that the patient is a person, something
6 the statistics fail to convey. Before November we used
7 to have a few, maybe five or seven COVID in-patients
8 daily. Now we have 60, sixty out of 190 in-patients.

9 One day this week, 9 out of the 10 patients in
10 the ICU had COVID, and seven were on respirators. A
11 70-year-old woman on a respirator had to communicate
12 with handwritten messages. Just before being sedated
13 to improve her oxygenation, she scribbled a note to the
14 outstanding resident doctor taking care of her, "I
15 love y'all. My life is in y'all's hands." A heart
16 with an arrow through it was attached to the bottom of
17 this note.

18 Endless lights, noise, strangers in the rooms,
19 not loved ones, everyone is gowned and mask. You
20 cannot really sit to talk with patients or hear their

1 fears. Even though the staff does their duty daily,
2 they are working in hell.

3 Control of COVID requires vaccine, billions of
4 doses. The Moderna vaccine offers real hope that this
5 pandemic can be truncated. And with published evidence
6 of lasting immunity, help to keep it permanently at
7 bay. Please advise the FDA to give this outstanding
8 vaccine full EUA status. Thank you very much.

9 **DR. ATREYA:** Thank you. The next speaker is
10 Mr. Sidney Wolfe.

11 **DR. WOLFE:** Good morning. I'm Dr. Sidney
12 Wolfe, Public Assistance Health Research Group. I have
13 no conflicts of interest. During the October 22nd
14 meeting of this committee before seeing data from
15 either Pfizer or Moderna vaccines, FDA's Dr. Doran Fink
16 pointed out that, "Deployment of a weakly effective
17 COVID-19 vaccine could result in more harm than good.
18 It could do so by providing a false sense of security
19 that interferes with measures to reduce SARS COVID
20 transmission, such as wearing of masks, other PPE, and

1 social distancing."

2 I would argue that, even with current evidence
3 that both vaccines are highly efficacious, there is
4 still understandable concern about the danger of a
5 false sense of security, if those getting vaccinated no
6 longer adhere to proven preventative public health
7 measures such as wearing masks and appropriate social
8 distancing. The FDA's 2017 EUA guidance include a
9 requirement for an FDA-approved patient fact sheet to
10 accompany the use of all EUA products, "...to ensure that
11 recipients are informed about the product they receive,
12 and to inform them of any available alternatives to the
13 product and of the risk and benefits of available
14 alternatives."

15 Since 2017, no EUA for a vaccine had been
16 granted prior to the Pfizer vaccine, but providing
17 written information about proven health measures, such
18 as wearing masks and appropriate social distancing, is
19 clearly necessary and appropriate for COVID vaccine
20 recipients. Flashing back to last week, less than 24

1 hours after the EUA for the Pfizer vaccine was granted,
2 the FDA posted a Pfizer fact sheet for recipients and
3 caregivers intended for recipients of their vaccine.
4 The fact sheet accurately states the Pfizer-BioNTech
5 vaccine may not protect everyone.

6 Unfortunately, it contains no mention of the
7 need for wearing masks and appropriate social
8 distancing. For further information, the fact sheet
9 suggested asking the vaccination provider or your local
10 or state government health department, and then lists
11 websites that do not state such preventive measures
12 should accompany vaccination. Though necessary as a
13 part of company's EUA submissions, such fact sheets
14 were not included in briefing packages provided to the
15 public or possibly the advisory committee for either
16 today's or last week's advisory committee meeting.

17 But this morning, Dr. Doran Fink mentioned
18 that FDA's review yielded -- FDA mentioned that the
19 review and revision of fact sheets, for vaccine
20 recipients, were part of what happened when FDA looked

1 at the EUA submission. So this is at least mentioned
2 in today's meeting which it hadn't been before.

3 I hope your advisory committee urges that
4 important public information, such as that, must
5 immediately be added to vaccine fact sheets before
6 millions more people are vaccinated. Thank you very
7 much and I hope you will ask the FDA questions about
8 this. It does not seem to be in their presentation for
9 this afternoon. Thanks again.

10 **DR. ATREYA:** Thank you, Dr. Wolfe. Next
11 speaker is Dr. Roberta Luskin-Hawk.

12 **DR. LUSKIN-HAWK:** Thank you. I'd like to
13 thank you for the opportunity to comment on today's
14 deliberations. My name is Dr. Roberta Luskin-Hawk and
15 while I'm employed by Providence Saint Joseph Health, I
16 am speaking as a private citizen today. And I have no
17 relevant financial disclosures.

18 I'm an infectious disease physician with
19 extensive experience in conducting and analyzing
20 clinical trials, in addition to experience in

1 overseeing healthcare delivery across both urban and
2 rural settings. My current role, as Hospital Chief
3 Executive serving remote area of Northern California,
4 provides a unique perspective on the potential impact
5 of emergency use authorization of mRNA 1273 COVID
6 vaccine on rural communities.

7 A current surge in COVID-19 is having a
8 devastating impact in communities across the country,
9 and the demand for care is starting to exceed capacity
10 in parts of the U.S. healthcare system, with further
11 increase in cases forecasted in coming weeks. While
12 the numbers of patients with COVID-19 in rural
13 communities may seem limited, even small numbers of
14 cases, or illnesses among healthcare workforce, can
15 threaten the fragile healthcare infrastructure and
16 limit the ability to provide critical care to people in
17 these communities.

18 This intervention is needed, and we are
19 fortunate to have had a robust response from the
20 scientific community. It is therefore essential that

1 we rapidly deploy vaccines that are found to be safe
2 and effective against SARS-CoV-2 to both rural and
3 urban communities across our country. The data
4 provided on the Moderna mRNA 1273 COVID vaccine
5 demonstrates exceptional vaccine effectiveness in the
6 reduction of symptomatic COVID-19 across all ages, in
7 addition to beneficial impact on the severity of
8 disease. The vaccine also seems to have a favorable
9 side effect profile in early evaluations.

10 Use of the vaccine with this efficacy will not
11 only save lives that could be lost to COVID, but will
12 help relieve ICU capacity available for the care of
13 patients with other acute medical conditions. The fact
14 that storage requirements can be met by healthcare
15 organizations, without access to ultra-low temperature
16 freezers, will have an added benefit to many small,
17 rural hospitals and clinics.

18 Vaccination of 21 million U.S. healthcare
19 workers and vulnerable populations is urgently needed
20 to protect our healthcare workers, our healthcare

1 infrastructure, and to change the tide of the pandemic.
2 Rapid and broad distribution of vaccine will require
3 EUA and eventual approval of more than one safe and
4 effective SARS-CoV-2 vaccine.

5 I urge you to provide Emergency Use
6 Authorization for mRNA 1273, which has met the
7 necessary safety and efficacy benchmarks in the
8 analysis of the clinical trial data. I personally
9 believe that this approval is needed to support our
10 healthcare workers and to save lives. Thank you.

11 **DR. ATREYA:** Okay. The next speaker is Ms.
12 Veronica Halloway.

13 **MS. HALLOWAY:** Good afternoon and thank you
14 for the opportunity to speak today. My name is
15 Veronica Halloway, Chief of the Center for Minority
16 Health Services at the Illinois Department of Public
17 Health. I have no conflicts of interest. I want to
18 recognize Dr. Damon Arnold who has been leading
19 community conversations and education about COVID-19
20 vaccine on behalf of Illinois' COVID-19 Equity Task

1 Force.

2 To ensure that disparately impacted rural and
3 urban communities of color are informed and engaged in
4 the process of building trust, raising awareness,
5 promoting the importance of vaccination, and creating
6 equitable access and distribution, we launched several
7 initiatives. We engaged with a diverse group of
8 community partners including faith-based, people with
9 disabilities, the homeless, refugee and immigrants,
10 returning citizens, seniors, and the LGBT communities
11 to discern a need for special assistance.

12 We launched a community ambassador's program
13 to ensure confidence with directed messages surrounding
14 COVID-19 vaccinations. These conversations made clear
15 that education and targeted communications regarding
16 misinformation and rebuilding trust, vaccine science,
17 and active collaboration with communities are key.
18 Accurate timely information, concerning the safety and
19 efficacy of the vaccines from the manufactures and
20 scientific community, is vital.

1 National and state data shows that COVID-19
2 kills more males than females, and Black males already
3 have a life expectancy 8 to 11 years shorter than their
4 white counterparts. Special outreach efforts should be
5 made to engage Black males in order to improve
6 participation in both outreach and vaccine uptake.
7 Messaging must be consistent with community beliefs and
8 perceptions about the vaccine.

9 We convened two meetings to collect
10 perspectives from communities mentioned. We noted that
11 both cultural and linguistically-appropriate language
12 is essential for effective communication and delivery
13 of quality healthcare. Providers appear to require
14 additional training with respect to cultural norms and
15 implicit bias. Providers must be intentional about
16 truly engaging with local gatekeepers and community
17 members about the vaccine. The current COVID-19
18 pandemic also underscores the need for a more diverse
19 healthcare workforce reflective of the communities they
20 serve.

1 In closing, there is concern that the access
2 and distribution of vaccines will encounter hurdles
3 within already negatively impacted rural and urban
4 communities of color. Federal, state, and local
5 support is needed such as additional funding to support
6 the use of tools, like COVID-19 Community Vulnerability
7 Index, which combines the CDC's Social Vulnerability
8 Index with epidemiological and health system factors,
9 to target areas most likely to be impacted. Thank you
10 for your time and attention to this important matter.

11 **DR. ATREYA:** Thank you. The next speaker and
12 the last speaker of the session is Dr. James Woody.

13 **DR. WOODY:** Hello. I'm Dr. James Woody and
14 I'd like to thank the FDA for the opportunity to speak.
15 I have no financial disclosures. I'm a pediatric
16 immunologist and a biotech executive, who in a prior
17 life discovered and developed a drug called Remicade.
18 I'd be interested in how patients on anti-TNF
19 inhibitors do with your vaccine. But that's not why
20 I'm here.

1 I talk about what I see as the optimal format
2 for deploying a COVID vaccine for the Navy and the
3 Marine Corp. My comments are my own and do not reflect
4 in any way the opinion of the Navy or Marine Corps. So
5 I'm a retired U.S. Navy Captain who spent 20 years in
6 the U.S. Navy as a medical officer. I ran worldwide
7 Navy medical R&D. One of our jobs was to be aware of
8 any infectious disease risk anywhere in the world where
9 a Navy ship might port, or personnel go into conflict.

10 By way of experience, as a former commanding
11 officer of the Navy's medical unit, NAMRU-3 a BL-3
12 force facility in Cairo, Egypt for four years, my team
13 of about 50 Navy people did surveys for infectious
14 disease over the entire Eastern Africa and Mid-East
15 region. And they included HIV, Hepatitis, Ebola,
16 Congo-Crimean, Rift Valley Fever, Lassa, and serious
17 stuff.

18 So as you know well, space on Navy ships is
19 very confined and berthing space is always limited, so
20 transmission of infectious diseases is a concern. We

1 have actually shut down ships in the past due to
2 chickenpox outbreaks.

3 As you have seen on the press, over 190 Navy
4 ships have had COVID cases, representing about 65
5 percent of all Navy ships at sea. Likewise, the Marine
6 Corps recruits who live in congested facilities have
7 also had significant numbers of COVID cases. So should
8 the Marines be required to deploy on ships, which is
9 the usual sequence, the overcrowding will be even
10 worse, and they'll even be at higher risk.

11 So assuming a two-dose schedule will work to
12 provide protective immunity, so what's the best format
13 for use by the Navy and Marine Corps? Common sense
14 needs to prevail here. Simple is better. Available
15 storage, no diluting.

16 So in situations where multi-doses are
17 required, the smaller shore-based clinic facilities,
18 and the shipboard facilities, must have similar kinds
19 of storage equipment and capacity, so that once a
20 Seaman or Marine is deployed with a first dose, they

1 can actually get a second dose that can be administered
2 anywhere onshore or in the fleet.

3 So most shore-based facilities have the usual
4 -20 degree home-type refrigerator/freezer, so vaccines
5 could be stored in any of these locations and the
6 second dose be administered quite easily. Use of the
7 much lower temperature specialized freezing, at -70 or
8 100, is not a reasonable option as such kinds of
9 equipment is only available on very few, very large
10 ships, or in shore-based hospitals.

11 So in summary, from someone who's actually
12 been in the trenches, common sense needs to prevail
13 here. Simpler is better. Thank you very much for the
14 opportunity and listening to my talk.

15 **DR. ATREYA:** Thank you, Dr. Woody. I would
16 like to thank all the OPH speakers at this point for
17 making the comments. This concludes the open public
18 hearing session. And then now I would like to
19 introduce Dr. Peter Marks. He wanted to make his
20 thanks as well. So, Dr. Marks are you ready?

1 **DR. MARKS:** Thanks very much. So thank you
2 very much to our public speakers. I just want to take
3 a moment, before we move on to the further questions
4 and then FDA presentation and then deliberations later
5 on. There wasn't an exact perfect time to thank
6 everyone today, but this may be a reasonable one just
7 to thank everyone for their participation.

8 This is somewhat of a historic events to have
9 these two advisory committee meetings so close
10 together. And we really thank all of the advisors for
11 taking the time to go through a very large amount of
12 material. Also need to thank our FDA staff who have
13 worked tirelessly, going through an amazingly large
14 amount of material over the past weeks. And that was
15 only made possible because they had worked for several
16 months with the companies internally, and with
17 stakeholders to prepare things so that this relatively
18 rapid EUA review would be possible.

19 So incredible thanks to our FDA colleagues and
20 thanks for all who are tuning into this process. I

1 also need to call out the advisory committee staff
2 which has done a remarkably great job in putting
3 together this meeting. So I won't hold us up anymore
4 and I'll turn this back to Dr. Monto.

5 **DR. ATREYA:** Thank you, Dr. Marks. Dr. Monto,
6 the floor is yours.

7

8 **ADDITIONAL Q&A FOR SPONSOR PRESENTERS**

9

10 **DR. MONTO:** Thank you very much. We're going
11 back to questions directed to the sponsor. And I see
12 Dr. Miller's ready and I'll re-address the question. I
13 interrupted when we broke, and that was about escape
14 mutants and what you're going to do about them,
15 sequencing, and the rest.

16 **MR. KAWCZYNSKI:** Jacqueline, you have your own
17 phone muted.

18 **DR. MILLER:** Thank you for the reminder that I
19 was still muted. Apologies for that. So thank you,
20 Dr. Monto. Yes, indeed. The question actually was

1 about whether we were intending to sequence the samples
2 we receive from breakthrough cases. And the answer is,
3 yes. We are in the process of deep-sequencing virus
4 from those cases. And I was going to invite Dr. Darin
5 Edwards, who is the head of our pre-clinical group, to
6 address the work that we have been doing to assess the
7 effectiveness and immunogenicity of the vaccine against
8 emergent mutants. Dr. Edwards?

9 **DR. EDWARDS:** Thank you for that. Thank you,
10 Dr. Miller. In addition to deep-sequencing of cases in
11 our Phase 3 trial, we're also performing additional
12 research assessments. These include the evaluation of
13 vaccinated, either animal or human sera, the ability of
14 that sera to neutralize these breakthrough, or these
15 variant strains. We're also additionally monitoring
16 for additional strain variance, both through our own
17 internal efforts as well as through collaborations with
18 external research partners.

19 We have thus far identified five strain
20 variants that are of key concern. And we have, at this

1 point, assessed both mouse and non-human primate sera
2 that were vaccinated with mRNA 1273 to protect against
3 these strain variants, and we see they equally protect.
4 In the future we are also performing assessments on
5 human sera. Thank you and I hope that addresses your
6 question.

7 **DR. MONTO:** Thank you. Let's go on to Dr.
8 Sawyer. I believe you have a question.

9 **DR. SAWYER:** Thank you. And thanks for the
10 great presentations. Given our new and unexpected
11 focus on anaphylaxis, I just wanted to ask if you've
12 seen anaphylaxis in any of the other -- I believe you
13 said eight -- vaccines that you had previously
14 developed and given to a quite small number of people?
15 Whether you've seen allergic hypersensitivity reactions
16 in any of your animal models? And whether you have
17 done, or are planning to do, any in vitro studies to
18 see if this mRNA lipid platform creates interactions
19 that would predict allergic-type reactions?

20 **DR. MILLER:** Yes. Dr. Sawyer, thanks for that

1 question. And indeed, we have been doing a very rapid
2 review of our overall clinical database in light of the
3 information that has come forward about the other mRNA
4 vaccines.

5 So as you mentioned, we do have a clinical
6 database across eight other vaccines. It includes
7 approximately 1,700 recipients of a similar lipid
8 nanoparticle with specific mRNA sequences. In those
9 cases, we've had one other report of anaphylaxis. It
10 was a woman with soy allergy in more than a few months
11 outside of her vaccination.

12 And I should clarify that although
13 participants have been excluded on the basis of a known
14 allergy to one of the components of the vaccine, we
15 have not routinely excluded participants who have a
16 history of allergies or anaphylaxis. And then your
17 second question was about potential in vitro studies.
18 In fact, Dr. Zaks has been in discussion actually with
19 thought-leaders at the NIH, BARDA, and so forth to talk
20 about what additional activities we might collaborate

1 to better understand what this potential (audio fades).

2 **DR. SAWYER:** Thank you.

3 **DR. MONTTO:** Dr. Lee.

4 **DR. LEE:** Yes. I had a question about the
5 unblinding. A number of people indicated that there is
6 a clinical trial supply that could be used for that
7 purpose, and that would not interfere with any supplies
8 that would be given, say, to the general public if the
9 EUA were to be granted. So my question is, what -- the
10 indication was that it had a limited shelf life. And I
11 think my first question, related to that, is how long
12 do you think that supply will last? And related to
13 that is would you have enough doses to vaccinate in two
14 doses, for all 15,000 placebo participants, were they
15 all to ask to do that?

16 **DR. MILLER:** Thanks for your question about
17 the vaccine supply. And yes, it is true that we have
18 sufficient supplies to be able to vaccinate our placebo
19 participants. The supply actually will be expiring
20 relatively soon. So by the end of the next month, the

1 supplies will be expired, so they cannot be used for
2 emergency use.

3 **DR. LEE:** Great. Thank you.

4 **DR. MONTO:** Dr. Cohen.

5 **DR. COHN:** Hi, Dr. Miller. Thank you. I was
6 wondering if you could give us a little bit more
7 information about -- I can't remember if you said three
8 or four cases of Bell's Palsy, including how many days
9 after vaccination symptoms started to occur and how
10 long symptoms occurred, and if those persons recovered.
11 And if they have a history of Bell's Palsy?

12 **DR. MILLER:** Thanks for that question, Dr.
13 Cohn. So the cases occurred between 17 and 32 days
14 after vaccination. They were either resolved or
15 resolving at the time of this presentation. And they
16 were -- three were non-serious, one was a serious
17 adverse event.

18 **DR. MONTO:** Dr. Kurilla.

19 **DR. KURILLA:** Thank you. Dr. Miller, in terms
20 of your efficacy evaluation, you began counting two

1 weeks after the second vaccine dose. But your Kaplan-
2 Meier curve between vaccine and placebo begin to
3 diverge after about two weeks after the first dose.
4 But your immunogenicity in your Phase 1 say that even
5 by two weeks, after the first dose, there's no
6 neutralizing titers, and there doesn't seem to be any
7 bump in T-Cells, which suggests that there's some kind
8 of non-specific antigen, vaccine-mediated protective
9 effect potentially going on.

10 And the question becomes, how long does that
11 actually manifest, and do you know what that is? With
12 reactogenicity, I would presume it's inflammation and
13 interferon, and K-Cells and that sort of thing. I'm
14 just wondering how much that might be bleeding into the
15 primary efficacy endpoint analysis?

16 **DR. MILLER:** Yeah. Thanks for that question.
17 So we did show a difference in the reported cases in
18 the Kaplan-Meier curve after randomization, as you
19 mentioned. We do know that our vaccine induces innate
20 immunity with the first dose, and the adaptive immunity

1 clearly increases the second dose. Understanding this
2 phenomenon a bit further is why we looked into that one
3 dose efficacy in several different ways.

4 So looking at it in terms of the time period
5 when the mRNA 1273 cases might be reported, as well as
6 looking at the PCR swabs and looking at the ability of
7 the -- or the differences between the vaccine and
8 placebo groups in terms of that positivity.

9 So I am also going to ask Dr. Melissa Moore if
10 there's anything else -- our Chief Scientific Officer -
11 - if there's anything else she'd like to add about
12 patterns of immunity we have observed with the platform
13 after the first dose.

14 **DR. MOORE:** Thank you, Dr. Miller. I actually
15 would like to send that question over to Dr. Tal Zaks
16 who has more experience with the clinical trials.

17 **DR. ZAKS:** Thank you both. So, yeah. I think
18 the salient parts here is that we see binding
19 antibodies come up very quickly. And while everybody
20 focuses on neutralizing antibodies in appropriate lid

1 cell, I think their sensitivity is lower than looking
2 at the binding assays.

3 And if you look at binding antibodies, they
4 actually come up within a couple weeks. And so I
5 suspect what happens here is that, as you get the first
6 dose you're primed, binding antibodies are going to
7 come up. And now you've got a race between is your
8 infection going to in a sense be a boost, because we
9 know this virus takes some time and you're still
10 protected against symptomatic disease.

11 So I suspect that's the reason for the
12 discrepancy we see between the neutralizing antibodies,
13 that are clearly measurable better after a boost, but
14 the sense that protection may start as early as the
15 first dose. And I think in that regard our results are
16 very concordant with that that were recorded here last
17 week.

18 So while there is some potentially innate
19 activation, I think the story here really is the SARS-
20 CoV-2, and the quick antibody binding and total

1 response that you see after the first dose, I'm sure
2 with further -- with the maturation and further
3 increase on that and now you start to measure
4 consistent neutralizing titers.

5 I will say though, that at the end of the day
6 for me, that first dose efficacy is really supportive
7 evidence overall. But coming back to the fact that
8 what we really studied was a prime-boost, and what we
9 see is clear boosting and a high level of protection
10 across all age groups, and now hopefully that will be
11 durable. And so, I would take the first dose efficacy
12 as supportive evidence, but remind us all that we
13 actually need both doses, as far as we know, to achieve
14 this high level of protection. Thank you.

15 **DR. MONTO:** Dr. Sylvester.

16 **DR. SYLVESTER:** Thank you, Dr. Monto. I
17 wanted to briefly revisit that blinding versus
18 unblinding issue. As the industry rep, you don't need
19 to convince me that a randomized double-blinded
20 clinical trial is our gold standard.

1 However, I don't believe this would be the
2 first study that would be the first RCT, that would
3 meet their primary endpoint and vaccinate the placebo
4 group before the protocol-described timeframe ends. I
5 believe that HPV-4 Gardasil and the original
6 pneumococcal conjugate vaccine, Prevnar 7, vaccinated
7 their placebo group after the primary endpoint was met,
8 and the data showed overwhelming evidence of benefit
9 similar to what we're seeing here today.

10 I don't know Dr. Baden, at Brigham and
11 Women's, but I share his concern about losing a
12 significant portion of his study population without
13 offering the COVID vaccine. And I think his open label
14 continuation seems like a practical solution. Thank
15 you.

16 **DR. MONTO:** Dr. Meissner.

17 **DR. MEISSNER:** Thank you, Dr. Monto, and thank
18 you Dr. Miller and others for a fascinating
19 presentation. I have a few questions related to the
20 vaccine that are all related. First of all, why do you

1 think you were successful with this particular
2 messenger RNA vaccine whereas the previous eight are
3 still in development? Number one.

4 Number two, when we see adverse reactions in
5 the first 48 to 72 hours, following the administration
6 of a vaccine, do you think that's a reaction to the
7 messenger RNA or more likely to the lipid nanoparticle?
8 And along that line, is there understanding that these
9 are proprietary issues? Can you say anything about
10 differences in the lipid nanoparticle between Moderna's
11 vaccine and the one that we spoke about last week?

12 And then finally, why did you select a 28-day
13 prime interval between the first and the second dose?
14 Was there a reason for that? Thank you.

15 **MR. KAWCZYNSKI:** Jacqueline, did you mute your
16 phone again?

17 **DR. MILLER:** I did to not interfere with my
18 colleagues. I apologize. So thank you, Dr. Meissner,
19 for those questions. And what I was saying was, I'm
20 going to start and then I'm going to pass the mic along

1 to our Chief Medical Officer, Dr. Zaks.

2 So with respect to our development program for
3 mRNA 1273, and the other development programs we have
4 ongoing. So our company has been in the clinic now for
5 about five years. Most of our programs actually have
6 been in the clinic now for about two years. And the
7 difference between the 1273 program and others, of
8 course, is the unique circumstances in which we find
9 ourselves and the strong medical needs which the
10 vaccine requires.

11 So we have expedited many elements of the
12 development program, including conducting the three
13 phases of our study staggered, but also much of the
14 conduct has been done in parallel. And that has
15 required an absolute focus and collaboration across
16 multiple groups with their focus as well, on the
17 scientific questions that have been raised throughout
18 the course of development. So for example, what safety
19 data did we need to have available in order to move
20 from one step to the next step?

1 With respect to your question about the
2 component of the vaccine that is responsible for the
3 reactogenicity, I'll ask Dr. Zaks to join the call now.

4 **MR. KAWCZYNSKI:** -- sir, you are still muted,
5 sir.

6 **DR. ZAKS:** I apologize for that. Look, for
7 the vaccine, I think it's also important to note that
8 we're in the midst of a pandemic and it's the paradox
9 event vaccine development for case-driven trial. You
10 know, cases are occurring, unfortunately, and that's
11 why these trials delivered information so quickly.

12 As it relates to the components -- and this
13 was a point of discussion yesterday with an expert
14 panel convened by the NIH where FDA also attended. I
15 think if you look at the lipid nanoparticle, and you
16 ask yourself about the anaphylaxis, people look at
17 three elements here. There's the PEG component, which
18 is actually not just the PEG, the PEG is connected to a
19 lipid. And in that regard, not all PEGs are the same.
20 And indeed, the PEG and the covalently-attached lipid

1 that's in our vaccine is different than the one in the
2 Pfizer vaccine.

3 The second potential culprit is the amino
4 lipid, and that's where we and Pfizer used very
5 different -- each are proprietary -- amino lipids. So
6 these are different components. The other components
7 are probably innocuous. Cholesterol, it's enough in
8 our body, the mRNA itself is unlikely to be the culprit
9 here because it's all naturally in cells.

10 The final element here is the physical-
11 chemical particle properties, right? Because we know
12 that these particles can actually induce responses in
13 and of themselves due to their physical properties.
14 And in that regard, I would expect that the physical-
15 chemical nature of our particles is actually going to
16 be very different than Pfizer's.

17 So while we all say, oh there's an LNP here
18 with some lipids and mRNA therefore they must be the
19 same, I actually think that as far as the components
20 likely to be the culprits here, I would not necessarily

1 assume that. Now, that being said, of course, we're
2 going to be looking very carefully, as has been noted,
3 and continue to collaborate with colleagues to try to
4 understand the mechanism here and make sure that we
5 understand this as the picture evolves.

6 I think though, the last question you asked
7 was about the 28-day interval. I think that's just
8 basic immunology. I don't think there's a big
9 difference between three weeks and four weeks. In the
10 history of our vaccines, as Dr. Miller alluded to,
11 we've always done a four-week interval between prime-
12 boost. That's sort of based on, you know,
13 immunological first principles of vaccination as we
14 understand it when it starts to be optimal for
15 primates.

16 But I would note here that the window for the
17 second vaccine actually in the protocol was reasonably
18 wide. It was minus three, plus seven. So, you know,
19 we say four weeks, but there's some spiel there. And I
20 think when we did our analysis, we made sure to include

1 all that. So I doubt that that is materially different
2 when the dust settles. Thank you.

3 **DR. MEISSNER:** Thank you. And can I ask one
4 follow up question? So --

5 **DR. MONTO:** Uh -- uh --uh --

6 **DR. MEISSNER:** No?

7 **DR. MONTO:** I'm in the unenviable position of
8 having about eight hands raised and five minutes to go,
9 so we're going to have to put that off until later.

10 **DR. MEISSNER:** Understood.

11 **DR. MONTO:** Mr. Toubman.

12 **MR. TOUBMAN:** Yes. Thank you for the
13 presentation. The data's impressive, but I'm still
14 nervous about only nine weeks median data. So to try
15 to put myself ease, a couple questions.

16 One is, with regard to the severe disease
17 endpoint. The supposition is that it prevents disease,
18 it prevents severe disease, but we really need data.
19 Pfizer did not really have data on that, they have very
20 few cases. And they were given the opportunity to

1 provide recent data, they declined.

2 You have 30 cases in the placebo group and
3 none in the vaccine group, which is great. But is
4 there more recent data? I assume you know how many
5 severe cases there have been since they closed on
6 11/21. How many cases has that been and has the split
7 reflected the 30 and the zero as before?

8 My other question is related to the
9 unblinding? This is really important because we don't
10 have enough data and maintaining the placebo-controlled
11 studies is the way to get more data. And your plan is
12 specifically to end that.

13 We heard a bunch of arguments for that, one of
14 which is you don't want to disadvantage trial
15 participants relative to others. And also that there
16 are supplies that have been set aside that you could
17 use for all the trial participants. You just answered
18 the question you had enough. But I think that's kind
19 of beside the point. The real question is what is the
20 expectation?

1 And I'd like to ask, if I understand what Dr.
2 Goodman was explaining, he indicated that the
3 participants in your trial were not told that they
4 would jump the line, that they'd be entitled to get the
5 vaccine before others in their same demographic group
6 and their same risk group. And if that's true, they
7 have no expectation of getting it different from
8 anybody else that's in their group.

9 Is there any other ethical reason why Moderna
10 think its trial participants that got placebo should be
11 getting the vaccine compared to Pfizer, which Pfizer
12 appears has rejected the blinded crossover study? But
13 they have -- according to this letter they just sent
14 out to one of the trial participants in my state --
15 it's only healthcare workers, 20 percent of our
16 healthcare workers, who are being offered this and the
17 rest are being told it will be at a later date.

18 I'd like to know if there's an ethical reason,
19 if you haven't told people they're going to all get it,
20 why you're any different than Pfizer and you couldn't

1 do the same with the 25 percent who are healthcare
2 workers in your trial? And then the rest will be
3 later, and that way you maintain the placebo-controlled
4 study for the remaining 75 percent.

5 **DR. MILLER:** Thank you for your questions, Mr.
6 Toubman. Maybe I'll start with the first question
7 about additional data. So as Dr. Fink reviewed in his
8 presentation, we've actually made two submissions to
9 the FDA. So the first was on what was intended to be a
10 first planned interim analysis.

11 There were so many cases reported in November
12 that actually we achieved our final primary analysis
13 approximately five months earlier than we anticipated.
14 We have continued to collect cases since that
15 submission on December 7th. And we currently have over
16 450 cases that are actually making their way through
17 the adjudication process.

18 And you can imagine that our adjudication
19 physicians also have been working extremely hard to
20 keep up with this real tsunami of data that are

1 becoming available, so I don't have that information
2 available for you today. Do intend, though, to
3 continue to make data cuts and update those efficacy
4 analyses. So that should be in the weeks to come.

5 Your second question was really about the
6 ethical basis for the proposal to unblind placebo
7 recipients. And I think some of your questions really
8 speak to the interface that Dr. Baden has with the
9 trial participants, so I'm going to turn the floor over
10 to him in a moment. I guess the one thing I would say
11 is, we do have one death that has been reported in our
12 trial, in a case of severe COVID, that occurred in a
13 placebo recipient. And that death weighs very heavily
14 on me.

15 But I do understand that that death occurred
16 at a time when we did not understand if this vaccine
17 was going to have the efficacy that it does, and we
18 didn't have a clear understanding of what the benefit-
19 risk profile looked like. I do think that with the 450
20 cases that I just mentioned, additional severe cases

1 and deaths are a question more of when than a question
2 of if. And I think the knowledge that that may be
3 waiting in some of our trial participant's future
4 weighs heavily on me. But Dr. Baden, will you please
5 also take the floor and discuss the question?

6 **DR. BADEN:** Yes. Oh, no, thank you, Dr.
7 Toubman, for raising those issues. I think the
8 question is not that they were promised. We should not
9 disadvantage the volunteers, but we have to be
10 practical of where we are.

11 Unblinding is going on, vaccine is available,
12 the vaccine availability is going to rapidly extend to
13 multiple groups. So it's not as if this will take
14 place over six months to a year; this is going to take
15 place over days to weeks in terms of the extending the
16 vaccine supply to additional groups, such as 1b and 1c.
17 And I think what we need to do is keep the volunteers
18 in the study.

19 And that keeping it in the study, there's not
20 only one flavor of study. It's not just a double-blind

1 study. There are other formats of the study that can
2 enable us to learn, particularly to learn about
3 asymptomatic transmission through the serology at the
4 transition point, the nasal swab to look at
5 contagiousness and infectivity. And that if we don't
6 come up with a plan that is easily understood and
7 practical for all of our volunteers, some of whom are
8 very health savvy and some of whom are not, then it
9 will become very confusing and disruptive and corrosive
10 in my view.

11 And so, I don't think it's an issue of a
12 double-blind study or nothing. There are different
13 formats of an ongoing clinical research trial that
14 leverages or accepts the reality that we are facing,
15 over the next two to six weeks in terms of the
16 transition, as vaccine becomes more available.

17 **MR. TOUBMAN:** Thank you.

18 **DR. MONTO:** Okay. We're going to have to go
19 on to Dr. Fuller. And let me say --

20 **DR. FULLER:** Great.

1 **DR. MONTO:** -- in advance that we're going to
2 eat into our lunch. I'm going to try to break for at
3 least a short period of time, because we have no breaks
4 scheduled from now to the end of the meeting. So we
5 will take a break for a short period of time, maybe for
6 15 minutes. But since I've got a lot of hands raised,
7 I'm going to continue to go. Dr. Fuller, please.

8 **DR. FULLER:** Thank you, Dr. Monto. And thank
9 you Dr. Miller and Moderna for your study and what
10 seems to be a very carefully crafted and executed
11 study. I have two hopefully quick questions.

12 One, you mentioned that you will be doing
13 surveillance on the follow-up in Phase 4, not only to
14 CDC and FDA, but your own system of real-time global
15 monitoring of events. The first question is, will that
16 be done in conjunction also with other vaccines that
17 may be approved, for example, the one that has already
18 been approved through Pfizer for EUA?

19 And then the second question is probably a
20 little bit more theoretical. You noted that you have

1 greater pain or third-degree pain for the second
2 injection than the first injection. And I've been
3 wondering about these vaccines that -- especially to
4 the S protein where they boost specific immunity. What
5 happens when people are exposed over and over again to
6 the virus, in a circulating pandemic, when they've been
7 highly boosted to something that binds to say the -- in
8 this case the H2 receptor?

9 Do you have any idea why there's more pain in
10 the second injection? And do you have any thoughts
11 about this idea of having highly boosted immune systems
12 in the middle of a pandemic, where they're continuously
13 challenged?

14 **DR. MILLER:** Yeah. So thanks for both of
15 those questions. And I'm going to go to the second
16 question first, so that afterwards I can turn the floor
17 over to Dr. David Martin who can then speak a bit to
18 the pharmacovigilance plans we have both in conjunction
19 with the safety surveillance systems at FDA and CDC,
20 and also the study we intend to undertake ourselves.

1 But your question about the reactogenicity
2 observed with the vaccine and could that potentially
3 have to do with vaccinating during a pandemic? So what
4 we've observed, in terms of the vaccine reactogenicity,
5 actually really parallels what we see in terms of the
6 vaccine immunogenicity. So the increase after the
7 second dose really goes along with the increase in
8 neutralizing antibody, that we see in all participants,
9 and the induction of our T-Cell responses.

10 We did actually have 2.2 percent of the
11 population in the study who did not have a history of
12 COVID-19 disease, but when we tested their baseline
13 swab for RTPCR, and we tested their serology for
14 existing antinucleocapsid antibodies, were found to be
15 baseline seropositive for SARS-CoV-2. And in fact, the
16 observed reactogenicity in that group was lower for
17 both local and general solicited systems.

18 So we think the vaccine can be safely given to
19 people who have previously been exposed to SARS-CoV-2;
20 and think it's more likely that the increases in

1 immunogenicity are rather related to the pattern of
2 reactogenicity. And so for the second question, Dr.
3 Martin, would you like to talk about the post-
4 authorization safety study that we are proposing?

5 **DR. FULLER:** Before you go to the second
6 question, just a quick follow up. So does that mean
7 that when people who are immunized get re-exposed, say
8 during -- you know, over the next three months, to
9 viruses circulating, that the boosted immune systems
10 should not have any systemic effect because of just
11 exposure to the virus? I just don't know the answer to
12 that, and I don't know if anyone does.

13 **DR. MILLER:** Yes. I think you're right, that
14 -- you bring up a good point. Only 2.2 percent of the
15 population were baseline seropositive in this study.
16 So certainly that is another important reason both to
17 keep the clinical trial ongoing and to follow the
18 patients who might get vaccinated in a cross-over
19 design for their safety events, but also to conduct the
20 post-marketing safety surveillance that we're proposing

1 to do. And so perhaps, Dr. Martin, do you want to talk
2 to the study that we're going to conduct?

3 **DR. MONTO:** Briefly, please.

4 **DR. MARTIN:** Excuse me?

5 **DR. MONTO:** Briefly.

6 **DR. MARTIN:** Oh, briefly. Okay. Absolutely.
7 Understood. Thank you, Dr. Fuller, for the question.
8 So as you were mentioning, visibility for the Pfizer
9 vaccine as well as the Moderna vaccine. So there are
10 vaccine-specific administration codes which are brand
11 specific. And so, the U.S. FDA and CDC surveillance
12 systems, which have described their activities publicly
13 in ACIP meetings in the last few weeks, they will be
14 able to observe both vaccines in a brand-specific
15 manner and certainly aggregate if they choose to do so.

16 Moderna, as is customary, will primarily focus
17 its monitoring on its own product and will obviously
18 work bilaterally if contacted by the FDA. We've been
19 notified by the U.S. government that we should expect
20 communications regarding safety signals from the U.S.

1 FDA. And so that is customarily how these things are
2 done.

3 **DR. FULLER:** Thank you.

4 **DR. MONTO:** Okay. Dr. Hildreth, please.

5 **MR. KAWCZYNSKI:** Dr. Hildreth, we're not
6 hearing you. Dr. Hildreth, let's just make sure you're
7 not on mute. There you go. Now we can hear you.

8 **DR. HILDRETH:** Can you hear me now? Oh.
9 Thanks.

10 **MR. KAWCZYNSKI:** Yes.

11 **DR. HILDRETH:** First, I was apologizing that
12 we're still not able to get my camera to work. I
13 apologize for that. My question relates to the
14 minorities you've enrolled in the study. My
15 understanding is that many of them, or large numbers of
16 them, enrolled late in the process. And I wonder if
17 you have the same median follow up for those
18 individuals as you have for the study overall?

19 **DR. MILLER:** So I don't have the specific data
20 about minorities and the follow up in each of those

1 groups. It is true that they were enrolled a bit later
2 in the process. And that was really because we
3 invested in working with community leaders to
4 understand what we needed to do in order to make
5 participation in clinical trials something that those
6 communities would -- that are -- again, to Dr. Baden's
7 previous point, building trust with those communities
8 and ensuring that they benefit from the clinical trial
9 in which they have so generously donated their time and
10 their willingness to be examined, is really critical, I
11 think, to encouraging a minority enrollment in future
12 clinical trials.

13 And we will continue to follow -- as we would
14 propose to transition to an open-label study, we will
15 continue to follow those individuals for further
16 breakthrough cases and for their safety outcomes to
17 generate these very important data.

18 **DR. HILDRETH:** Thank you.

19 **DR. MONTO:** Dr. Perlman, please.

20 **DR. PERLMAN:** Yes. I just have a relatively

1 quick question. So this vaccine can be kept at room
2 temperature for some number of hours and at four
3 degrees for a long time. And since it's an RNA
4 vaccine, how much degradation of the RNA occurs during
5 that time? I worry when it goes out to more distant
6 places that conditions won't be so perfect. So how
7 long is it really stable?

8 **DR. MILLER:** Yeah. So to speak to the
9 stability studies I am going to as our CMC expert, Dr.
10 Nedim Altaras, to take that question.

11 **DR. ALTARAS:** Hello. Hi. Can you hear me?
12 Yes? We have started performing our stability studies
13 very early on in January when we started developing
14 this vaccine. And we have generated/collected
15 significant amount of stability since that time, which
16 we have shared with FDA including our stability at 228
17 and room temperature. Which basically we provided to
18 FDA to be able to make the shelf-life claim that we are
19 making. And FDA, as you have noted in their briefing
20 document, have agreed with our CMC package that's

1 suitable for emergency authorization.

2 **DR. PERLMAN:** But is there any degradation?

3 **DR. ALTARAS:** mRNA have degradation over time
4 at different temperature. And yes, we characterized it
5 and we assured that in terms of the shelf-life, our
6 product remains potent and maintains the quality
7 attributes across all quality attributes to maintain
8 effectiveness. And also during the Phase 3 study, we
9 actually utilized -- we actually put loss in the study
10 representing the quality attributes across the shelf-
11 life of the product.

12 **DR. MONTO:** Okay. Final question before we
13 break, from Dr. Rubin, please.

14 **DR. RUBIN:** (Audio skip) -- and do you think?
15 And how long does the mRNA stick around for inside the
16 cells?

17 **DR. MILLER:** I apologize, Dr. Rubin. I missed
18 the first part of your question. The audio took a
19 moment to come up. Would you mind repeating it,
20 please?

1 **DR. RUBIN:** Okay. Sorry. So which cells do
2 you think are important for antigen presentation, and
3 how long does the mRNA last intracellularly?

4 **DR. MILLER:** So to answer your question, I'm
5 going to ask Dr. Melissa Moore, our Chief Scientific
6 Officer, to come up in a minute. But the cells that we
7 believe are important for the antigen presentation are
8 the dendritic cells and the subcapsular macrophages.
9 But to give you more detail, Dr. Moore.

10 **DR. MOORE:** Thank you for the question. Yes.
11 The main cells, as illustrated on the slide I'm showing
12 here that take up the lipid nanoparticles and express
13 them in the draining lymph nodes, are the monocytes and
14 dendritic cells, also known as antigen-presenting
15 cells. In terms of how long the RNA sticks around, the
16 peak antigen expression is about 48 hours and it's gone
17 by 72 hours. The mRNA is generally gone by around 24
18 hours. So the protein sticks around longer than the
19 mRNA.

20 **DR. RUBIN:** Thank you.

1 **DR. MONTO:** Okay. I am going to have to call
2 a mercy rule here for everybody and apologize to the
3 six people with their hands raised right now. Your
4 turn will come later on. We're about 15 minutes late
5 and to allow everybody a little bit of time off, let's
6 start at 2:05. So a 20-minute break right now.

7 **[BREAK]**

8

9 **FDA PRESENTATION AND VOTING QUESTIONS**

10

11 **MR. KAWCZYNSKI:** All right. Welcome back to
12 the Vaccines and Related Biological Products Advisory
13 Committee Meeting. We just came back from our last
14 break, and now we will go into the last portion of
15 today's agenda. With that, Dr. Monto, go ahead and
16 take it away.

17 **DR. MONTO:** I would like to introduce next for
18 the FDA presentation and also a description of the
19 voting questions to Rachel Zhang, who is our next
20 presenter. Dr. Zhang, please.

1 **DR. ZHANG:** Hi, good afternoon, everyone. So
2 this is a brief outline of what we will be covering
3 today. First, I will start with an introduction of the
4 Moderna COVID-19 vaccine and a quick run-through of the
5 clinical development program to date. Then, we'll take
6 a dive into the efficacy and safety data from the phase
7 3 study. We'll discuss the pharmacovigilance plan and
8 plans for future studies, and finally we'll finish with
9 a benefit-risk assessment in context of proposed use
10 under EUA.

11 So very quick introduction. Moderna COVID-19
12 vaccine is based on the SARS-CoV-2 spike glycoprotein
13 antigen encoded by RNA, formulated in lipid
14 nanoparticles. It's given as an intramuscular
15 injection two dose series spaced 28 days apart. Each
16 dose is 100 micrograms. Their proposed indication and
17 usage under EUA is for active immunization, for the
18 prevention of COVID-19 caused by SARS-CoV-2, in
19 individuals 18 years of age and older.

20 So really quickly, looking at the clinical

1 development program to date, there are three ongoing
2 studies with the Moderna COVID-19 vaccine. The phase 1
3 study was co-sponsored by the NIH and is an open-label,
4 dose-ranging study in individuals 18 years of age and
5 older. The phase 2 study is a randomized, placebo-
6 controlled dose confirmation study, also in individuals
7 18 years of age and older.

8 Safety and immunogenicity data from phase 1,
9 and additional safety data from phase 2, help inform
10 the dose selection and study design for phase 3. Phase
11 3, which we will talk a little bit more in depth, is a
12 randomized, placebo-controlled efficacy study in
13 individuals 18 years of age and older.

14 So looking at the phase 1 study, they enrolled
15 a total of 120 participants in three age cohorts.
16 There were 60 between the ages of 18 and 55, 30 between
17 the ages of 56 and 70, and 30 participants 71 years of
18 age and older. There were four dose levels tested,
19 ranging from 25 micrograms to 250 micrograms.

20 The immunogenicity assessments from the study

1 showed that two doses induced SARS-CoV-2 binding and
2 neutralizing antibodies, and Th 1-biased CD4 T-cell
3 response was elicited. The safety profile supported
4 further clinical development, and there were no
5 concerning safety findings. As of the time of the EUA
6 request, there has been no serious adverse events
7 reported from the phase 1 study.

8 The study was staggered in design where the
9 younger cohorts were enrolled earlier than the older
10 cohorts, and some doses were later added on to the
11 study. So there's a range in follow up duration. At
12 this time, all participants from this study have had at
13 least three months of follow up after dose 2, and a
14 very small number has had up to a six month follow up.

15 So now looking at the phase 2 study. So in
16 this study there were 600 participants, half between
17 the ages of 18 and 54 and half 55 years of age and
18 older. Subjects were randomized one to one to one, to
19 either the 50-microgram dose, 100 microgram dose, or a
20 placebo. Similar to the phase 1 study, two does

1 induced comparable SARS-CoV-2 binding and neutralizing
2 antibodies in both age cohorts. No concerning safety
3 signals were found.

4 As of the time of the EUA request, there has
5 been three SAEs that were reported in the vaccine
6 group, but none were assessed as related. The
7 immunogenicity and safety data are from the Day 57 data
8 cut, which comes to about one month after dose 2. But
9 SAEs are reported more in real time, so the three SAEs
10 are current as of the beginning of December.

11 So moving on to the phase 3 study. So in this
12 study 30,351 adults, 18 years of age and older, were
13 randomized one to one and vaccinated with two doses of
14 the vaccine or placebo 28 days apart. Randomization
15 was stratified by age and risk factor for severe COVID-
16 19 into one of these three categories: those 18 to 64
17 years of age without risk factors; 18 to 64 years of
18 age with risk factors; and individuals 65 years of age
19 or older regardless of risk factors. The protocols
20 specified that the latter two categories should make up

1 25 to 50 percent of the total study population.

2 And the risk factors for severe COVID-19
3 specified in the protocol are chronic lung disease,
4 significant cardiac disease, severe obesity, which is
5 BMI 40 or greater, diabetes, liver disease and HIV.
6 All subjects were followed for solicited adverse
7 reactions for seven days after each dose, unsolicited
8 adverse events for 28 days after each dose, and SAEs
9 and medically-attended adverse events for the entire
10 study duration. The planned study duration is two
11 years.

12 So this is a graphical depiction of the study
13 timeline in terms of scheduled visits and also when the
14 two efficacy analysis timepoints occurred. So starting
15 on the left-hand side, subjects were administered two
16 doses of the vaccine or placebo one month apart. A
17 nasopharyngeal swab for SARS-CoV-2 RTPCR was collected
18 prior to each dose, as well as blood for
19 immunogenicity.

20 There are further scheduled study visits for

1 safety and immunogenicity assessments during the follow
2 up phase of the study. Throughout the study, subjects
3 are given weekly e-diary prompts, as well as monthly
4 safety phone calls. And active surveillance for COVID-
5 19 symptoms begins after dose one. Looking at the top
6 of this graph, you'll see the dates of the two analyses
7 that contributed to the data that we will look at
8 today.

9 So this slide just shows the case definitions
10 used for the efficacy endpoints. So starting from the
11 left-hand side, the primary efficacy endpoint for
12 COVID-19 disease, the case definition is positive SARS-
13 CoV-2 PCR plus at least two of the following systemic
14 symptoms: fever, chills, myalgia, headache, sore
15 throat, new olfactory -- sorry, my screen disappeared -
16 - new olfactory and taste disorders or -- I'll just
17 keep going since I have backup slides -- at least one
18 of the following respiratory signs or symptoms: cough,
19 shortness of breath or difficulty breathing, or
20 clinical or radiological evidence of pneumonia. Let me

1 know if I need to click something, too.

2 **MR. KAWCZYNSKI:** Yeah. Just give us a second.
3 Somebody accidentally hit "stop sharing," so let me
4 pull it back up. All right? It'll just take a moment
5 here. Let's see. I've just got to check the names, so
6 it'll just take a moment. Did you try to hit the arrow
7 accidentally and -- was that it there?

8 **DR. ZHANG:** I didn't touch anything.

9 **MR. KAWCZYNSKI:** What's the title of yours?
10 Oh, okay. Share document. Hold on. We're just going
11 to take a quick little break. Chad, pull us up on a
12 break just while we pull this up. I want to make sure
13 we get it.

14

15 **[BREAK]**

16

17 **DR. ZHANG:** -- severe systemic illness based
18 on one of the vital signs, respiratory failure or ARDS,
19 shock, significant acute renal, hepatic, or neurologic
20 dysfunction, ICU admission or death.

1 So this slide shows the primary efficacy
2 endpoint and how it was analyzed. The primary endpoint
3 is, confirmed COVID-19 occurring at least 14 days after
4 dose 2 in participants without evidence of SARS-CoV-2
5 infection prior to dose 1. And baseline SARS-CoV-2
6 status is based on RTPCR for SARS-CoV-2 and serology
7 against a nucleocapsid prior to dose 1.

8 For the primary endpoint, an independent
9 blinded clinical adjudication committee confirmed
10 whether each case met this case definition and should
11 be counted. Vaccine efficacy was defined as the
12 percent reduction, vaccine versus placebo, in the
13 hazard of the primary endpoint, so $V=1-\text{hazard ratio}$
14 from the Cox model. The primary objective would be met
15 if the null hypothesis of H_0 vaccine efficacy less than
16 or equal to 30 percent is rejected at any of the
17 interim or primary analyses at the pre-specified
18 O'Brien-Fleming boundary.

19 There were two protocol specified interim
20 analyses timepoints. The first after 53 cases have

1 accrued, and the second after 106 cases have accrued.
2 Because of the rapid rise in cases around the time that
3 the first interim analysis was triggered, there were
4 actually 95 cases included in the interim analysis data
5 cut. Similarly, for the primary analysis, which is
6 specified in the protocol to occur at 151 cases, there
7 were actually 195 cases by the time of the data cuts.

8 These are just two of the key secondary
9 efficacy endpoints included in the study. The first is
10 efficacy against severe disease, using the definition
11 we just looked at a few slides ago, starting 14 days or
12 later after dose 2 in participants without evidence of
13 SARS-CoV-2 infection prior to dose 1. And the second
14 is a less restrictive definition of COVID-19, based on
15 the list of symptoms for COVID-19 by the CDC. And
16 similarly, these are cases confirmed 14 days or later
17 after dose 2, in participants without evidence of SARS-
18 CoV-2 infection prior to dose 1.

19 Cases of severe COVID-19 are reviewed in real
20 time by the DSMB to monitor to possible signal for

1 vaccine-enhanced respiratory disease. And a protocol-
2 specified study stopping rule will be triggered if the
3 one-sided probability of observing the same or more
4 extreme case split was less than or equal to 5 percent,
5 when the true incidence of severe disease was the same
6 for the vaccine and placebo participants. This was not
7 triggered for this study. Okay.

8 Next slide, these are the key analysis
9 populations defined in the study. So the full analysis
10 set are all randomized participants who received at
11 least one dose of vaccine or placebo. Participants are
12 analyzed according to the group to which they were
13 randomized. The modified intent to treat set are all
14 participants in the full analysis set, who had no
15 evidence of prior SARS-CoV-2 infection day one before
16 the first dose.

17 The per protocol set are all participants in
18 the modified intent to treat set, who received the
19 planned doses per schedule and have no major protocol
20 deviations. The safety set are all randomized

1 participants who received at least one dose -- and
2 sorry for the typo here. As opposed to the full
3 analysis set, in the safety set they are analyzed
4 according to the treatment they actually received.

5 So this slide will hopefully make it easier to
6 see the difference in median follow-up duration for the
7 two different analysis that we're going to look at
8 today. So on November 30, Moderna submitted data from
9 their interim analysis to support an EUA, and as you
10 can see in the orange bars, the median follow-up for
11 safety and efficacy in these subjects at the time of
12 the interim analysis was seven weeks after dose 2. To
13 align with the expectation for a minimum of two months
14 of follow up, as outlined in FDA's guidance, Moderna
15 later submitted on December 7 additional data from the
16 scheduled final analysis as an amendment to the EUA.
17 As you can see in the blue bars, the median follow up
18 for safety and efficacy at the time of the final
19 analysis was around nine weeks after dose two.

20 So the majority of the slides that I will

1 present today will show data from the interim analysis
2 unless it's otherwise specified as the final analysis
3 data. However, I just want to note that we have
4 independently verified the vast majority of the
5 analysis from the final analysis, and this includes the
6 primary endpoint, the associated subgroup analyses with
7 the primary endpoint, the key secondary endpoints, and
8 the solicited and unsolicited safety data, including
9 serious adverse events. We have not identified any
10 notable differences in terms of efficacy or safety
11 profile with these additional two weeks of data, so
12 these data did not alter the conclusions that we had
13 already arrived at after thorough review of the interim
14 analysis data.

15 So moving on into the efficacy data, so this
16 table shows the demographic characteristics of the
17 study population, and you can see that it was very
18 similar among the vaccine and placebo participants.
19 The median age was 53 with a range of 18 to 95. Around
20 25 percent of participants were 65 years of age and

1 older. Looking at race and ethnicity, we have 9.7
2 percent of subjects self-identified as African-
3 American, 4.7 percent Asian, 0.8 percent American
4 Indian or Alaska Native, 0.2 percent Native Hawaiian or
5 Pacific Islander, 2.1 percent other, and 20 percent of
6 subjects self-identified as Hispanic or Latino. Around
7 25 percent of the study participants were healthcare
8 workers, and based on protocol defined risk factors for
9 severe COVID-19, around 22 percent of study
10 participants had at least one high-risk condition
11 present.

12 So this is a subject disposition table, and
13 looking at this you can see around 8 percent of
14 subjects were excluded from the per protocol set, which
15 is the set used for the primary efficacy analysis. And
16 the primary reason was the subject being positive or
17 having an unknown baseline SARS-CoV-2 status prior to
18 dose 1. Around 95 percent of the subjects completed
19 two doses in the per protocol set, and discontinuation
20 from the study was rare, with only 0.2 percent from

1 either group.

2 So now here is the primary efficacy endpoint
3 at the scheduled final analysis, so if we can look at
4 the top line, in all subjects there were 11 cases of
5 COVID-19 in the vaccine group compared to 185 in the
6 placebo group, with a vaccine efficacy of 94.1 and a 95
7 percent confidence interval of 89.3 to 96.8. Dividing
8 that up into age subgroups, in the 18 to less than 65
9 years age group the vaccine efficacy point estimate was
10 95.6, so very similar to the efficacy in the overall
11 population. In the 65 years and older age group, the
12 vaccine efficacy point estimate was slightly lower at
13 86.4 percent. However, the number of cases are small,
14 and the confidence intervals overlap with those in the
15 younger age cohort and the overall study population.

16 This is a subgroup analysis of the primary
17 efficacy endpoint broken down into further age
18 categories, stratification categories, and sex. And
19 you can see that vaccine efficacy in each subgroup was
20 comparable to the over study population. And again,

1 going through these next few slides, shown here is the
2 interim analysis, but we have verified the final
3 analysis for these subgroups. And there's no notable
4 difference.

5 This is the subgroup analysis of the primary
6 efficacy endpoint by race and ethnicity. As you can
7 see, efficacy was uniformly high across the groups.
8 However, I do want to point out that for many of the
9 subgroups the sample size and the case numbers are
10 small, and that limits the interpretability of the
11 individual efficacy results.

12 This is a subgroup analysis of the primary
13 efficacy endpoint by the protocol defined risk factor
14 for severe COVID-19 and also includes at the bottom a
15 post-hoc analysis of obesity, defined as BMI greater
16 than 30. Again, as you can see, efficacy across the
17 board is consistent with what was seen at primary
18 endpoint, but for some of these groups, it is, again,
19 limited by the small number of cases in the population.

20 So this is a subgroup analysis of the primary

1 efficacy endpoint by baseline SARS-CoV-2 status, and
2 just as a reminder, that is based on RTPCR and serology
3 against a nucleocapsid protein prior to dose 1. Just
4 over 2 percent of the study subjects were positive at
5 baseline, so you can see that there is just one single
6 case in the seropositive. So there's not really any
7 sufficient data to make any conclusions on vaccine
8 efficacy in participants with a prior history of SARS-
9 CoV-2 infection.

10 This is the secondary efficacy analysis of
11 severe COVID-19 at the scheduled final analysis, so
12 looking at all subjects, there were 30 cases in the
13 placebo group. And nine of these cases resulted in
14 hospitalization, and one resulted in death. In the
15 vaccine group, we do note that there was one severe
16 case in a vaccine recipient which occurred two months
17 after dose 2, requiring hospitalization, but had not
18 been adjudicated by the time of the data cutoff.

19 This is the cumulative incidence curve of
20 COVID-19, starting after randomization in the modified

1 intent to treat set, and the arrow's showing where the
2 vaccine doses were given. And as you can see, the
3 curve starts to diverge a little bit after the two
4 weeks mark, and the divergence becomes more prominent
5 as time goes on and more cases start accumulating in
6 the placebo group.

7 This is a post-hoc analysis of COVID-19 cases
8 from time of randomization in the full analysis set, so
9 that means this includes all participants who have
10 received at least one dose of either placebo or
11 vaccine. And it's regardless of baseline SARS-CoV-2
12 status. So just looking at the second line, efficacy
13 any time after dose 1 to before dose 2 was around 69
14 percent, so this could suggest some protection after
15 the first dose. But data's limited by the very short
16 follow up, so around 28 days, as the majority of the
17 study subjects received a second dose. Okay.

18 Now moving on into the safety data, this again
19 is a graphical depiction of the scheduled safety visits
20 and safety calls throughout the study. Just as a

1 reminder, all solicited adverse events are collected
2 from all study subjects via an e-diary for seven days
3 after each dose. Unsolicited adverse events are
4 collected for 28 days after each dose, and serious
5 adverse events and medically attended adverse events
6 are captured throughout the entire study.

7 This is a subject disposition table, and you
8 can see a vast majority of subjects completed two doses
9 and very small percentage discontinued the study. And
10 it was similar between the vaccine and placebo groups.
11 Okay. The next few tables are going to show the
12 solicited local and systemic reactions, but, again,
13 before we dive into it, I just want to reiterate that
14 although the data shown are from the interim analysis
15 data, we have verified the data from the final
16 analysis. And there was no notable difference compared
17 to the interim analysis data shown here.

18 So looking at the solicited local reactions
19 after dose 1, you can see the most commonly reported
20 local reaction was pain. Grade 3 events were rare

1 after the first dose, and something that you see
2 through the next few tables is that there is a lower
3 rate of solicited reactions in the elderly cohort
4 compared to the younger cohort. This is looking at
5 solicited local reactions after dose 2. It is slightly
6 higher compared to after dose 1. Grade 3 events are
7 still pretty low.

8 Now switching to systemic reaction after dose
9 1, similar to the local reaction, there's a lower rate
10 in the elderly compared to the younger adults. And
11 after dose 1, grade 3 or 4 events were rare. And
12 finally looking at solicited systemic reactions after
13 dose 2, you can see there is a higher rate after dose 2
14 compared to dose 1, including a higher rate of grade 3
15 events. So for example, fatigue, myalgia is around 10
16 percent grade 3. Overall, based on review of these
17 last four slides, there were no serious safety concerns
18 based on the data. Okay.

19 Shown here is an overview of solicited safety
20 by baseline SARS-CoV-2 status. The rates of solicited

1 adverse reactions were comparable or sometimes slightly
2 lower in participants with baseline positive SARS-CoV-2
3 status. But again, this group is much smaller in size
4 compared to participants with negative SARS-CoV-2
5 status at baseline.

6 This table shows unsolicited adverse events
7 rates overall and then further broken down into which
8 of those are related, which are considered serious, and
9 medically related adverse events and then also broken
10 down by baseline serostatus. So again, the rates of
11 these events are comparable or a little bit lower in
12 those who are baseline SARS-CoV-2 positive compared to
13 those who are negative at baseline, but, again, that
14 subgroup population is small. Unsolicited adverse
15 events in general was comparable between the vaccine
16 group and the placebo group.

17 So FDA conducted standard MedDRA queries,
18 SMQs, using FDA developed software to evaluate for
19 constellations of unsolicited adverse events with onset
20 following dose 1 through the data cutoff. The SMQs

1 were conducted on adverse events preferred terms that
2 could represent various conditions, including, but not
3 limited to, allergic, neurologic, inflammatory, and
4 autoimmune disorders. Here, we just highlight the
5 unsolicited adverse events which had a higher frequency
6 in the vaccine group versus placebo.

7 So starting with hypersensitivity related
8 events, there was 1.5 percent in the vaccine group
9 versus 1.1 percent in the placebo group. And the most
10 frequently reported AEs in the hypersensitivity SMQs
11 were injection site rash, injection site urticaria, and
12 maculopapular rash. This we thought had a possible
13 relationship to the vaccination. And then also of
14 note, no anaphylactic or severe hypersensitivity
15 reactions with close temporal relation to the vaccine
16 were noted.

17 Lymphadenopathy-related events -- that's
18 outside of the solicited period -- was noted in 1.1
19 percent of vaccine recipients and 0.6 percent of
20 placebo recipients. The most frequently reported

1 lymphadenopathy SMQs were injection site
2 lymphadenopathy, lymph node pain, and lymphadenitis.
3 Again, we thought this had a plausible relationship to
4 vaccination. We also noted delayed localized injection
5 site reactions with onset after seven days, seen mostly
6 after dose 1. And this was noted in 1.4 percent in the
7 vaccine group versus 0.4 percent in the placebo group.

8 There was a numerical imbalance in Bell's
9 palsy cases with three cases in the vaccine group and
10 one case in the placebo group. The case in the placebo
11 group occurred 17 days after dose 1. The three cases
12 in the vaccine group occurred 22, 28, and 32 days after
13 dose 2. The observed rate was consistent with the
14 background rate in the general population. And there's
15 no clear basis upon which to conclude a causal
16 relationship at this time.

17 Moving on to serious adverse events and
18 deaths, as of December 3, there were 13 total deaths
19 reported in the study, with six in the vaccine group
20 and seven in the placebo group. None of these deaths

1 were assessed as related. Really quickly, in the
2 vaccine group the first three participants listed all
3 had underlying cardiac disease. The first subject died
4 of cardiac arrest 21 days after dose 1. The 77-year-
5 old participant died of myocardial infarction 45 days
6 after dose 2. The 70-year-old subject was found
7 deceased at home 57 days after dose 2.

8 The next participant was a 56-year-old subject
9 with hypertension and chronic back pain being treated
10 with opiate pain medication who was found deceased at
11 home 37 days after dose 1, and the official cause of
12 death was head trauma. Then, we have a 72-year-old
13 participant with Crohn's disease and short bowel who
14 was hospitalized 40 days post-dose 2 due to
15 thrombocytopenia and acute kidney failure and then
16 later developed complications during the hospital stay,
17 including a perforated ulcer that resulted in multi-
18 organ failure and death 59 days after dose 2. And
19 last, we have a 62-year-old participant who died of
20 suicide 21 days after dose 1.

1 There were three SAEs thought related by the
2 FDA. One is a 65-year-old participant with a history
3 of severe headache and nausea requiring hospitalization
4 who developed intractable nausea/vomiting requiring
5 hospitalization one day post dose 2. And there were
6 two subjects who reported facial swelling one day and
7 two days post dose 2. Both of these subjects had a
8 prior history of dermal filler cosmetic injections in
9 the cheeks. For one subject, it was about two weeks
10 before vaccination, and for the other subject, it was
11 about six months before vaccination.

12 Also related, but there was one subject who
13 had lip angioedema about two days after vaccination,
14 and that subject also had prior dermal filler injection
15 in the lip. Interestingly, that subject reported a
16 similar reaction after a previous influenza vaccine. I
17 do want to point out that for these three subjects that
18 I just mentioned -- so the two with the facial swelling
19 and the one with the lip swelling -- the swelling was
20 only localized. There were no systemic symptoms

1 observed.

2 Women were screened for pregnancy prior to
3 each vaccination, and a positive test resulted in
4 exclusion or discontinuation from vaccination. As of
5 December 2, there were 13 pregnancy in the study, six
6 in the vaccine group and seven in the placebo group.
7 Vaccination occurred prior to last menstrual period in
8 two vaccine recipients and three placebo recipients.
9 Vaccination occurred within 30 days after LMP in two
10 vaccine recipients and three placebo recipients, and
11 vaccination occurred greater than 30 days after LMP in
12 one vaccine recipient and one placebo recipient. The
13 LMP is not known in one vaccine recipient. In terms of
14 outcomes, there's one case of spontaneous abortion and
15 one elective abortion in the placebo group. Otherwise,
16 all the other pregnancies are ongoing, and the outcomes
17 are not known at this time.

18 So in summary, for the efficacy, the totality
19 of the clinical data submitted with the EUA request
20 meets the expectations for duration of follow up. In

1 the scheduled final analysis, vaccine efficacy 14 days
2 or later post dose 2 was 94.1 percent with a confidence
3 interval of 89.3 to 96.8 in participants without prior
4 evidence of SARS-CoV-2 infection. Efficacy outcomes
5 were consistent, greater than 93 percent, across
6 demographic subgroups. In the scheduled final
7 analysis, there were 30 severe cases of COVID-19 in the
8 placebo group and one still unadjudicated case in the
9 vaccine group. The data suggest the potential efficacy
10 following a single dose, but interpretation is limited
11 because almost all participants received a second dose.

12 As far as for safety, the totality of the
13 clinical data submitted with the EUA request meets the
14 expectations for duration of follow up in greater than
15 30,000 participants. Reactogenicity was generally more
16 frequent after dose 2 in all age groups, mostly mild to
17 moderate and less frequent and severe in adults 65
18 years of age or older. There were no safety concerns
19 identified in subgroup analyses by age, sex, race,
20 ethnicity, health risk for severe COVID-19 or prior

1 SARS-CoV-2 infection.

2 Lymphadenopathy reported as solicited and
3 unsolicited adverse events were more frequent in the
4 vaccine group compared to placebo. A delayed localized
5 injection site reaction with onset after seven days was
6 more frequent in the vaccine group compared to the
7 placebo and mostly seen after dose 1. Hypersensitivity
8 related events were more frequent in the vaccine group
9 compared with placebo, but no anaphylactic or severe
10 hypersensitivity reactions with temporal relation to
11 vaccination was noted. As of the scheduled final
12 analysis, three cases of Bell's palsy were reported in
13 vaccine recipients and one in placebo recipients.
14 Although there's no clear basis upon which to conclude
15 a causal relationship at this time, FDA recommends
16 further surveillance if vaccine is authorized for
17 widespread use.

18 Moving on to the pharmacovigilance plan,
19 Moderna submitted a pharmacovigilance plan to monitor
20 safety concerns that could be associated with the

1 Moderna COVID-19 vaccine. The sponsor identified
2 vaccine associated enhanced disease, including vaccine
3 associated enhanced respiratory disease and
4 anaphylactic reactions, including anaphylaxis, as the
5 important potential risks. Use in pregnant and
6 breastfeeding women, use in pediatric population, long-
7 term safety and long-term effectiveness, immunogenicity
8 in subjects with immunosuppression, and concomitant
9 administration with non-COVID vaccines are areas the
10 sponsor identified as missing information.

11 Pharmacovigilance activities, including
12 adverse events reporting -- adverse events reporting
13 under EUA, may come from vaccine recipients,
14 vaccination providers, or the sponsor. First, the
15 vaccine recipients will be notified that an adverse
16 event can be reported to VAERS in the fact sheets for
17 recipients and caregivers. Another source of adverse
18 event reports from recipients is the V-Safe program,
19 which is a smartphone-based program that uses text
20 messaging from web surveys from the CDC to check in

1 with vaccine recipients for health problems after
2 vaccination.

3 Reports from vaccine recipients are voluntary.
4 Adverse events reported by vaccine providers and the
5 sponsor is mandatory. Both the sponsor and vaccine
6 providers administering the Moderna COVID-19 vaccine
7 must report to VAERS the following information
8 associated with the vaccine: vaccine administration
9 errors, whether or not associated with an adverse
10 event; serious adverse events irrespective of
11 attribution to vaccination; cases of multisystem
12 inflammatory syndrome in adults; cases of COVID-19 that
13 result in hospitalization or death.

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

1 special populations -- such as pregnant women -- and
2 adverse events of special interest, newly identified
3 safety concerns in this interval and actions taken
4 since the last report because of adverse experiences.
5 Both FDA and CDC will take a collaborative and
6 complementary approach to reviewing adverse events.

7 FDA will individually review all serious
8 adverse events on a daily basis. FDA will also examine
9 other sources for adverse events, such as the
10 literature, and will perform datamining to determine if
11 adverse events are disproportionately reporting for the
12 candidate vaccine compared to all other vaccines in
13 VAERS. Any potential safety signals identified will be
14 investigated.

15 The sponsor provided a description of studies
16 they are currently planning on conducting. The studies
17 will include completion of long-term follow up from
18 ongoing clinical trials, as well as the following two
19 planned safety surveillance studies. The pregnancy
20 cohort, the sponsor plans to establish a passive

1 pregnancy registry to monitor vaccination during
2 pregnancy with populations expected to receive the
3 vaccine under an EUA and to submit a protocol for FDA
4 review and approval. Active follow up for safety, this
5 study is an active safety surveillance activity
6 conducting retrospective analyses of medical and
7 pharmacy claims data to address three objectives:
8 estimation of background rates of 23 pre-specified
9 adverse events of special interest, descriptive
10 analyses of observed versus expected rates, and self-
11 controlled risk interval analyses that will be
12 conducted if certain criteria are met from the
13 descriptive analyses. FDA will provide feedback on
14 these studies after further review of protocols once
15 submitted by the sponsor.

16 Proposed revisions to the ongoing phase 3
17 study if an EUA is issued is still in discussion. We
18 have not yet received a revised protocol for review.
19 In general, Moderna's proposing that there will be no
20 changes for participants who choose to remain blinded,

1 but for participants who chose to be unblinded, they
2 will proactively re consent and offer vaccine for those
3 in the placebo group. Regardless of whether the
4 participant remains blinded or unblinded or which
5 treatment they receive, all participants will continue
6 to be followed for two years.

7 Finally, we will now go into the benefit-risk
8 assessment. So the known benefits of the vaccine:
9 reduced risk of confirmed COVID-19 at least 14 days
10 after completing a two-dose vaccination regime in
11 individuals without prior history of SARS-CoV-2
12 infection; reduced risk of confirmed severe COVID-19 at
13 least 14 days after completing a two-dose vaccination
14 regimen in individuals without prior history of SARS-
15 CoV-2 infection. And in the subgroups, efficacy
16 findings are consistent across subgroups by age, race,
17 ethnicity, and comorbidities.

18 The known risks, so local and systemic adverse
19 reactions are reported at a higher rate after a second
20 dose and a higher rate in younger adults compared to

1 older participants. There were three SAEs we thought
2 related to vaccination, and they were all temporarily
3 associated and biologically plausible. And this
4 includes the one subject with a history of severe
5 nausea that had the intractable nausea and vomiting and
6 then the two cases of facial swelling in subjects that
7 had a prior dermal filler injection.

8 Serious hypersensitivity reactions have not
9 been reported in this study but have been reported in
10 clinical experience with Pfizer mRNA vaccine. No
11 specific safety concerns were identified in analyses of
12 subgroups, including prior SARS-CoV-2 infection. The
13 limitations of our risk assessment include the short
14 follow up duration and the fact that pregnant women
15 were excluded.

16 Here, just to remind everyone the question
17 that we would like the Committee to discuss, in
18 considering Moderna's plans for unblinding and
19 crossover of placebo recipients, please discuss the
20 most critical data to further inform vaccine safety and

1 effectiveness to support licensure that should be
2 accrued in ongoing clinical trials with Moderna COVID-
3 19 vaccine, other studies, such as additional clinical
4 trials or observational studies with the Moderna COVID-
5 19 vaccine. And here is the question for vote. Based
6 on the totality of scientific evidence available, do
7 the benefits of the Moderna COVID-19 vaccine outweigh
8 its risks for use in individuals 18 years of age and
9 older? And this is the end of my presentation. I
10 welcome any questions.

11

12

COMMITTEE DISCUSSION AND VOTING

13

14 **DR. MONTTO:** Thank you, Dr. Zhang, for not only
15 being succinct and comprehensive but also keeping us to
16 time. What I propose is that first we entertain
17 questions for Dr. Zhang on her presentation and then go
18 into a broader questioning of both Dr. Zhang and the
19 sponsor about issues related specifically to the
20 vaccines and the vaccine trials as has been reported.

1 We should reserve the discussion about the unblinding
2 issues to the later comprehensive discussion that the
3 Committee has, which will go on for a couple of hours,
4 including the voting discussion.

5 So first, let's ask questions if you have them
6 for Dr. Zhang, and then we can have broader discussion.
7 And I've alerted the sponsor to be ready for these
8 questions. And when we get into the Committee
9 discussion about unblinding, we really need to focus on
10 that issue. We got a hybrid discussion last week for
11 those who were on with the Committee, and I think we
12 want to avoid that and focus on the FDA discussion
13 points. So Dr. Offit, please.

14 **DR. OFFIT:** Thank you, Dr. Zhang, for a clear
15 presentation. I just want to follow up on something
16 that both Dr. Cohn and Dr. Gans brought up earlier,
17 which is just briefly this issue of Bell's palsy. And
18 I understand that we're looking through -- there's the
19 tyranny of small numbers derived from the large
20 database, and you can't determine causality from such

1 small numbers. And I'm really glad that you're doing
2 follow up, but I don't quite see how we're comfortable
3 that what we're calling -- what we're seeing with both
4 the Pfizer trial and Moderna trial are background
5 rates.

6 If you look at the Pfizer trial, it was four
7 cases of Bell's palsy in a group of 22,000 vaccinees
8 per three months, which works out to about eight cases
9 per 10,000 per year. If you look at the Moderna trial,
10 it's three cases per 15,000 per few months, which also
11 works out to about eight cases per 10,000 per year. If
12 you look at the one placebo case and if you add the two
13 placebo groups -- it's roughly 37,000 over a few months
14 -- that works out to about 1.2 cases per 10,000 per
15 year, which at least what I had read was roughly the
16 background rate.

17 That in combination with the fact that SARS-
18 CoV-2 has been reported to be a cause of Bell's palsy
19 in a handful of people and presenting actually -- the
20 first presentation being Bell's palsy and then found to

1 have SARS-CoV-2 offers at least some biological
2 plausibility. And in fact, it may be true that SARS-
3 CoV-2 is a more common cause of Bell's palsy than this
4 vaccination, and we'll find this all out in follow up.
5 But I'm just not quite sure how we are so comfortable
6 that this was a background rate. I guess that's my
7 question. Thank you.

8 **DR. ZHANG:** Sorry, I just had to find the
9 unmute button. Yes, this is something we're also
10 looking into and thinking a lot about. Just based on
11 each of these individual studies, we're looking at the
12 cases -- there is still no clear basis upon which to
13 conclude a causal relationship, but we definitely see
14 your point with the two studies combined -- the
15 numbers. And it's something that we are looking into
16 and thinking much about.

17 **DR. OFFIT:** Thank you.

18 **DR. MONTO:** All right. Thank you. Dr.
19 Wharton, please.

20 **DR. WHARTON:** Thanks. I'm interested in these

1 three cases of facial swelling associated with the
2 prior injection of the dermal fillers. How long did
3 those swelling reactions take, and should this product
4 be authorized, will this information be included in the
5 information for healthcare providers?

6 **DR. ZHANG:** Okay. I can just give you a
7 little bit more information on those cases. Again, all
8 three of those cases that I mentioned were just
9 localized, like swelling in the cheeks or swelling in
10 the lips, and they resolve with either antihistamines
11 or a steroid course. And again, no systemic reactions
12 were noted, and it was really interesting that one
13 participant who reported a similar reaction after
14 previous vaccine.

15 And we did a literature search, and it seems
16 that this is something that has been reported -- that
17 with these dermal filler injections there could be some
18 interaction with the immune response after a natural
19 infection, such as, like, an influenza-like illness,
20 with these dermal fillers that create this temporary

1 swelling that usually resolves pretty quickly with
2 steroids or by itself. So we are planning to note this
3 in the prescribing information.

4 **DR. MONTO:** Thank you. Dr. Gans?

5 **DR. GANS:** Thank you. Thank you for that. I
6 just had one question about a clarification. You had
7 noted some of the regulatory events that will happen in
8 terms of adverse events, and you listed it only under
9 EUA, which obviously is what we're considering now.
10 And I just wanted to clarify that those functions will
11 continue as we move out of an EUA into maybe a BLA or
12 other forms in which we should still be looking at
13 adverse events as this vaccine is rolled out. So I
14 just wanted to make sure that it wasn't so specific to
15 just under an EUA.

16 **DR. ZHANG:** Yes, so if you remember that
17 really busy slide with a lot of boxes and arrows -- so
18 the surveillance and follow up for an EUA is not any
19 less demanding or more demanding than a regular BLA, so
20 all of those will continue.

1 **DR. GANS:** Thank you.

2 **DR. MONTTO:** Dr. Sawyer?

3 **DR. SAWYER:** Thank you. My question relates
4 to the anaphylaxis story, and you described an
5 imbalance in hypersensitivity reactions between the
6 vaccine and placebo groups but that there was no cases
7 of anaphylaxis. I wonder if you can characterize for
8 us what those hypersensitivity events are because I
9 wonder if some of the media reports are reflecting
10 hypersensitivity reactions that aren't truly
11 anaphylaxis, things like simple hives -- at least until
12 those cases get fully adjudicated.

13 **DR. ZHANG:** Sure. Thank you for that
14 question. So like I mentioned, when we searched by the
15 SMQs, the most common preferred terms event that we
16 found under the hypersensitivity related events were
17 injection site urticaria, injection site rash or rash
18 in general or hives or itching. So nothing that really
19 are close even to anaphylaxis.

20 **DR. SAWYER:** Thank you.

1 **DR. MONTO:** Dr. Neaton?

2 **DR. NEATON:** Thank you. Thanks for the
3 presentation. I wondered a couple things on the
4 safety. I noticed for the safety kind of cohort that
5 was looked at there was an excess of withdraws of
6 consents in the placebo group. Did you notice that,
7 and was there anything -- reasons for those withdraws
8 that could make you question the blinding or whether
9 due to adverse events? There was quite an excess.

10 **DR. ZHANG:** Yeah. It was a little bit
11 imbalanced in terms of withdraw by subject, but it
12 wasn't due to adverse events or physician decision due
13 to any medical conditions or anything. Overall, the
14 numbers are still very small. There's a difference of
15 maybe, like, 60 subjects between the vaccine and
16 placebo group, so looking at the overall safety set, it
17 doesn't really make any impact.

18 **DR. NEATON:** More the difference I was
19 thinking about -- it's like three or four standard
20 error difference, which seems potentially not due to

1 chance. Okay. My other question was is in the FDA
2 book you provided more information about the duration
3 of some of the solicited symptoms, and I noticed that,
4 for example, a lot of the symptoms -- if you just take
5 myalgia as an example, there's a pretty striking
6 difference if you look at solicited symptoms, but the
7 difference is very, very small with unsolicited
8 symptoms. And is that, do you think, primarily
9 attributable to the timing of when those measurements
10 were made?

11 **DR. ZHANG:** Yes, correct. The solicited
12 symptoms were collected within the first seven days
13 after vaccination. That's when we expect most of these
14 symptoms like myalgia, fatigue, and things like that to
15 occur.

16 **DR. NEATON:** Is there any medication provided
17 to patients or recommendations for medications to
18 prevent kind of some of the symptoms that were
19 recorded?

20 **DR. ZHANG:** I don't have that data offhand,

1 but there is -- a use of antipruritics was also
2 collected in the e-diary.

3 **DR. NEATON:** Thank you. That's all for now.

4 **DR. MONTO:** Thank you. Dr. Kurilla.

5 **DR. KURILLA:** Thank you. Yes, this is about
6 the potential for correlates of protection out of this
7 trial. There was no immunogenicity data that was
8 presented as part of the phase 3. But looking at the
9 phase 1 immunogenicity, particularly in the elderly
10 population in the two-and-a-half-month period, there
11 was rather substantial drop-offs in both the total
12 ELISA as well as the neutralization titers that were
13 measured. And I'm wondering, from your presentation,
14 it looks like there was a blood draw at day 57 but not
15 another one until 209, and I'm wondering if there's
16 just an adequate measurement of immunogenicity in that
17 phase 3 to try to derive potential correlates of
18 protection.

19 **DR. ZHANG:** Maybe I'll ask Moderna to address
20 how they're planning to assess correlate of protection

1 in their studies.

2 **DR. MILLER:** Sure. Happy to do so. So the
3 correlate of protection, as you noted, are the
4 immunogenicity assays that were not yet available at
5 the time of submission of the EUA. We're anticipating
6 that the immunogenicity analyses should be available in
7 the coming months. And so trial actually routinely got
8 blood samples at various time points, so pre-dose 1;
9 pre-dose 2; at day 57, which is one-month post-dose 2;
10 and then at three, months, six months, and 12 months
11 afterwards. And the idea would be that we would first
12 present the immunogenicity analyses, and then once we
13 have sufficient break through cases to be able to
14 perform the zero correlate analysis, that will be done
15 as well. We're actually working in collaboration with
16 the NIH, so Dr. Follmann and Dr. Peter Gilbert, to pull
17 together this analysis. And it actually will be done
18 with NIH assays in order to be able to look at
19 consistency across other products.

20 **DR. MONTTO:** Dr. Fuller?

1 **DR. FULLER:** Yes, thank you. So Dr. Zhang,
2 there's some side effects which are expected with most
3 vaccines, and they're just part of what happens.
4 Especially in this time when COVID is such a major
5 issue, what is FDA or CDC or Moderna -- perhaps Moderna
6 has a plan for informing people of what to expect. In
7 other words, we can handle things if we know that this
8 is part of what's expected and it's only going to be a
9 few days and we have somewhere to report it to if we
10 think otherwise. So I don't remember the plan for how
11 people will be informed of what the side effects may be
12 as they go to take this vaccine. Can you help remind
13 me, please?

14 **DR. ZHANG:** Well, I do know that the side
15 effects are going to be described in detail in the fact
16 sheets for providers, as well as for the recipients.
17 I'll open up for other people to chime in the other
18 things.

19 **DR. FULLER:** So I guess I'm asking if there's
20 going to be some sort of campaign to make sure that

1 people -- you know, we all get fact sheets with our
2 medicines or our vaccines or whatever, and we read them
3 sometimes. And sometimes we don't. And you could say
4 that's on the person who's taking it, but for something
5 like this it would be really helpful and build trust if
6 there's a major effort to say "This is what you should
7 expect. These have been seen often, and these have not
8 been seen." That would, I think, give people a lot
9 more confidence.

10 **DR. FINK:** Hi. So as you've heard, we have an
11 intensive safety surveillance system stood up for
12 distribution of vaccine under EUA. We'll be monitoring
13 the system closely. If we detect any signals, we will
14 investigate those rapidly. And if we conclude that
15 there is a need to inform vaccine providers or
16 recipients or the general public about a risk that has
17 not been previously appreciated, we will do so in
18 revisions to labelling or sooner through safety alerts
19 if we determine that that's warranted.

20 **DR. MONTTO:** Thank you. Dr. Hildreth? Dr.

1 Hildreth?

2 **DR. HILDRETH:** Did you call my name? I'm
3 sorry.

4 **DR. MONTO:** I did. You had your hand raised.

5 **DR. HILDRETH:** Yes, sir. I did. My question
6 relates to the fact that for every diagnosed case of
7 COVID-19 there are probable several others that go
8 undiagnosed. And I'm wondering if by giving the
9 persons who've already been infected a single injection
10 of the vaccine could that serve as a boost and achieve
11 the same goal as giving two injections of the vaccine?
12 In other words, infection serves as the prime and one
13 vaccination will serve as the boost. Is that something
14 that Moderna or FDA has considered as a possibility,
15 just out of curiosity?

16 **DR. ZHANG:** I'll defer this to Moderna. This
17 was not in the scope of the data or the study design.

18 **DR. HILDRETH:** Okay.

19 **DR. MILLER:** So just to make sure, Dr.
20 Hildreth, I understood your question, are you asking

1 about the interchangeability of our vaccine with the
2 other mRNA vaccine -- whether you could get a mixed
3 schedule of both?

4 **DR. HILDRETH:** No, I'm referring to the fact
5 that we now know that there are probably tens of
6 millions of Americans who've already been infected by
7 the SARS-CoV-2, and we know they can get reinfected.
8 We also know that all of them make an antibody response
9 through the virus, but it appears not to be protective
10 against -- they can get reinfected. What I'm asking
11 is, if you took the ones who've already been infected
12 and gave them an injection of your vaccine, could that
13 possibly serve as a boost whereas the infection itself
14 served as the prime?

15 **DR. MILLER:** Okay. Thank you for that
16 clarification. So I think it's something that we may
17 be able to tease out a bit in our booster study. I
18 mean, again, we had only 2.2 percent of the study
19 population that indicated that they were previously
20 SARS-CoV-2 positive.

1 **DR. HILDRETH:** Okay.

2 **DR. MILLER:** We are intending to evaluate
3 booster doses, and as we review the immunogenesis, that
4 is certainly something we can look at. And once the
5 immunogenicity data are available, we'll be able to see
6 what the initial vaccination looked like in the mRNA
7 1273 group. So we don't have data unfortunately to
8 share with you today, but we are anticipating those
9 data in the coming weeks and months.

10 **DR. HILDRETH:** Thank you.

11 **DR. MONTO:** Thank you. And Dr. Miller, don't
12 go away because we're expanding the discussion right
13 now. Dr. Meissner has been waiting to ask some
14 questions of you.

15 **DR. MEISSNER:** Thank you. One question I'd
16 like to ask is about the forest plots that are on
17 Figure 7 and 8, and I realize you probably don't have
18 this right in front of you. But my question is there
19 were approximately 9,000 white subjects in the placebo
20 arm and 5,000 from communities of color. But the rates

1 of infection were 16 per 1,000 versus eight per 1,000
2 in the communities of color, that is they were lower.
3 And usually, we think of COVID-19 causing more disease
4 in the community of color. Is there a ready
5 explanation for that? Perhaps it's the small numbers.
6 Do you think that was truly representative of minority
7 groups?

8 **DR. MILLER:** So thank you for that question.
9 I'm attempting to pull up that forest plot slide now so
10 that -- just to reorient everyone to the discussion
11 we're having. So to your question about the small
12 numbers, it is true that enrollment of minorities in
13 the trial was a priority for us. We received lots of
14 help and advice from our collaborators and from thought
15 leaders in those communities.

16 Nonetheless, the study was not designed to
17 look at individual efficacy estimates in various
18 demographic groups. And so indeed, the numbers in each
19 specific group are quite small. The study was actually
20 powered only for the symptomatic COVID-19 disease.

1 Hopefully, we'll have some refinement of those numbers.
2 Regardless of what happens with the evolution of the
3 clinical trial, we will continue to follow the
4 participants who have been vaccinated with vaccine,
5 placebo, or have been crossed over for COVID-19 disease
6 using the same methods that we've used. I and think
7 that the trial has assessed the cases of COVID-19 that
8 occur (audio skipped) our overall attack rate was 56
9 approximately per 1,000 person years, which is close to
10 reported rates in the literature. So hopefully we'll
11 be able to further add to those numbers and get some
12 more refinement on them.

13 **DR. MEISSNER:** Thank you. I'd like to ask
14 secondly a question in regard to sterilizing immunity.
15 I think your preliminary figures are very promising --
16 that the vaccine may reduce infectious virus and the
17 risk of transmission of fully replication competent
18 virus. Has there been any effort to look at antibodies
19 in respiratory secretions from the upper respiratory
20 tract or the lower respiratory tract because I -- if

1 this is in fact true, I guess it means the
2 intramuscular injection stimulated sufficient
3 circulating IgG so that it gravitated out into the
4 mucus membranes of the respiratory tract? Is that
5 reasonable?

6 **DR. MILLER:** So I think you're correct that
7 it's certainly reasonable to expect that IgG is playing
8 an important role in what we're seeing from an efficacy
9 perspective. I don't have data on the IgA, but what we
10 will have to hopefully be able to help us better
11 understand viral shedding and burden of infection are
12 the viral shedding samples that were taken from cases
13 confirmed by RTPCR to be SARS-CoV-2. So those subjects
14 submitted a sample every few days over the month of
15 their convalescence. And ultimately, we'll take those
16 results and compare in the breakthrough case -- the
17 placebo cases what viral shedding --

18 **DR. MONTTO:** All right. And Dr. Meissner,
19 that's something you may want to bring up in our
20 discussion about other studies the sponsor might be

1 asked to do. Dr. Pergam?

2 **DR. PERGAM:** Thanks for a great presentation,
3 guys. My question is specifically around additional
4 data transparency. A lot of what you're talking about
5 here is things that are coming down the line, and I'm
6 just trying to figure out additional shedding data,
7 additional follow ups that you're talking about.
8 Moderna has been really transparent with data so far.
9 I'm curious about what the FDA's approach is going to
10 be in presenting this additional data to the public and
11 to other community members as this moves forward.

12 **DR. MILLER:** Apologies, Dr. Pergam. I think
13 that was a question for Dr. Zhang, but I just want to
14 be sure I understood that correctly.

15 **DR. MONTO:** Dr. Fink?

16 **DR. FINK:** Yes, so we will continue to update
17 the prescribing information and fact sheets as
18 appropriate as we get new information. And if we
19 determine that information is necessary to inform
20 vaccine providers and recipients about the benefits and

1 risks of the vaccine, of course we will include as part
2 of our review process for any licensure application a
3 transparent review of the data to support that
4 application as well.

5 **DR. MONTO:** Thank you. Dr. Perlman?

6 **DR. PERLMAN:** Yes, so I just had a question
7 about the vaccine adverse events, the respiratory
8 disease and the general systemic problems that occur
9 after vaccination. It's mentioned in the protocol, but
10 there aren't really very many details of what's going
11 to actually be looked at. And the fact it's so
12 efficacious may make this -- makes it less of an issue,
13 but still what's the exact plan for measuring adverse
14 events after vaccination -- the respiratory disease and
15 the other (audio fade out)?

16 **DR. MILLER:** Sure. I can take that one and
17 speak to the various ways in which we're measuring
18 safety in the protocol. So after vaccination, subjects
19 had an electronic diary on which they recorded
20 solicited local symptoms, so the injection site

1 reactions and then solicited systemic symptoms, like
2 fatigue, headache, myalgia. After seven days, the e-
3 diary, as well as safety phone calls from the site,
4 prompted subjects to respond back about unsolicited
5 adverse events. So these were any adverse events that
6 may have happened to them, and we followed those 28
7 days after each vaccination.

8 Then, for some specific categories of adverse
9 events, including medically attended AEs, as well as
10 serious adverse events, we are going to continue with
11 the safety phone calls throughout the duration of study
12 for the subjects and capture that information. And so
13 that's really the framework in which the respiratory
14 illnesses you're speaking about will be captured. Then
15 as part of the efficacy surveillance, there's also the
16 surveillance for COVID-19 disease, and for those
17 subjects who are not COVID-19 positive or SARS-CoV-2
18 virus positive, we'll also be looking at a respiratory
19 panel of viruses to try to understand that respiratory
20 disease. And again, some of these endpoints are not

1 yet available to be reported out, but we intended to
2 continue that surveillance throughout the study.

3 **DR. PERLMAN:** Yes. I guess I really meant
4 vaccine enhanced --

5 **DR. MONTO:** Okay. Thank you. We're going to
6 have two more questions, and then we're going to be
7 shifting and going to a discussion among the Committee
8 of FDA questions. So Dr. Chatterjee next.

9 **DR. CHATTERJEE:** Yes, thank you, Dr. Monto. I
10 have two questions, Dr. Miller. The first one is with
11 regard to the nanoparticles. I think we heard today
12 about the rate of decay of the mRNA and the protein
13 that it codes for, but what about the nanoparticles?
14 How long do they hang around?

15 **DR. MILLER:** Yes. So the nanoparticles have
16 been evaluated in biodistribution studies, and they
17 hang around for approximately 48 hours.

18 **DR. CHATTERJEE:** I see. And then the follow
19 up question to that is, is there a theoretical
20 possibility that the body will mount an immune response

1 to the nanoparticles, the lipid itself? And if that
2 happens, would it then preclude the use of these
3 nanoparticles for any future vaccines that are
4 developed in the same manner?

5 **DR. MILLER:** So to answer that question, I'm
6 going to ask our chief medical officer Dr. Zaks to take
7 that one.

8 **DR. ZAKS:** Thank you, Dr. Miller. Not as far
9 as we know. So let me make a few comments here. The
10 particles -- traces are gone by 48 hours, just to be
11 clear. They hang around for just a few hours. The
12 components of those particles, as far as we know, are
13 non-immunogenic in the sense that, as I described to
14 you, you've got the PEG with a lipid. Most of us are
15 walking around with antibodies against PEG, but they're
16 not really meaningful in the sense of preventing
17 further utility of drugs.

18 And in fact, lipid nanoparticles, both by us
19 and other companies, are being used for routine
20 administration of other drugs and other experimental

1 medicine so far without any evidence of that kind of
2 reactogenicity. So I don't think we have any basis to
3 expect that, neither based on our totality of
4 preclinical data from our experience nor based on the
5 history with these kinds of LNP medicines used in other
6 applications. And those applications are even using
7 much, much larger amounts and quantities, so in short,
8 I don't believe that's the case.

9 **DR. CHATTERJEE:** Thank you.

10 **DR. MONTO:** And finally, Dr. Kim.

11 **DR. KIM:** So this is a question for Dr.
12 Miller. I'd like to ask how you, Moderna, came about
13 selecting 100 micrograms as the vaccine dose for phase
14 3. In your briefing material for phase 1, you outlined
15 your considerations for comparing 100 micrograms to 25
16 and 250 micrograms, and in Study 201 you concluded that
17 the data support of a two-dose schedule of either 50
18 micrograms or 100 micrograms for rapid induction of
19 functional antibodies against SARS-CoV-2 and then
20 selected the 100 microgram dose for phase 3.

1 What other considerations did you weigh in
2 selecting 100 microgram over 50 microgram? And I ask
3 this question because reports of any local reaction to
4 the 100 microgram vaccine were around 70 to 80 percent
5 in phase 3 and wonder what the safety profile might
6 have looked like otherwise.

7 **DR. MILLER:** Yes. Thanks for that question,
8 and I would like to emphasis that at the time the phase
9 1 study was ongoing. And when we had to select the
10 dose to be able to start phase 3, the 50-microgram data
11 were not yet available in the phase 1 study.
12 Nonetheless, I mean, it's hard to look backward and say
13 what you would have done, but I'm not sure we would
14 have taken a different decision. At the moment, we're
15 quite comfortable with the consistence and high
16 efficacy that we've observed. But at that point in
17 time, all we knew was that we were in the midst of the
18 pandemic and we wanted to be sure that if we were going
19 to undertake this large-scale safety and efficacy trial
20 and we were going to expose people to a novel vaccine

1 that we had the best possible chance of demonstrating
2 efficacy.

3 Another important point, as the 50-microgram
4 data became available later and particularly in the
5 subjects over 71 years of age, there was an indication
6 that the 100-microgram dose was more immunogenic. And
7 so knowing that the older age group is a group that is
8 at significant risk for severe complications of COVID-
9 19, that was another reason really to choose the dose.
10 And then the final reason is duration of efficacy is
11 going to be important as we hopefully ultimately exit
12 this pandemic, and we believe that the highest possible
13 antibodies might lead to the longest possible duration
14 of protection.

15 So for all of those reasons, the 100-microgram
16 dose was selected. Nonetheless, again, recognizing
17 that we are in a pandemic and now that we have data
18 from the phase 2 available in 50 microgram doses,
19 that's why we put such emphasis on that correlative
20 protection work we're doing in the phase 3 study to see

1 if there may be possibilities for immuno-bridging based
2 on that correlate in the future.

3 **DR. MONTA:** Thank you and thank you to Moderna
4 and FDA for your presentations. Now, we're going to be
5 moving on to the item for Committee discussion without
6 a vote, and is it possible to put up the questions?
7 I'll read them off while I've got them in front of me.
8 In considering Moderna's plans for unblinding and
9 crossover of placebo recipients, please discuss the
10 most critical data to further inform vaccine safety and
11 effectiveness to support licensure that should be
12 accrued in -- and let's do this one at a time --
13 ongoing clinical trials -- so it's ongoing clinical
14 trials -- with the Moderna COVID-19 vaccine. And then
15 we'll talk afterwards about additional studies. So
16 this is the ongoing studies. Let's see. Dr. Gans?

17 **DR. GANS:** Thank you for this. So ongoing
18 critical data, we still have multiple time points at
19 which the Moderna is going to be collecting blood, and
20 I think it's a really missed opportunity, particularly

1 if they are actually collaborating with the NIH who
2 have quite sophisticated ability to look at T-cell
3 immunity, which we know is very important to maintain
4 our humoral immunity and will be very, very important.
5 So there's two elements to this moving forward which I
6 think are very critical: A, to get them any time points
7 at which you're collecting other blood samples -- so it
8 was mentioned six months and further -- but
9 specifically when there's breakthrough. It's going to
10 be very important to be able to do the parallel T-cell
11 studies to our B cells because if the B cells aren't
12 present, it's going to be very important to understand
13 what T-cell immunity was there that could be
14 potentially boosted. So in both of those scenarios,
15 that's critical data in which to move forward and be
16 able to understand this better.

17 The other critical piece of ongoing
18 information that I think is going to be very important
19 is to look at this idea of whether people who are
20 vaccinated can continue to be spreaders of the disease.

1 And so looking in household contacts to see if there's
2 any disease in those individuals who are not
3 prioritized to receive vaccine is going to be very
4 important, so following those forward. And then
5 lastly, doing the viral studies that are needed to be
6 done within the vaccinated population, so continue to
7 do those surveillance of the PCRS for RNA.

8 But it will be really important not only to
9 look for the positive trends but the negative trends so
10 we can understand that this is viable virus. So
11 outside of the populations that they've already talked
12 about in terms of ongoing, these are the critical
13 things that I think are important. Thank you.

14 **DR. MONTO:** Thank you. Dr. Rubin?

15 **DR. RUBIN:** Thank you. I echo what Dr. Gans
16 said and a couple more things. Antibody studies and T
17 cell studies so we can look at correlates of immunity
18 because that will be very, very helpful in the further
19 development of the vaccine and for following waning
20 immunity. So I think that those immunologic studies

1 continue to be important. And of course, monitoring
2 asymptomatic infection, as Dr. Gans said, is critical,
3 and, as has already been brought up -- and it sounds
4 like it's already a plan -- looking at escape mutants
5 for loss of neutralization by the antibody or loss of T
6 cell reactivity.

7 I do want to go back, though, to Dr. Goodman's
8 talk because that is all part of this. And the current
9 -- it seems to me, at least, that the trial should have
10 been designed as a blinded crossover study from the
11 start. And my guess is that it's relatively
12 impractical at this point to do it, disappointingly,
13 because it's so late in the game, but I would encourage
14 FDA -- I know it's not quite a level playing field.
15 But as new sponsors come in, I would encourage FDA to
16 really consider that going forward. For now, I think
17 they're going to stuck with an open label study of the
18 kind that Dr. Baden outlined. I'll stop there.

19 **DR. MONTO:** Thank you for bringing us back to
20 the nub of the question. Dr. Wharton?

1 **DR. WHARTON:** So I am particularly interested
2 in continued safety follow up as well as follow up on
3 the duration of protection. I think those are really
4 critical factors that need to be taken into account as
5 the study continues.

6 **DR. MONTTO:** Any suggestions?

7 **DR. WHARTON:** Well, there will be
8 opportunities to learn more based on other studies
9 being done, but in terms of the ongoing clinical
10 trials, it's just important that the safety follow up
11 be continued and that there be attention to the
12 duration protection question.

13 **DR. MONTTO:** Okay. Dr. Neaton?

14 **DR. NEATON:** Okay. Yeah. Thank you. So I
15 want to go back to the presentation that Dr. Goodman
16 gave this morning and also Dr. Baden. And I guess it's
17 all in reference to -- speaking to one factor, and
18 that's the durability of this vaccine. So it seems no
19 matter whether you're going to do a blinded crossover,
20 as was suggested by Dr. Goodman, or you're going to do

1 an open label kind of approach that Dr. Baden thought
2 was appropriate given the situation -- and practically,
3 that's what could be done right now -- there's an
4 opportunity to at least do immediate versus deferred
5 kind of vaccination of the vaccine subgroups which were
6 identified as at different risk, so the healthcare
7 workers, the high-risk older people.

8 And so I would take advantage of that because
9 right now there's only 17 percent of the participants
10 that have 90 days of follow up, and I think additional
11 follow up -- which I guess is accruing right now
12 another couple of weeks -- I think we need more follow
13 up with this vaccine versus placebo to understand more
14 the kind of durability of protection. That's what I
15 would suggest doing.

16 **DR. MONTO:** Thank you. Dr. Schooley?

17 **DR. SCHOOLEY:** Thanks very much, Dr. Monto. I
18 also want to emphasize that I think this planned
19 crossover study is a great opportunity to get some of
20 the data about durability of immunity in a very

1 structured way, and I'd encourage these sponsors to
2 consider carefully constructed cohorts representative
3 of the populations that are of most interest, ranging
4 from age to gender, ethnicity and so forth, that would
5 let us look at decay of both humoral and cellular
6 immunity. The crossover would be a chance to reset the
7 clock and get cellular immunity from the outset and to
8 incorporate mathematical models to look at decay
9 kinetics based on the induced immunity in individual
10 people and decay across different groups based on their
11 demographics and hypotheses about immunogenicity in
12 different patient populations -- and to correlate that
13 with viral shedding that is in break through cases, not
14 just dichotomous data but quantitative data to get a
15 good idea -- a better idea about durability of immunity
16 and to start thinking about how this might play into
17 studies later about when to boost and when to
18 revaccinate because we know about the durability of
19 coronavirus immunity in general. And there's no reason
20 for this virus to be any different.

1 **DR. MONTO:** Dr. Chatterjee?

2 **DR. CHATTERJEE:** Yes, thank you, Dr. Monto.

3 With regard to the ongoing clinical trials, my
4 understanding is that there are pediatric trials
5 ongoing, so this is not in reference to the trials that
6 we were discussing today but certainly would encourage
7 those trials to continue and for us to be brought those
8 data. As far as pregnant women, my understanding,
9 again, is that according to the criteria for inclusion,
10 efforts were made to not include women of childbearing
11 potential, but I think it's critical given the
12 workforce and the role that those women have in our
13 workforce and the high risk that they incur caring for
14 patients with COVID that the studies be also conducted
15 in that population.

16 **DR. MONTO:** Dr. Sawyer?

17 **DR. SAWYER:** Thank you. I think in the
18 ongoing trials we have an opportunity to learn more
19 about asymptomatic infection in that a significant
20 percentage of the study participants are healthcare

1 workers, and many healthcare systems are starting now
2 to do routine testing of all healthcare workers. In my
3 system, it's every week. And I would encourage the
4 sponsor to try to collect that data and make some
5 comparisons between vaccine and placebo group.

6 **DR. MONTA:** Dr. Pergam?

7 **DR. PERGAM:** Thanks, Arnold. So I think two
8 things that make sense to me is when they're -- and I
9 really hope that if there is this crossover design that
10 they continue to do additional viral testing within
11 those individuals because that's a critical piece to
12 know about potential transmission in that sub-cohort
13 and particularly to look at viral load. I know that's
14 sort of a -- it sometimes can be a difficult process
15 with nasal samples. But when we're thinking about
16 transmissibility and the levels of virus that are
17 there, that might be one of the potential advantages of
18 the vaccine.

19 I'm also curious within this study if Moderna
20 could speak to us about some point about how many of

1 the 25 percent that are in the study that are
2 healthcare workers have already opted out because they
3 know they might be eligible to get the Pfizer vaccine.
4 That would be an interesting piece of data. It might
5 be too early to know that. That would be an
6 interesting piece of data for us to know sort of what
7 expectations might look like for other groups who may
8 be deciding to go and get the actual available vaccine.

9 **DR. MONTO:** What I'm hearing from our members
10 is two streams of discussion: additional studies that
11 can be done whatever the specific design, unblinding
12 with open label crossover design, and additional
13 studies that might be done. I'm not sure how to bring
14 the two together. What I think we might want to do in
15 our discussions is to focus on what happens with the
16 issue that I think is troubling to some of us, and that
17 is the inevitable loss of the placebo group which
18 occurs whatever you do, whether it's unblinding and
19 open label or a crossover design without unblinding.

20 Can we focus on that with some of our

1 questions? Then, we'll get back to some of the
2 additional immunologic shedding, viral shedding. This
3 is a very difficult thing for us to do in a virtual
4 setting. If we were around the table talking to each
5 other, we could address these issues much more
6 efficiently. But let's try to talk about the placebo
7 group first. And Dr. Gans, are you going to be talking
8 about the placebo group?

9 **DR. GANS:** Yes. Thank you. I did want to
10 just raise an important component that I think may the
11 twist hasn't quite been raised yet. We're all
12 concerned about losing that placebo group and really
13 the integrity of the data moving forward, but I think
14 we do realize that that is something that is going to
15 be offered to individuals who got the placebo. So the
16 only way that I see that we can really hold on to the
17 integrity and continue learning something is to
18 continue the blinding of the study.

19 So it doesn't impact -- everyone gets what
20 they want. It doesn't impact the participants.

1 They're all going to be vaccinated, and within six
2 weeks everyone will actually know that they've fully
3 been vaccinated. We need two doses, and we know that
4 that's what you need to be sufficiently immune -- you
5 know, for this to be efficacious.

6 So everyone gets what they want. You can use
7 the vaccine that actually now is coming to expiration,
8 but you do it in a blinded manner. And in that way,
9 you uphold the integrity and the ability to really look
10 forward. It's going to change everyone's behavior
11 otherwise, and that will actually impact the results.
12 So that is what I would plead to Moderna and to say
13 that it seems that everyone gets actually what they
14 want at that point. Thank you.

15 **DR. MONTO:** Thank you, Dr. Gans. Mr. Toubman?

16 **MR. TOUBMAN:** Can you hear me?

17 **DR. MONTO:** We can, yes.

18 **MR. TOUBMAN:** I'm thinking in a broader view
19 of this that the study was funded in part by the
20 taxpayers through Operation Warp Speed, and therefore

1 the government does have some ability to impose some
2 rules. And it seems to me there's an assumption that
3 they're just going to -- Moderna's going to do what
4 it's going to do, and it's going to unblind the entire
5 placebo group. And it doesn't have to be that way. We
6 haven't been asked to vote on it, but we could vote on
7 it as well. But we could say that we don't think it's
8 acceptable for the Moderna plan to go forward if it's
9 granted EUA.

10 And as just an example, it could be either you
11 do exactly what Pfizer is doing, and Pfizer ignored the
12 advice from Dr. Goodman, basically, last time -- do the
13 blinded crossover. So they're not doing that.
14 Instead, they just unblinded the -- offered unblinding
15 to all the healthcare workers, and the other 80 percent
16 stay in the placebo. That's one option.

17 Another option would be the blinded crossover.
18 But if we aren't very clear that we think strongly that
19 that's what should happen, one or both of those -- or
20 one or the other, then what's going to happen is that

1 Moderna's just going to do what it's going to do, as
2 happened with Pfizer. So I would strongly urge that we
3 discuss the possibility of having a vote or directing
4 what we think -- we're only advisory. I totally
5 understand that.

6 But if the Committee felt strongly that this
7 is the way it should be handled in the existing study
8 because of the worry about losing placebo folks, I
9 think that would have significant impact with FDA, and
10 FDA -- federal government dollars here -- could say
11 these are the conditions upon the EUA being granted is
12 we want the study to be maintained in a certain way.

13 **DR. MONTA:** You've raised some specific
14 questions. I would urge the members to try to address
15 some of these questions so we get a sense of the
16 Committee. Dr. Meissner?

17 **DR. MEISSNER:** Mr. Toubman, I think that's a
18 very reasonable suggestion. Take a vote. Maybe give
19 some support to Moderna. I would also like to go back
20 to the point that Dr. Melinda Wharton raised and the

1 importance of having a blinded cohort in this study
2 because eventually this will go for a BLA. And it will
3 then be added to the vaccine injury compensation table,
4 and it's going to be so difficult to add this to the
5 table without some evidence of well-established adverse
6 reactions if they occur. And without a blinded trial,
7 it's going to be -- or a blinded group, it's going to
8 be very difficult to answer that question.

9 So what I would like to do is to ask Moderna
10 if they have a sense of how soon they might submit a
11 BLA to the FDA. Because once that happens, it'll be
12 the end of any randomized trial. And how quickly might
13 the FDA turn around a BLA that they receive from either
14 of these two companies?

15 **DR. MONTA:** Thank you, Dr. Meissner. You've
16 raised some points that we may need some guidance from
17 FDA and perhaps from Moderna as well. Dr. Gruber?

18 **DR. GRUBER:** Hi. Can you hear me? I'm sorry.

19 **DR. MONTA:** We can.

20 **DR. GRUBER:** Good. I just wanted to make a

1 comment regarding Dr. Toubman's suggestion to turn this
2 discussion point into a voting question. I believe --
3 I mean, we had discussed that -- if we should do this,
4 but we decided because of the complexity of the
5 situation -- and as you said, we have not only one. We
6 have the two companies -- to not turn this into a vote
7 at this time. We didn't really ask this discussion
8 point to be a voting question a week ago.

9 But I think what we would like to hear from
10 the Committee -- and I have heard some Committee
11 members here opining very clearly that some said we
12 support the open label design or crossover that Moderna
13 is suggesting. And others are pleading with really
14 entertaining a blinded crossover. So if we hear the
15 Committee members to speak out on these very specific
16 issues, what they would suggest and what they think
17 should be done, then I think we have reasonable
18 guidance on the Committee on how to proceed in our
19 discussions with the respective companies over the next
20 couple of weeks.

1 In terms of BLA, biologics license
2 application, and how fast we could move to that and
3 what data we need, I mean, we all realize that the
4 placebo-controlled blinded follow up is the gold
5 standard of every clinical study that is conducted. At
6 the same time, we do realize that it may at a certain
7 point not be longer feasible. I think we would be, you
8 know, working with the companies over the next couple
9 of months to see what data do we need to support
10 license application and what can be done.

11 And it is not only our -- and then I'll stop.
12 It's not only the clinical data. It's also the
13 manufacturing information, the facilities information
14 that will be very critical here and will be a deciding
15 factor as to when we would be able to move to accepting
16 the biologics license application. Over.

17 **DR. MONTO:** Thank you, Dr. Gruber. And I
18 would urge the Committee members in their comments that
19 are coming up when I recognize them to speak to some of
20 these points. We're trying to get a sense of the

1 Committee without a vote about some of these issues:
2 unblinding, blinded crossover, or continuing whatever
3 we can with a blinded placebo-controlled design. Dr.
4 Fuller?

5 **DR. FULLER:** Thank you, Dr. Monto. So yes,
6 that's exactly what I wanted to comment on. It is a
7 research (inaudible) when you want to get the best data
8 you can, you must have the controls there. But in this
9 case, these are people who may decide that they don't
10 want to stay in the study because it is such a severe
11 issue. And so even if we kept the study as a blinded
12 study and they're not there, then we wouldn't have the
13 data that we want.

14 So I think Moderna has done a great job of
15 designing their study so far. And if that's what they
16 recommend and because we want the people who are in the
17 study to remain available and acceptable to get
18 whatever data we can, I would probably go with the
19 unblinding to keep them in the study to get what we
20 can. And then the second point I want to make is --

1 **DR. MONTO:** And so when would you unblind?
2 Dr. Fuller, when would you unblind, before or after
3 they become eligible based on the priorities?

4 **DR. FULLER:** I think I would unblind when the
5 study has gotten from them what they need in terms of
6 the timing. So if I were in the study and they told me
7 "You are eligible in three weeks, but if you stay in,
8 in five weeks or six weeks we will be able to get this
9 much information. And we can make sure that you get
10 this vaccine" -- so I guess it's communication to me.
11 And then, very quickly I do want to re-emphasis -- this
12 was said earlier -- the important of having pregnant
13 and lactating women studies here because that's a huge
14 piece of our population. So however we do it to make
15 sure those people are kept in. Thank you.

16 **DR. MONTO:** Dr. Kurilla?

17 **DR. KURILLA:** Thank you. Gee. My -- oh,
18 there we go. It's actually working now.

19 **DR. MONTO:** It is.

20 **DR. KURILLA:** Yes. In terms of what we can

1 get out of the ongoing studies, I think we need to take
2 transmission off the table. That needs to be a
3 separate study. The two issues, I think, that we can
4 derive information about are the potential of
5 asymptomatic infections because if we actually are
6 inducing sterilizing immunity, that's good. But if all
7 we're doing is converting mild infection to
8 asymptomatic, that's good, but it's not as good because
9 there may be still ongoing transmission.

10 But the other more important thing to me is
11 duration. That's the one issue that I'm most concerned
12 about with very, very limited data. The blinded
13 crossover would allow us to continue to collect
14 duration data, which I think is very important. But
15 it's not going to permit asymptomatic infection data to
16 be accumulated, so we would lose that. And so I would
17 -- if there's going to be a, quote, pseudo-unblinding,
18 the blinded crossover, I think, would be the way to go.

19 **DR. MONTO:** Thank you. Next is Dr. Moore.

20 **DR. MOORE:** There's one question I have -- or

1 it's not a question. It's a comment, and I don't
2 really have an answer for it. But with two large
3 vaccine trials that are now currently blinded and
4 they're ongoing, the vaccines are shortly going to be
5 released publicly in some way, or at least Pfizer has
6 been released. That suggests that there's going to be
7 some people that are blinded in, for example, the
8 Moderna study who are in the study because they're
9 personally, tremendously afraid of getting COVID. And
10 they may move over to get vaccinated. And if they've
11 already been vaccinated, then we have a risk of over-
12 vaccination and also adverse events occurring that we
13 don't recognize are actually due to the fact that
14 people are not being vaccinated according to the
15 protocols that we have. I don't have an answer -- I
16 don't have an answer to whether it's better to unblind
17 or blind to address that question.

18 But the other point is, is that I do disagree
19 with Dr. Kurilla. I do think that transmission is
20 perhaps the most central thing that we need to address

1 as of right now in this epidemic and to try and get our
2 best handle on that probably is not the nasal or the
3 nucleocapsid antibody but rather direct detection of
4 nucleic acid. So that's one reason why I'm pushing for
5 repeated NP swabs.

6 More importantly than that, perhaps, is, even
7 if we don't have an answer as to whether these vaccines
8 do limit transmission, is that I would hope that both
9 Moderna and Pfizer would work with public health
10 officials to try and establish (audio skip) with their
11 well-defined cohorts. For example, are there protocols
12 for (inaudible) vaccination that we could use that will
13 work or have the best chance of working? Because
14 ultimately we anticipate that by next summer we will
15 have a low rate of transmission, and then we will be
16 putting out fires. And we need to know how to put out
17 those fires with these vaccines if they do interrupt
18 transmission.

19 **DR. MONTTO:** Okay. Dr. --

20 **DR. KURILLA:** Arnold, can I just respond real

1 quickly to Patrick's comment? I didn't mean --

2 **DR. MONTO:** Okay. Very quick.

3 **DR. KURILLA:** -- that transmission isn't
4 important. I simply meant that I don't think you can
5 get it out of this trial design.

6 **DR. MONTO:** I understand. Having done a lot
7 of observational studies on transmission, I tend to
8 agree with you. It's a very difficult thing to study
9 unless you're studying that -- that subject. Dr. Cohn?

10 **DR. COHN:** I just wanted to add to Dr. Fuller
11 and other's comments that I agree that Moderna's plan
12 sounds reasonable, especially given the logistical
13 challenges that a study sponsor would potentially face
14 in terms of when a particular individual in the study
15 becomes eligible. I think given the variability that
16 will happen at the state and local level in those
17 criteria it would be hard for them to implement that
18 across the board. And I also believe that given the
19 large number of observational studies that are being
20 implemented in combination with multiple different

1 groups that some of these questions, while it's not
2 perfect to -- while a clinical trial blinded would be
3 ideal, I think that if you can look at some of these
4 questions from a multitude of other observational
5 studies, we will be able to understand -- we'll be able
6 to answer some of these questions through a similar
7 degree of confidence.

8 **DR. MONTO:** Dr. Offit.

9 **DR. OFFIT:** Right. Just to get to Dr.
10 Kurilla's point, there is an ongoing trial that is
11 being planned for early next year on college campuses
12 where people will be vaccinated or not. And then those
13 that are vaccinated will be followed to see to what
14 extent they're contagious by doing extensive contact
15 tracing, which is really the best way to do it, as Dr.
16 Monto alluded to, and then look at these sort of -- you
17 know, the nasopharyngeal secretions to see if you can
18 eventually have a biomarker for what that
19 contagiousness is. But that is being planned and
20 apparently is being funded, so good news.

1 **DR. MONTO:** Dr. Moore. Again, let's try to
2 get a sense of the Committee about the
3 unblinding/crossover issues.

4 **DR. MOORE:** I didn't hang up my -- I didn't
5 have a question. Sorry.

6 **DR. MONTO:** Oh, you didn't? You're still
7 there? Okay. Dr. Pergam.

8 **DR. PERGAM:** Yeah. So I think I really like
9 Dr. Cohn's comment. I definitely like the idea of
10 continuing the blinding portion in the crossover design
11 because of the advantages it gives you in terms of
12 following placebo individuals, but I think the
13 realistic piece of this and the challenges that will
14 entail for the differential groups in terms of when
15 they will get access to vaccine will make this really
16 difficult to do. And I worry in terms of different
17 states and their approaches to this that that will be
18 difficult.

19 So I'm sort of -- I was leaning towards the
20 side of we would be doing blinded because that would

1 provide some real advantages. But I think in some ways
2 the realistic aspect of this really makes this -- going
3 to be difficult, so it may be impossible to approach
4 that side. So I think in an ideal world I think we
5 would like to keep a blinded -- the blinded portion of
6 the crossover design, but I think the reality of what's
7 happening may make that two difficult to do.

8 **DR. MONTTO:** Thank you. Dr. McInnes.

9 **DR. McINNES:** Thank you. I'm in favor of the
10 blinded crossover approach. I think it's powerful, and
11 I think we may have a little bit more time than we
12 actually think. I could imagine it's an area where you
13 could articulate the priorities, and it could be even
14 on a state level. I don't think there's going to be
15 this much vaccine floating around for a few weeks. So
16 even though people may want to walk and get in the
17 queue to get an EUA, I'm just not sure what the supply
18 is going to look like. And you may have a little bit
19 more time than we think.

20 So I think in principle I like the blinded

1 crossover. I think it's powerful, maybe the best we
2 can get in terms of being able to continue to assess
3 safety. I think the crossover could be tailored to a
4 particular geographic area. I'm not saying it's easy
5 to do, but I would entertain it.

6 And my third point is we've been talking about
7 pregnancy registries, and I just want to iterate that
8 what I think we're talking about is pregnancy exposure.
9 We're not actually proposing a pregnancy registry but
10 for exposure of FDA regulated products. So those are
11 my three points. Thank you.

12 **DR. MONTO:** Thank you. Dr. Toubman [sic] has
13 a suggestion for us.

14 **MR. TOUBMAN:** Thank you. Right. So I do have
15 a suggestion for framework of discussing this, but I
16 think we addressed the ethical issue. There's really
17 no ethical issue with not -- with having to unblind
18 these folks. They don't have to be.

19 So the issue is really, I think, boiling down
20 to what's practical, what's workable. And I guess when

1 people say it's not feasible to maintain those who are
2 not in priority groups in the blinded study, you're
3 saying that what Pfizer's doing is completely
4 impractical because that's what they're doing. What
5 they've told all their folks, at least in my state -- I
6 assume it's the same letter everybody got -- is that
7 "The vaccine transition option is a voluntary process.
8 It offers all participants 16 and older in the placebo
9 group an option to transition to the vaccine group.
10 Interested participants can transition at two time
11 points. To determine the order in which participants
12 can begin the vaccine transition option, Pfizer and
13 BioNTech are following the guidance of the U.S. Center
14 for Disease Control Advisory Committee for Immunization
15 Practices, ACIP, which has prioritized healthcare
16 workers for direct patient contact."

17 Now, there's also commentary that we got. You
18 know, there's 148 of current trial participants who
19 specifically recommend -- they're fine with saying
20 that, as a vaccine developer achieves EUA, it should be

1 permitted and, indeed, encouraged to unblind members of
2 the placebo arm who would naturally qualify for
3 vaccination under their state vaccine distribution
4 plan. Dr. Cohn pointed out there's variance, and I
5 understand that. But all we need is a few more weeks.
6 If we just can get a few more weeks of data by
7 maintaining placebo control for those who are not in
8 the priority groups -- and that will be in this case
9 for Moderna 25 percent will go out as healthcare
10 workers -- then we gain a lot. So it is feasible, or
11 if you're saying it's infeasible, you're saying that
12 what Pfizer's doing is not feasible.

13 And I think a last point here -- and Dr.
14 Goodman explained this -- there's a real reason to have
15 uniformity here between the different sponsors. And
16 since Pfizer's doing this, there's no reason -- there's
17 no ethical problem with having Moderna follow the exact
18 same practice -- protocol. So my suggestion would be
19 that we recommend that Moderna do what Pfizer's doing
20 because it is feasible for a period of time, just a few

1 weeks, which would be really helpful. And then the
2 secondary thing would be support for the blinded
3 crossover.

4 **DR. MONTTO:** Okay. I've been asked by
5 Committee members if we are going to have a vote on
6 this. My sense, Marion, from what you've told us is
7 that you would rather we did not and just give you the
8 sense of the Committee. Am I correct?

9 **DR. GRUBER:** Yeah. You're correct, and I
10 really thank the Committee for being very clear here
11 over the last couple of minutes to really speak out on
12 their preference. It is complicated, and I was trying
13 to sort of keep a tally a little bit here on what I was
14 hearing.

15 **DR. MONTTO:** So was I and having great
16 difficulty because there were nuances.

17 **DR. GRUBER:** That's right. You know, I --
18 again, I feel that -- I'm speaking here for the Office
19 of Vaccines, but at the same time, I have not had a
20 chance to confirm it with my colleagues. So if you

1 could give -- if you could continue the discussion for
2 a bit longer because I don't think that all the
3 Committee members really opined here, and I would like
4 to take a minute to get some responses because I asked
5 the question of my Committee members -- of my people
6 here to weigh in with their opinions on this as well.
7 So if you could spend maybe a couple of more minutes
8 discussing this very important question.

9 **DR. MONTO:** Right, Marion. We'll talk among
10 ourselves about this, but I just want you to think
11 about, if we do have a voting question, what that would
12 be because I'm not clear. This is not a black and
13 white issue.

14 **DR. GRUBER:** Yeah. I know. I know.

15 **DR. MONTO:** And I'm not clear what the vote
16 would be about, so please, if this is going to be a
17 voting question, let's have a clear question because
18 I'm not sure -- we don't want a lot of abstentions and
19 things like that. We'd defeat the purpose.

20 **DR. GRUBER:** This is why we tried to --

1 **DR. MONTO:** Right. I understand. That's why
2 you didn't want to vote in the first place.

3 **DR. GRUBER:** Yes.

4 **DR. MONTO:** Because it's so difficult. Could
5 I ask all the hands to be lowered, and those people who
6 have not spoken on this question -- because that's what
7 we're hearing -- please try to tell us what they would
8 think about it? I see Dr. Hildreth.

9 **DR. HILDRETH:** Dr. Monto, are you inviting me
10 to comment?

11 **DR. MONTO:** Yes, please, Dr. Hildreth. If
12 you've got a comment and an opinion, we're looking for
13 opinions. Opinions are usually pretty cheap, so let's
14 get them from everybody.

15 **DR. HILDRETH:** Sure. I want to express my
16 strong support for the plan that was outlined by Dr.
17 Baden to have an open label crossover. We can still
18 get a lot of information about safety. As a matter of
19 fact, I totally agree with him that the participants
20 who got the placebo should not be disadvantaged

1 because, after all, we are still under a national
2 health crisis. And the whole point of this was to get
3 a vaccine that could be used to slow down COVID-19. So
4 I have strong opinion that it might even be unethical
5 for us not to offer the vaccine to the placebo
6 recipients, and I agree with him that if we would do
7 that --

8 **DR. MONTO:** This would be -- right. This
9 would be right now or when their priority group comes
10 up if that's feasible?

11 **DR. HILDRETH:** For me, it would be okay either
12 way. When their group comes up, they should be given
13 the opportunity to get the vaccine. I just really feel
14 strongly if we don't do that we're going to lose the
15 placebo participants and maybe do harm for future
16 recruitment of vaccine trials. So I just think that I
17 agree with his plan for an open label crossover, and
18 that's what I would recommend to the FDA. Thank you.

19 **DR. MONTO:** Dr. Sawyer?

20 **DR. SAWYER:** So the point was brought up

1 earlier that people -- the blind is already going to be
2 severely eroded by the local and systemic side effects
3 of the vaccine. And I think now that that information
4 is being widely publicized in the media people are
5 really going to figure out whether they got vaccine or
6 placebo. If you got two injections and each time your
7 arm hurt and you got malaise the next day, you're going
8 to figure out that you got the vaccine. So I think
9 behaviors are going to be modified based on that, and
10 so I'm -- my opinion is the blind is already eroded to
11 the point where it probably won't matter. So I'm going
12 to support the crossover approach, and I prefer the
13 crossover approach to allow people to be vaccinated
14 when their tier comes --

15 **DR. MONTO:** That's blinded. The crossover is
16 blinded.

17 **DR. SAWYER:** No, I'm supporting nonblinded
18 crossover.

19 **DR. MONTO:** You're supporting an open label,
20 then.

1 **DR. SAWYER:** Open label crossover but when the
2 people come up in their tier.

3 **DR. MONTO:** Okay. Dr. Wharton?

4 **DR. WHARTON:** So since I didn't really
5 specifically address this point when I spoke earlier, I
6 wanted to say that although the blinded crossover seems
7 really powerful and has a lot of -- and seems very
8 valuable, right now healthcare workers being vaccinated
9 in many different parts of the country, and to ask the
10 24 percent of healthcare workers in the placebo group
11 to go unvaccinated while a blinded crossover change in
12 the protocol was implemented really doesn't seem
13 feasible to me. And it is preferable that people be
14 kept in this study, and that can best be done by
15 offering vaccination in the appropriate tiers as they
16 come up. And additional data can be collected on those
17 vaccinated persons as the study continues. So that
18 would be my suggestion.

19 **DR. MONTO:** Thank you. Dr. Rubin?

20 **DR. RUBIN:** I'm going to echo Dr. Wharton, but

1 I wanted to go a little bit farther saying that the
2 open label study is -- seems like the only choice. But
3 it's not a terribly good choice, so I think we should -
4 - it's better to keep them in a study. But for future
5 sponsors and for future trials, you can derive a lot
6 more information out of the crossover design
7 particularly around AEs. That's what I think we'd
8 learn a lot more about, so I would favor that in the
9 future. But I'm supportive of an open label trial now.

10 **DR. MONTO:** I agree. And the problem is we're
11 dealing with an unprecedented situation, and there are
12 a few things that people didn't think about going in.
13 Dr. Sylvester?

14 **DR. SYLVESTER:** Yes, thank you, Dr. Monto. I
15 agree with what Dr. Rubin just said. I think that it's
16 not a perfect world. The open label makes sense at
17 this point and time, and maybe in the future we ought
18 to be thinking about the crossover that's blinded. I'm
19 worried also that with a greater than 90 percent
20 vaccine efficacy will people enroll in future vaccine

1 trials knowing that they're not going to be able to get
2 it? So I think the inevitability towards the crossover
3 makes sense, and let's work on this one at this point.
4 So I'm in favor of open.

5 **DR. MONTO:** Dr. Meissner?

6 **DR. MEISSNER:** Thank you.

7 **DR. MONTO:** Any further comments? I know what
8 you said before.

9 **DR. MEISSNER:** Yeah. And after listening to
10 this fascinating discussion, it's very hard to reach a
11 conclusion. I will just say that this will be -- if we
12 don't do the blinded crossover, this will be the last
13 opportunity because once a vaccine is licensed, no more
14 placebo-controlled trials. So we will be throwing out
15 that opportunity. Now --

16 **DR. MONTO:** If I could interrupt, I think
17 that's one of the reasons we have question or
18 discussion item number 2. What in the world do we do
19 to collect in the future placebo-controlled data?

20 **DR. MEISSNER:** Yes. At least in the United

1 States, that will be very --

2 **DR. MONTA:** Well, that brings up another
3 question.

4 **DR. MEISSNER:** Yes. And also, it's going to -
5 - what is this going to mean for the other vaccines
6 when they start their -- or are already in their phase
7 3 trials? Will they follow the same regimen that
8 Moderna and Pfizer follow and there won't be the option
9 of a blinded crossover because why would a subject
10 participate in that trial if she or he could get an
11 authorized vaccine? And I think that what Dr. Sawyer
12 said is also true. And remember, anyone who wants can
13 go out and get an antibody test and find out whether
14 they got the vaccine or the placebo, so it's not --

15 **DR. MONTA:** That too.

16 **DR. MEISSNER:** It's not that secret. And I
17 think Dr. Cohn's comment about practicality is very
18 important. So I would still prefer a blinded
19 randomized crossover, but it's also going to be very,
20 very hard to do that. Over.

1 **DR. MONTO:** Thank you. Dr. Perlman?

2 **DR. PERLMAN:** Yeah. So the only thing I would
3 -- I would agree with all the panel's discussion. I
4 just wanted to give my opinion. I like the blinded
5 crossover, but it sounds like it's not going to be
6 feasible because of this ability for people to just
7 walk into the vaccine limb, particularly people who are
8 in healthcare settings now. So if it could be
9 instituted immediately, that would be one thing, but it
10 doesn't sound like that's really going to happen.
11 That's, I think, what Dr. Baden was saying this morning
12 -- that it was logistically going to be very difficult
13 to do that. So that's why the Moderna approach may be
14 the best.

15 **DR. MONTO:** Dr. Kim?

16 **DR. KIM:** I don't have any specific reason to
17 add to all the discussion that's taken place already,
18 but I just want to go on record in saying that I would
19 support the open label.

20 **DR. MONTO:** When? Right away after the EUA

1 or after the individual's priority group comes up?

2 That's what Pfizer is doing. Okay. Let's move on to

3 Jim Neaton. Dr. Neaton?

4 **DR. NEATON:** Yeah. I prefer the priority
5 based unblinding. I mean, this morning it was pointed
6 out that there's nothing in the consent about -- that
7 you get the vaccine, once the study's over with, if
8 you're in the placebo group and it's effective. But I
9 think all consents have a requirement to explain the
10 data to the people, from the trial that you're in, and
11 its implications for them. That and the press that
12 this trial, and the Pfizer trial, and the AstraZeneca
13 trial have already received I think makes it very
14 difficult, plus the local circumstances of healthcare
15 workers being vaccinated.

16 So I think try to maintain the blind between
17 the vaccine and placebo as long as possible. Try to
18 keep the people in the cohort because you want to
19 follow everybody for another two years. But in order
20 to do that, the practicalities, I think, are such to do

1 it in some type of a stage by priority kind of setting
2 if people can structure it that way.

3 **DR. MONTO:** Dr. Schooley?

4 **DR. SCHOOLEY:** You know, as much as we'd like
5 -- as I'd like to see things remain blinded as a
6 scientist, I think from the factual perspective and
7 from the perspective of the realities of vaccine
8 availability and logistics, we need to realize that the
9 trial participants are going to want to know what they
10 were in. They're going to walk if they don't know, and
11 I think it's really important to keep them in the
12 trial. So I would support an unblinded crossover.

13 I think we have to also -- I think it's going
14 to be complicated trying to understand when the vaccine
15 is really going to be available in each location with
16 the way our country works, and it will take some time
17 to get the logistics of even the unblinded crossover
18 set up in a synchronous way starting today. So I would
19 favor going ahead and beginning to make those changes
20 in the bureaucracy and then being ready to do it when

1 it's in place in a synchronous way as best we can with
2 the bureaucracy we have to deal with.

3 **DR. MONTO:** Dr. Cohn and then the final word
4 from Dr. Toubman [sic] before we look very briefly at
5 the second point.

6 **DR. COHN:** Just to clarify what I said
7 earlier, I think you can very easily separate out the
8 healthcare workers from the other groups, but there's
9 not going to be some sort of "This person is going to
10 be eligible now." Health departments will be opening
11 up vaccination for different groups more organically,
12 so I think if you could vaccinate the healthcare
13 workers now, like Mr. Toubman said, and keep the blind
14 for a majority of participants for several more weeks -
15 - I think if a participant believes they're in a group
16 that is now being recommended for vaccination, the
17 sponsor should not be policing that, similarly to how I
18 don't think health departments will necessarily be
19 policing that. So that just clarifies my previous
20 comment.

1 **DR. MONTO:** Dr. Lee?

2 **DR. LEE:** So I would agree with the open
3 label. Although normally I would suggest the
4 prioritization, I would agree with Dr. Schooley that
5 it's such a hodgepodge here it's impractical. And the
6 other consideration I think we need to keep in mind in
7 starting this as soon as possible is they do have this
8 drug supply that apparently they have available that
9 they could use for this purpose, which has something of
10 an expiration date. But I favor the open label
11 crossover. Thank you.

12 **DR. MONTO:** And quickly Dr. Chatterjee.

13 **DR. CHATTERJEE:** Yeah. My comment, Dr. Monto,
14 was actually about the other studies. It's not about
15 this first --

16 **DR. MONTO:** Okay. Why don't you wait for a
17 minute while I recognize Dr. Toubman [sic], and you can
18 kick off that discussion?

19 **MR. TOUBMAN:** Thank you, Dr. Monto. By the
20 way, it's not Dr. Toubman; it's just mister.

1 **DR. MONTO:** It's Mr. Toubman. I keep trying,
2 but we do it by a knee jerk reaction.

3 **MR. TOUBMAN:** Thank you. I just wanted to see
4 if I have this right from just listening to folks. It
5 sounds like there's some disagreement, but
6 predominantly people are okay with open label. But I
7 didn't hear anybody objecting to the prioritization,
8 meaning that, yes, you unblind, but you do it when
9 their group comes up.

10 We just heard there is -- obviously, there's
11 some variance in states, and there's going to be some
12 problems with it. As Dr. Cohn pointed out, healthcare
13 workers are a very clear group, and the other groups
14 when we get to them are going to be not so clear. But
15 Pfizer believes that that's doable, so we can at least
16 try it. They can try it, and to the extent it doesn't
17 work, it doesn't work.

18 But in the meantime, since people aren't going
19 to be able to access vaccine now anyway for a period of
20 time if they're not healthcare workers or nursing home

1 residents, then we gain something by saying, yes, open
2 label but when their group comes up. And also, we
3 avoid any ethical issues by doing that.

4 **DR. MONTO:** Dr. Gruber, do you have some
5 comments?

6 **DR. GRUBER:** Yeah. I just wanted to make a
7 brief comment. I had the chance to confer with some of
8 my colleagues, and the consensus is, as I stated
9 before, that we will keep this question as a discussion
10 point. And it should not be voted on. Thank you.

11 **DR. MONTO:** Thank you. And Dr. Chatterjee,
12 you had a comment to start us off on what happens if we
13 don't have a placebo group -- what other additional
14 studies can be done.

15 **DR. CHATTERJEE:** Yes, thank you, Dr. Monto.

16 **DR. MONTO:** And we don't want any open
17 discussion of all the observational studies to learn
18 about how vaccines work but focus on this current issue
19 of the lack of a placebo group.

20 **DR. CHATTERJEE:** Okay. Well, what I was going

1 to talk about was actually additional studies such as
2 co-administration of other vaccines.

3 **DR. MONTO:** Okay. That's on the table. I
4 didn't want to get into studies of transmission and
5 things of that sort. Okay. Please. Please go ahead.

6 **DR. CHATTERJEE:** I'm not sure if I should
7 continue.

8 **DR. MONTO:** Yeah. Please go ahead. Yes,
9 please.

10 **DR. CHATTERJEE:** Okay. Other populations that
11 should be studied I thought should include older
12 adults, those who are 75 and above, because the numbers
13 of participants in that group I think are relatively
14 quite small and then also residents of long-term care
15 facilities. And I'm not sure that those folks were
16 included in these trials.

17 **DR. MONTO:** Thank you. Very helpful. Dr.
18 Hildreth.

19 **DR. HILDRETH:** I'm here. I was going to -- I
20 agree with the previous comment that it would be nice

1 to do some studies in people living in assisted living
2 facilities since that wasn't specifically part of this.
3 And that's a crucial group that we need to have some
4 data from. Thank you.

5 **DR. MONTO:** Dr. Pergam?

6 **DR. PERGAM:** Thanks. I have to say I
7 completely agree with Dr. Chatterjee. One of my
8 concerns was the small number of elderly patients in
9 the 75 and older. That's important. We need to expand
10 on that. I also --

11 **DR. MONTO:** What were the -- let me just ask
12 you. What would the design be because we can't do a
13 placebo-controlled design?

14 **DR. PERGAM:** Yeah. I think it's --

15 **DR. MONTO:** How would you study that?

16 **DR. PERGAM:** Yeah. I would study it just as
17 potentially immunogenicity alone. That might be
18 sufficient. I mean, it's probably -- we can't do -- we
19 can't do a placebo-controlled design, but I think you
20 at least have the data from the primary trial to see

1 what immunogenicity looks like between the two. And I
2 think that's probably going to be the best you could
3 do.

4 I think that's also true in the
5 immunosuppressed population, which I think is a really
6 -- I know they are working on these trials, but I think
7 that's going to be really important. There aren't
8 going to be the ability to do placebo-controlled trials
9 in that sense, and I think you'd have to look at
10 immunogenicity as well. So you're looking at patients
11 who necessarily can't produce as robust an immune
12 response and see how much less of a response you'd get
13 in those groups. I think those are going to be really
14 important studies for the larger population,
15 particularly since immunosuppressed patients will make
16 up 4 to 5 to even 6 percent of the entire U.S.
17 population.

18 **DR. MONTTO:** Thank you. Dr. Gans?

19 **DR. GANS:** Since we're talking about other
20 studies, a couple of points that haven't been raised.

1 I'm trying not to repeat things, but I know that
2 there's a lot of overlap here. The other studies that
3 we actually haven't talked a lot about are really
4 looking at other conditions. We talked about Bell's
5 palsy, but there's other neurologic outcomes that I
6 really think have to be high on the list. So we really
7 need to consider, especially when we go down into the
8 children studies -- so I want to urge those particular
9 things to be looked at.

10 The other part of it is the cardiac findings.
11 We think most of this -- likely from the SARS-CoV-2
12 receptors there may be specific to the virus, but we
13 haven't figured out if their immunologic or not. And
14 we're seeing a lot of different cardiac manifestations.
15 So this needs to be studied not only just as potential
16 outcomes of the disease versus the vaccine but also in
17 people with cardiac disease, so I think that's a really
18 important piece to keep in the forefront as we're
19 moving forward and to think critically about.

20 In terms of some of the studies that need to

1 happen, again, we talked about some of the immunologic
2 studies, but studies in children, I think, are going to
3 be particularly important because we can extrapolate,
4 particularly studies that we've done in children where
5 the T and B cells do not follow the same pattern as
6 each other and as an adult because they have different
7 maturation of particularly the T cell responses. And
8 therefore, it's going to be really important as we
9 understand this to really -- I want to just reiterate
10 really doing those studies ongoing. Thank you.

11 **DR. MONTO:** Thank you. And next, Dr. Sawyer.

12 **DR. SAWYER:** One of the things we eventually
13 need to learn is what happens if you get one dose of
14 the Pfizer vaccine and then a second dose of the
15 Moderna or vice versus. That mistake is going to
16 happen a lot as we start to disseminate vaccine around
17 the country. The interim guidance that's been issued
18 so far to immunization registries is to not give a
19 third dose, in other words to assume that, even though
20 you're mixing products, that's an adequate -- you're

1 going to get an adequate immune response. So at some
2 point, it would be nice to know if that's really true.

3 **DR. MONTO:** Dr. Rubin.

4 **DR. RUBIN:** I know that we're not supposed to
5 propose other studies, but again correlates of
6 protection are going to become extremely important in
7 investigating a non-placebo --

8 **DR. MONTO:** That's okay.

9 **DR. RUBIN:** Okay. Correlates of protection
10 are going to be really important in interpreting these
11 trials because of the lack of placebo. We're going to
12 have much more difficulty assessing safety, and there's
13 no easy way to do that when we have no placebo-control.
14 But we can at least get at efficacy if we have some
15 good idea of what protection looks like.

16 **DR. MONTO:** Dr. Lee?

17 **DR. LEE:** I think one of the interesting
18 things we might want to consider that does not require
19 placebo control is a non-inferiority trial of two doses
20 versus one because I think you're going to have a

1 certain subset that doesn't get the second dose. And
2 if you have reasonably good vaccine efficacy with one
3 dose, then I think we really need to think about that.
4 So just we would be looking at it pretty much at the
5 incidence of COVID-19 in the two groups. But I think a
6 non-inferiority one would be really one to think about.
7 Thank you.

8 **DR. MONTO:** And how about different doses? We
9 hear some questions raised about the dose that was
10 suggested or the timing of vaccination.

11 **DR. KURILLA:** Especially for children, Arnold.

12 **DR. MONTO:** Especially for children. I'm
13 trying to get a discussion going. It's hard virtually.
14 Dr. Kurilla, was that you?

15 **DR. KURILLA:** Thank you, Arnold. Yeah. Let
16 me just echo Dr. Rubin's point about the correlates of
17 protection. I think this is probably one of the most
18 critical features not just for this vaccine but for
19 future vaccine trials. It will really make other
20 vaccines realistically approachable in terms of their

1 clinical trials going forward. If we could move
2 towards some sort of accelerate approval, the
3 immunogenicity I think would be a very good endpoint in
4 that work.

5 The other thing in regards to the one versus
6 two doses, I think that's an important trial, but I
7 would also like to emphasis that in the follow ups that
8 what's being done, this sort of surveillance for under
9 the EUA, I think there needs to be some aggregated data
10 to look at who only got one dose because there are
11 going to be people who are not going to come back for
12 that second dose and to see whether there are any clues
13 that may be quite informative without having to go
14 through a formal trial to sort of get an assessment as
15 to whether that's a feasible approach.

16 **DR. MONTTO:** Dr. Schooley.

17 **DR. SCHOOLEY:** I just wanted to reemphasis the
18 immunocompromised patient population, not just because
19 we need the data but because they also are a place
20 where we can have a wider spray -- splay of immune

1 correlates to look at and might get some correlates of
2 immunity data in a relatively short period of time if
3 they are starting at a lower point in terms of their
4 vaccine induced immunity.

5 **DR. MONTO:** All right. Immune correlates are
6 a recurring theme, and it looks like we may be blessed
7 with an immune correlate here with this vaccine, which
8 we haven't seen with other vaccines. And clearly
9 that's a message that immune correlates are paramount.
10 Dr. Gans?

11 **DR. GANS:** Thank you. I just wanted to follow
12 up on a thought. I kind of mentioned it in my last
13 comment, and I think Dr. Offit had started out with
14 this -- is as we're investigating this disease further
15 and we know that hopefully populations get immunized,
16 one important component will be to look at the adverse
17 events as they follow in natural disease versus the
18 adverse events that follow vaccination because, as we
19 all know, vaccination is highly protective, although
20 often not 100 percent. But as long as they reduce the

1 actual events of the severe adverse events, then
2 actually that should be an issue of protection that is
3 studied ongoing, so for instance the Bell's palsy and
4 other of the outcomes that we've seen. Thank you.

5 **DR. MONTO:** Dr. Sylvester?

6 **DR. SYLVESTER:** Yeah. Dr. Monto, you raised
7 an interesting question about the timing between the
8 doses. And I think that there've been some interesting
9 studies that we've seen in the vaccine world where the
10 longer you wait for your second dose the higher your
11 antibody levels may be. I think the practicality of
12 that in a pandemic may be difficult.

13 I think people are going to want to line up,
14 and Pfizer's got a three-week window. And Moderna now
15 has a four-week window. I don't think many people will
16 say "I'll just wait eight weeks or 12 weeks before I
17 get my second dose." So I like the question, and it's
18 a great academic question. I'm not sure in a pandemic
19 it's a practical one.

20 **DR. MONTO:** Dr. Gans, is that -- no. Dr.

1 Pergam.

2 **DR. PERGAM:** Thanks. You know, Arnold, the
3 dose issue that you brought up is a really important
4 one that I want to come back to because, again,
5 thinking about populations that tend to have less
6 response to -- or less side effects, it looked like the
7 older population had less complications from the second
8 dose of the vaccine, which might suggest they could
9 tolerate a higher dose. And we've seen in other
10 vaccines that higher doses are more beneficial for --
11 whether it's zoster, whether it's influenza, it could
12 be beneficial. And so it could be a real value in
13 targeting those populations with maybe a slight
14 difference in immunity, either the immunocompromised
15 population or the older population, as targets to do
16 studies looking at higher dose. And I know Moderna had
17 the -- I think the 250 was the highest dose. I think
18 that's right -- would be at least an option to try and
19 see if there was better outcomes in immunity from the
20 higher dose of the vaccine in those groups.

1 **DR. MONTO:** Thank you. Dr. Perlman and then
2 finally Dr. Fuller before we go on to the voting
3 question.

4 **DR. PERLMAN:** Yeah. So I just wanted to
5 reinforce the idea of doing a pediatric trial and also
6 pointing out the problems because children don't get
7 much -- don't get particularly sick with this. So
8 it'll be very important to think about whether we're
9 going to measure serial serology, serial culturing.
10 And for little children, this will be very hard, but I
11 think this is really important because this may be the
12 major group that's unvaccinated in a short time.

13 **DR. MONTO:** Okay. And Dr. Fuller, final
14 comment before we discuss the voting question.

15 **DR. FULLER:** Yes, thank you, Dr. Monto. So
16 looking really far ahead, a couple questions which have
17 to do with duration of protection. What will happen if
18 this vaccine isn't a lifelong vaccine, which we expect
19 that it is not? So how will we know when somebody
20 needs a boost, or how will we know if they're protected

1 against new strains that may evolve from coronavirus?
2 And I know that's not an easy study to design, but I
3 just want to put it out there because if we really want
4 to co-exist with this virus or variations thereof, we
5 need to be thinking about those sorts of things.

6 **DR. MONTO:** Thank you all for this very
7 vigorous discussion. I think we have given FDA a sense
8 of our wish that we could do a crossover blinded design
9 but the realization that that may be impossible. We
10 know what Pfizer has proposed, and FDA will be
11 negotiating with Moderna about the way they will
12 address this problem. So I think we've really had the
13 time, fortunately, to go over this in the kind of
14 detail that it really needs.

15 Now, we're going to have a discussion of the
16 voting question. We will then have an electronic vote,
17 and then I will ask the Committee members who wish to
18 explain their vote -- don't need it from everybody --
19 to explain their votes. So the question is, based on
20 the totality of scientific evidence -- it's very

1 carefully phrased. Based on the totality of scientific
2 evidence available, do the benefits of the Moderna
3 COVID-19 vaccine outweigh its risks for use in
4 individuals 18 years of age and older? So hands up for
5 commenting as you wish on this question. Dr. Gans, you
6 were the first.

7 **DR. GANS:** Thank you. Thank you for allowing
8 us just to opine about this really important topic. I
9 think that this is a really opportune time for us to
10 move science forward, and I would say that the evidence
11 that has been studied in great detail on this vaccine
12 highly outweighs any of the issues that we've seen.
13 And I think it really supports us being able to, with
14 the pandemic in our background, really move forward and
15 finally provide a safe and effective way to get to herd
16 immunity. Again, understanding that this is for 18
17 years and older and that obviously we need to be able
18 to provide this to all of our population to get there,
19 but it's a first step. Thank you.

20 **DR. MONTTO:** Thank you. Dr. Kurilla?

1 **DR. KURILLA:** Thank you, Dr. Monto. Yeah. I
2 have some serious reservations about this question
3 because we've been discussing -- this whole meeting has
4 been focused on the emergency use authorization for
5 this vaccine, not for full approval under a BLA. And
6 the question really doesn't reflect that. It could
7 easily be seen as full approval.

8 There's quite a bit of confusion, I think, not
9 only in the general public but many in the media
10 reports of last week and this week talk about this
11 panel approving the vaccine or recommending this
12 vaccine for approval. And we even heard today during
13 the open public hearing session several medical
14 professionals who talked about approving. I think that
15 the distinction between an EUA product, which is still
16 an investigational product, and the full approval -- a
17 product under full approval with a BLA is a distinction
18 we need to maintain. And I think we're losing that
19 simply by looking at this as an age related -- anyone
20 over the -- 18 years of age and older.

1 It doesn't strike me as really addressing the
2 emergency, which is severe and serious life threatening
3 COVID disease in specific populations. So I have a lot
4 of problems because this could be interpreted as us
5 actually recommending full approval of the vaccine.
6 And in the minds of the general public, that may happen
7 and may preclude adequate -- not only adequate
8 evaluation of this vaccine but other future and ongoing
9 COVID vaccines in development.

10 **DR. MONTO:** Thank you. I appreciate your
11 concern. I wonder if Dr. Gruber could address amending
12 the (audio skip) because (audio skip) the emergency use
13 authorization. But the question doesn't really state
14 that.

15 **DR. GRUBER:** So when we published the agenda
16 for this VRBPAC Committee meeting, the topic is "The
17 Committee will meet in open session to discuss
18 emergency use authorization of the Moderna COVID-19
19 vaccine for the prevention of COVID-19 in individuals
20 18 years of age and older." So that is the topic of

1 today's VRBPAC discussion.

2 It is to discuss emergency use authorization.
3 That's what the agenda says. We phrased this question
4 the way we phrased it because, as was stated, a vaccine
5 authorized under an EUA is a product that has not been
6 approved. It's a non-approved product. And under the
7 EUA, in order for us to lend or issue an EUA, we have
8 to make a determination that the benefits of the
9 product outweigh its risks. Does that --

10 **DR. MONTO:** Marion, what if we just add the
11 words "EUA -- under an EUA" to this voting question?
12 Would that be possible?

13 **DR. GRUBER:** Based on the totality of
14 scientific evidence available, do the benefits of the
15 Moderna COVID outweigh its risk for use --

16 **DR. MONTO:** For use under an EUA in
17 individuals --

18 **DR. GRUBER:** For use under an EUA in
19 individuals 18 years of age and older? We can do that.

20 **DR. MONTO:** Do you have to take this to your

1 lawyers, or can you make a determination?

2 **DR. GRUBER:** We can do that. We can say, "For
3 use under an EUA in individuals 18 years of age and
4 older," if the Committee needs that clarification.
5 Then I think we can safely do so.

6 **DR. HILDRETH:** Dr. Monto, may I make a
7 comment?

8 **DR. MONTO:** Yes. Yes, please, Dr. Hildreth.

9 **DR. HILDRETH:** The question is very clear. Do
10 we think that this vaccine's benefits outweigh the
11 risks? And if we think that, then the FDA will make a
12 decision as to whether or not to issue an EUA. That's
13 not what we're voting on. We're voting on whether the
14 benefits of this vaccine outweigh the risks, and then
15 it's up to the FDA to make a decision as to whether or
16 not they're going to issue an EUA. So I think the
17 question should be left exactly as it is.

18 **DR. MCINNES:** I completely support Dr.
19 Hildreth.

20 **UNIDENTIFIED MALE:** Ditto.

1 **DR. MEISSNER:** Dr. Monto?

2 **DR. MONTO:** Okay. Yes, please.

3 **DR. MEISSNER:** Cody Meissner. Dr. Gruber, I
4 have a little trouble with it the way it's written also
5 because it's going to be very hard to study other
6 vaccines -- experimental vaccines -- when a person
7 looks at this sentence. And what I would suggest is
8 that we write "through two months of follow up," or put
9 some qualification in there that defines the length of
10 time that it's been evaluated. Because this is a
11 blanket statement that everybody over 18 years of age
12 should get it.

13 **DR. GRUBER:** No, this is the question that is
14 phrased the way it's phrased because we want to know if
15 under an EUA whether the vaccine -- the product is
16 still considered a nonapproved product but needs to --
17 could be given during a public health emergency if the
18 benefits of this product outweigh the risks. It does
19 not imply that under an EUA, then, of course -- if we
20 determine that the benefits outweigh the risk under the

1 authorization -- under an EUA authorization, it can be
2 given then to individuals 18 years of age and older.
3 But that does not equal that the product is approved.

4 **DR. MEISSNER:** But a lot of people won't
5 understand that thinking. Could you say at least "this
6 experimental vaccine?"

7 **DR. MONTO:** No, no.

8 **DR. GRUBER:** That too --

9 **DR. MONTO:** No. I think once we start
10 qualifying in terms of the duration or anything like
11 that, it's going to be so confusing because the
12 duration may get longer as we go forward.

13 **DR. MEISSNER:** Arnold, let me offer an
14 alternative. Marion, instead of an age --

15 **DR. MONTO:** Okay. Well, you offer an
16 alternative, and --

17 **DR. MEISSNER:** -- what about "people at risk
18 for serious COVID disease"?

19 **DR. MONTO:** No, no. And let me just say that
20 we have a question now. We are advisory to FDA. They

1 have put in a question that they feel comfortable with.
2 Am I correct, Marion? And that is what we are voting
3 on. If the vote is not in favor, then we can discuss
4 this further. Marion, how should we proceed?

5 **DR. GRUBER:** I would like to proceed with
6 keeping the voting question as currently phrased.

7 **DR. MONTO:** Okay. There it is.

8 **DR. FULLER:** Dr. Monto, may I ask a question
9 not about the phrasing?

10 **DR. MONTO:** Excuse me. Dr. Hildreth? Yes.

11 **DR. HILDRETH:** Are we going to go back and
12 retrospectively change the question we voted on for
13 Pfizer?

14 **DR. MONTO:** Well, that's another issue I was
15 thinking of.

16 **DR. HILDRETH:** This is exactly the same
17 question.

18 **DR. MONTO:** How would I explain that we have a
19 different question?

20 **DR. HILDRETH:** Yeah. How would we explain

1 that?

2 **DR. MONTO:** Yes, I get it. I get that.

3 **DR. FULLER:** Dr. Monto, may I ask a question
4 that's not related to the phrasing, but a very
5 important one to the question?

6 **DR. MONTO:** Yes, please, Dr. Fuller, and then
7 we'll try to go in order. It's a lot easier to manage.

8 **DR. FULLER:** Thank you. Dr. Gruber, I
9 definitely hope this does not happen, but what if there
10 is some adverse event that appears, that is very broad,
11 that this does not -- if we think the benefits outweigh
12 the risk, but it turns out the risks are so high. How
13 does this EUA get withdrawn? What will be the
14 conditions to say that we can no longer do this?

15 **DR. GRUBER:** So as Dr. Fink had elaborated on
16 in his introductory remarks, an EUA -- and he did say
17 this last week, and I believe he said it today, too --
18 can be revoked. And there can be several reasons. So
19 one could certainly be if we see that the risks
20 outweigh the benefits of that product, then we can

1 revoke the EUA. So that is an -- but that's -- right
2 now, we're voting on the data.

3 We're looking at benefit and risk based on the
4 data available to us and as we have presented them
5 today. And we, of course -- as was stated, we will
6 have continued follow up, active safety follow up, of
7 the recipients of this vaccine under an EUA. And if we
8 determine that the risks are no longer, well,
9 acceptable and that the risks outweigh the benefits,
10 then we can revoke the EUA, Dr. Fuller.

11 **DR. FULLER:** And FDA would do that?

12 **DR. GRUBER:** And the FDA would do that, yes.

13 **DR. FULLER:** Okay. Thank you. Thank you for
14 the clarification.

15 **DR. GRUBER:** Yeah.

16 **DR. MONTTO:** Dr. Offit, let's just go by
17 recognized -- individuals I recognize.

18 **DR. OFFIT:** Thank you. So yeah, I disagree
19 with Dr. Meissner. I think the question that's being
20 asked us is do we have enough evidence in hand to say

1 that the benefits of this vaccine outweigh what, at the
2 moment as far as severe safety issues, are theoretical
3 risks. I think the answer to that question is clearly
4 yes. I mean, the question is never when do you know
5 everything? It's when do you know enough?

6 You know, we have trials of 44,000 and 30,000.
7 That's as big as any general pediatric vaccine trial.
8 The difference is length of follow up, so we don't know
9 whether or not it's going to be effective six months
10 from now or a year from now. But there are systems in
11 place to know that. We don't know whether or not it's
12 going to have a rare serious side effect, which is true
13 of any medical product. But there are systems in place
14 to know that. And frankly, given what we know so far
15 about the height of the immune response, about what we
16 have with T helper cell and cytotoxic T cell response
17 and so forth, we can feel pretty comfortable that this
18 vaccine is going to have a benefit that lasts for more
19 than the three months or so that we've studied it.

20 I think it's a pretty easy answer. You can't

1 qualify things as being experimental because you could
2 always say that about any medical product. I mean,
3 when the HPV vaccine came out, we could say, "Well, we
4 think that it's okay for seven years because that's all
5 we have data for." So I think the answer to this
6 question, at least as far as I'm concerned -- I
7 completely agree with Dr. Gans -- is clearly yes.
8 Thank you.

9 **DR. MONTO:** Dr. Cohn. And we're going to be
10 discussing this until 5:00 Eastern, and at that time,
11 we're going to put it to the vote because there's also
12 another chance to explain your vote afterwards. Dr.
13 Gans? Dr. Cohn, excuse me. Go ahead.

14 **DR. COHN:** Ditto to what Dr. Offit just said.
15 I completely agree that the question is the right
16 question and the data clearly show that the benefits
17 outweigh the risks.

18 **DR. MONTO:** Okay. Dr. Pergam.

19 **DR. PERGAM:** Thanks. I completely agree with
20 Dr. Offit and Dr. Gans. I think the preponderance of

1 data is totally in support of moving this forward. I
2 don't see any value in changing the terminology of this
3 particular voting question.

4 I also think this idea that the EUA process is
5 going to change future vaccine trials, et cetera, feels
6 a little bit strange to me. We're talking about a
7 pandemic, which is not very common, where we really
8 need to move this forward. And there's really an
9 effort to get this done quickly. I don't see as much
10 of a risk in the long-term that this process is going
11 to be used on a regular basis for other vaccine trials.
12 So I think we need to focus on what's at hand and focus
13 on the question here, and I think there's no doubt in
14 my mind that the data is -- it looks like the benefits
15 outweigh the risks from what I've seen.

16 **DR. MONTTO:** Mr. Toubman.

17 **MR. TOUBMAN:** Yes. My camera's not coming on,
18 but can you hear me?

19 **DR. MONTTO:** Yeah. We can hear you.

20 **MR. TOUBMAN:** So I'm fine with the question as

1 is because it says, "based on the totality of
2 scientific evidence available," meaning that's what we
3 have today. And based upon that, on balance, strong
4 data particularly on severe disease, I think the
5 balance supports it. I did have a concern though with
6 -- I'm glad there was discussion about whether to
7 change the question or not, because I was troubled by
8 the fact that FDA was weighing in again on us changing
9 the question. And basically, we've been told this is
10 an independent committee, and we want to be
11 transparent.

12 If the Committee feels that a question should
13 be changed, the Committee should change it. There
14 doesn't seem to be a willingness to trust the
15 Committee's decision, and the answer Dr. Gruber gave
16 is, "Well, first, vote on my questions, and then after
17 that, if it doesn't pass, we can do a different
18 question." That in reality doesn't work because almost
19 nobody's going to want to vote no to this question as
20 written.

1 You deprive people the opportunity -- and this
2 happened last time -- not to bring up the whole story.
3 But with Pfizer there was strong feelings about
4 including 16 and 17-year-olds. And because that was
5 not presented as a separate question, which it should
6 have been, people were sort of forced to have to make a
7 choice. So I think the Committee really should be
8 independent and decide for themselves whether the
9 question is acceptable or not. In this case I think
10 it's fine.

11 **DR. MONTO:** Dr. Meissner.

12 **DR. MEISSNER:** I didn't realize my hand was
13 still up.

14 **DR. MONTO:** Okay. Well, then, thank you,
15 unless you have some burning thing to say.

16 **DR. MEISSNER:** No, all I wanted to say,
17 Arnold, is that I agree with what everyone has said,
18 and I am in favor of yes on this question. My only
19 point is I don't want people to interpret this the same
20 way they would a licensed vaccine. It is, as has been

1 stated, based on the available evidence, but that's
2 limited. But if everyone else is comfortable with
3 this, I'm fully comfortable. Thank you.

4 **DR. MONTO:** And in reality, Cody, whatever we
5 say, the media is going to interpret it in whatever way
6 they want.

7 **DR. MEISSNER:** Yes.

8 **DR. MONTO:** Dr. Wharton?

9 **DR. WHARTON:** So the question as written seems
10 to be aligned with how we think about EUAs. And based
11 on the totality of scientific evidence available, I
12 strongly support that the benefits of the vaccine
13 outweigh its risk for use in individuals 18 years of
14 age and older.

15 **DR. MONTO:** Okay. Dr. Neaton?

16 **DR. NEATON:** -- question. The answer is yes
17 to the question. Thank you.

18 **DR. MONTO:** Okay. Well -- okay, then you
19 don't have to explain your vote afterwards.

20 **DR. NEATON:** All right.

1 **DR. MONTO:** Dr. Chatterjee and then finally
2 Dr. Rubin. And then we will vote the question.

3 **DR. CHATTERJEE:** Thank you, Dr. Monto. I just
4 wanted to follow up on several of the previous
5 Committee members that commented on this, and I
6 understand the difficulty that some people are having
7 with the wording, perhaps. As scientists, we tend to
8 be very precise in what we say, and we want it to be as
9 to the point as possible. But I think what is not
10 mentioned in the question -- and of course what we are
11 all talking about -- is that we're making this decision
12 during a pandemic. And so there is this really unique
13 circumstance that is forcing us, in some ways, to word
14 the question in this way and to answer the question in
15 this way. So I would say I'm comfortable with the way
16 the question is written and willing to vote on it.

17 **DR. MONTO:** Thank you. And finally Dr. Rubin.

18 **DR. RUBIN:** Thank you. You can hear me?

19 **DR. MONTO:** Yes, we can and see you, too.

20 **DR. RUBIN:** Thanks. I'm glad to be

1 recognized. I just want to remember why we're here.
2 We're here for two reasons that I can think of: to
3 provide the FDA advice, and to see (audio skip) that
4 they want. So I wouldn't get so hung up on the
5 question because they make the decision and we don't.

6 And the second reason we're here is to inspire
7 confidence in the public that we've looked carefully at
8 the data. And I think when we just -- when we worry
9 about the details of the wording, I'm not sure that
10 we're helping people understand that what I almost
11 certainly will be a very strong vote in favor is just a
12 strong vote in favor.

13 **DR. MONTA:** Thank you, Dr. Rubin. It's a
14 delight to come to the end when I don't see any hands
15 raised, which was not the case last week. So now,
16 let's call the question. So we are going to be voting,
17 and then after the vote, those who wish to explain the
18 vote will have a chance to do so by raising their
19 hands.

20 **MS. HAYES:** Thank you, Dr. Monto. Can

1 everybody hear me okay?

2 **DR. MONTTO:** Yes, we can.

3 **MS. HAYES:** Okay. So our members and
4 temporary voting members, as seen on the next slide,
5 excluding the industry representative, will be voting
6 in today's meeting. And in regard to the voting
7 process, Dr. Montto will read the question for the
8 record, and afterwards, all members and temporary
9 voting members will cast their vote by selecting one of
10 the voting options. These include yes, no, or abstain.
11 You will have two minutes to cast your vote after the
12 question has been read.

13 Once all the votes have been placed, we will
14 broadcast the results and read the individual votes
15 aloud for the record. Please note that once you cast
16 your vote you can change your vote within the two-
17 minute timeframe. However, once the vote has closed,
18 all votes will be considered final. Does anybody have
19 any questions related to the voting process before we
20 begin? Okay. I don't see any questions. So Dr.

1 Monto, if you'd like to go ahead and read the question.

2 **DR. MONTO:** The question that we are voting on
3 is, based on the totality of scientific evidence
4 available, do the benefits of the Moderna COVID-19
5 vaccine outweigh its risks for use in individuals 18
6 years of age and older?

7 **MS. HAYES:** Thank you. So members and
8 temporary voting members, you have two minutes to go
9 ahead and cast your vote.

10 **DR. SAWYER:** Arnold, this is Mark Sawyer. I
11 want to point out that my vote says Pfizer-BioNTech,
12 not Moderna.

13 **UNIDENTIFIED MALE:** Right. This is the wrong
14 vote.

15 **DR. MONTO:** You are right. I was busy trying
16 to find where the voting was.

17 **MS. HAYES:** Yes, we will be taking a revote.
18 Just one moment.

19 **DR. MONTO:** We've got the right one up now.

20 **MS. HAYES:** Yes, I believe the question has

1 been updated, so we will restart the timer and clear
2 out the current results so we can take another revote.
3 We have 30 seconds remaining. Okay. Our two minutes
4 is up, so if we could go ahead and close the vote and
5 broadcast the results. And I will read the individual
6 votes aloud for the record.

7 So Dr. Cohn, we have a yes vote. Dr. Sawyer
8 voted yes. Dr. Rubin, yes. Dr. Kurilla abstained.
9 Dr. Perlman, yes; Dr. Schooley, yes; Dr. Gans, yes; Dr.
10 Lee, yes; Dr. Moore, yes; Dr. Chatterjee, yes; Dr.
11 Meissner, yes; Dr. Fuller, yes; Dr. Hildreth, yes; Dr.
12 Neaton, yes; Dr. Offit, yes; Dr. Wharton, yes; Dr. Kim,
13 yes; Dr. Pergam, yes; Dr. McInnes, yes; Dr. Monto, yes.
14 Mr. Toubman, yes. And that concludes the vote. It
15 looks like we have a favorable vote. So I will pass
16 the floor back to Dr. Monto. Thank you, everybody, for
17 putting in your votes today.

18 **DR. MONTO:** Thank you. Now, anybody who would
19 like to explain their vote should raise their hands.
20 Mr. Toubman is first.

1 **MR. TOUBMAN:** Thank you. I voted yes because
2 the balance is strong. Last time (audio skip). Can
3 you hear me?

4 **DR. MONTTO:** We can.

5 **MR. TOUBMAN:** The balance is strong for
6 approval, so that's why I voted last time. I did
7 recommend that we not grant EUA broadly, but rather
8 limit it to priority groups to allow for further data
9 to be collected, and since there is a limited supply
10 anyway. And that would be to preserve the data we
11 would get going forward. That was not accepted by
12 folks. But we were assured that when Pfizer moves
13 forward people who were not in priority groups would be
14 maintained in the study. And that was really important
15 to me.

16 I'm very concerned about Moderna's proposal --
17 and it does sound like from the discussion -- I know
18 FDA did not want to vote on that. I can see why. But
19 it seemed like there was strong support for, if they're
20 going to unblind, they should do it on the basis of

1 when a group comes up in its priority and not unblind
2 everyone right away, which is what Moderna has
3 proposed. I think that would be really a disservice.

4 Finally, I did want to say thank you to the
5 FDA folks, though, because they put a tremendous amount
6 of work into this. I think Dr. Meissner said this at
7 the beginning of the meeting. In terms of very long
8 hours, reviewing the data, understanding this, working
9 with the sponsors, they've been under tremendous
10 pressure here and even they've been under improper
11 political pressure, even bullying and threats. And I
12 think they valiantly resisted that and showed that
13 science is going to prevail here. So a big debt of
14 gratitude to the hard-working FDA folks, Dr. Marks on
15 down. Thank you.

16 **DR. MONTO:** Thank you, Mr. Toubman. Dr.
17 Fuller, you'd like to explain your vote?

18 **DR. FULLER:** Yes, I would. Thank you. First
19 of all, I want to thank the FDA for the incredible work
20 they've done, and this Committee itself for the

1 transparency that went in today's schedule and having
2 more time. We're in an unparalleled crisis.

3 I did not think an EUA was the way to go, but
4 since the train has left the station, I appreciate that
5 Moderna has given us a very transparent and thorough
6 study that even from the beginning seemed to be very
7 well organized with getting people with underlying
8 conditions, with monitoring activity throughout the
9 study, with even including the serology and nasal
10 swabs, which are not completely analyzed at the moment
11 but which have great potential to look at important
12 aspects. And then lastly the care for the study
13 participants throughout, including a plan for
14 monitoring adverse effects, as well as what to do with
15 people who now may want to move from the placebo. So I
16 appreciate the way that they've conducted a much more
17 transparent and clean study.

18 And lastly, I know that now that we have
19 vaccines available that we still have to use the
20 preventions that are available such that we can keep

1 each other safe as we go through getting to the type of
2 protection -- however long it lasts. So I want to
3 thank FDA and all of you for helping with this
4 discussion today, and that's why I said yes. I didn't
5 feel that way last time. Thank you.

6 **DR. MONTTO:** Thank you, Dr. Fuller. Dr.
7 Kurilla and then for the final word, Dr. Hildreth.

8 **DR. KURILLA:** Yeah. Thank you, Arnold.
9 Camera not working again. I abstained because I'm very
10 uncomfortable with the language. I think in the midst
11 of a pandemic and with limited vaccine supply
12 available, a blanket statement for individuals 18 years
13 and older is just too broad. I'm not convinced that
14 for all of those age groups the benefits do actually
15 outweigh the risks.

16 And I would prefer to see it more targeted
17 towards people at high risk of serious and life
18 threatening COVID disease. And we have that -- they
19 have that information, and we understand to a certain
20 extent those high-risk groups. So it could be

1 targeted.

2 Lastly, I would have preferred to have seen
3 rather than an emergency use authorization route an
4 expanded access program. I think it would have given
5 us a lot more opportunities to continue to collect the
6 data, and my concern about future vaccines was not on
7 non-COVID vaccines but other COVID vaccine candidates
8 that are in various stages of development. Thank you.

9 **DR. MONTO:** Dr. Hildreth.

10 **DR. HILDRETH:** Thank you, Dr. Monto. Sorry
11 about the train. I just want to make the point that
12 what a remarkable scientific achievement this is and
13 say thanks to all the scientists present and past who
14 contributed to this. To go from having a sequence of a
15 virus in January to having two vaccines available in
16 December is a remarkable achievement, and I just want
17 to say that and congratulate all those who were
18 involved. Thank you.

19 **DR. MONTO:** Thank you, Dr. Hildreth. You've
20 echoed my feeling about what a remarkable achievement

1 has been reached here having the sequence less than a
2 year ago. I just wanted to make one or two comments
3 before closing. Our vote was even more overwhelming
4 tonight than last week. I don't think that anyone
5 should interpret the difference in the vote being one
6 way or another comparing the two vaccines that we have
7 considered. Academics have a way of getting involved
8 in details, and what we have done for the last eight or
9 nine hours was to go over the details. And some people
10 took the issues last week, especially those involving
11 different age groups -- the 16- and 17-year-olds -- to
12 drive the decision that they made, which clearly was
13 made based on that issue and not on the overwhelming
14 evidence for risk being less than benefit -- a clear
15 benefit with these vaccines.

16 So I'd just like to close by thanking the
17 Committee members, thanking FDA for giving us an agenda
18 which allowed much more open discussion, which I think
19 benefits all of us, including trying to advise FDA on
20 some of these very tough issues that we are facing.

1 And congratulations to us all for achieving this
2 emergency use authorization for a second vaccine, which
3 along with other events will eventually and sooner, we
4 hope, break the back of the pandemic. Now, I'd like to
5 hand the floor over to Dr. Atreya to formally close the
6 meeting.

7 **MR. KAWCZYNSKI:** Dr. Atreya, your phone's
8 muted.

9 **DR. ATREYA:** I'm sorry. Thank you all. Dr.
10 Monto described my sentiments, and you all did a great
11 job. And thank you for all your service and input. We
12 greatly, greatly appreciate it. And then so I would
13 formally close this meeting. This meeting is adjourned
14 now. Thank you very much. Have good evening.

15

16 **[WHEREAS MEETING ADJOURNED]**