FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

(AMDAC)

Virtual Meeting

Tuesday, November 30, 2021

9:00 a.m. to 5:33 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Joyce Yu, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBERS

(Voting)

Lindsey R. Baden, MD

(Chairperson)

Director of Clinical Research

Division of Infectious Diseases

Brigham and Women's Hospital

Director, Infectious Disease Service

Dana-Farber Cancer Institute

Professor of Medicine, Harvard Medical School

Boston, Massachusetts

Timothy H. Burgess, MD, MPH, FACP

Captain, Medical Corps, U.S. Navy

Director, Infectious Disease Clinical Research Program

Uniformed Services University of the Health Sciences

Bethesda, Maryland

Michael D. Green, MD, MPH

Professor of Pediatrics, Surgery and Clinical & Translational Science

University of Pittsburgh School of Medicine

Division of Infectious Diseases

Director, Antimicrobial Stewardship & Infection Prevention

Co-Director, Transplant Infectious Diseases

Children's Hospital of Pittsburgh

Pittsburgh, Pennsylvania

W. David Hardy, MD

Scientific and Medical Consultant

Co-Investigator – CoVPN, CDU/UCLA CTRC

Charles Drew University School of

Medicine and Science

Los Angeles, California

Sally A. Hunsberger, PhD

Mathematical Statistician

Biometrics Research Branch

National Institute of Allergy and

Infectious Diseases

National Institutes of Health

Rockville, Maryland

Jennifer Le, PharmD, MAS, FIDSA, FCCP, FCSHP, BCPS-ID

Professor of Clinical Pharmacy

University of California, San Diego

Skaggs School of Pharmacy and

Pharmaceutical Sciences

La Jolla, California

Richard A. Murphy, MD, MPH

Staff Physician, Infectious Diseases

VA White River Junction Medical Center

Medicine Service

White River Junction, Vermont

Federico Perez, MD, MS

Infectious Disease Physician

Louis Stokes Cleveland VA Medical Center

Associate Professor of Medicine

Case Western Reserve University

Cleveland, Ohio

George K. Siberry, MD, MPH

Medical Officer, Adult Clinical Branch

Office of HIV/AIDS

Bureau of Global Health

United States Agency for

International Development

Washington, District of Columbia

Sankar Swaminathan, MD

Don Merrill Rees Presidential Endowed Chair

Professor and Chief

Division of Infectious Diseases

Department of Internal Medicine

University of Utah School of Medicine

Salt Lake City, Utah

Roblena E. Walker, PhD

(Consumer Representative)

Chief Executive Officer

EMAGAHA, INC.

Mableton, Georgia

Peter J. Weina, PhD, MD, FACP, FIDSA

Colonel, Medical Corps, US Army

Director, Office of Research Protections

Defense Health Agency

Defense Health Headquarters

Falls Church, Virginia

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Richa S. Chandra, MD, MBA

(Industry Representative)

Clinical Development Head

Communicable Diseases

Global Health Development Unit

Novartis Pharmaceuticals

East Hanover, New Jersey

TEMPORARY MEMBERS (Voting)

John M. Coffin, PhD

American Cancer Society Research Professor

Molecular Biology and Microbiology

Tufts University

Boston, Massachusetts

Janet D. Cragan, MD, MPH

Medical Officer

Division of Birth Defects and Infant Disorders

National Center on Birth Defects and

Developmental Disabilities

Centers for Disease Control and Prevention

Atlanta, Georgia

Sascha Dublin, MD, PhD

Senior Scientific Investigator

Kaiser Permanente Washington Health Research

Institute

General Internal Medicine Physician, Kaiser

Permanente Washington

Affiliate Professor of Epidemiology

University of Washington School of Public Health

Seattle, Washington

David A. Eastmond, PhD

Professor and Toxicologist, Emeritus

Environmental Toxicology Graduate Program

Department of Molecular, Cell and Systems Biology

University of California, Riverside

Riverside, California

A. Oveta Fuller, PhD

Member, African Studies Center

International Institute

Associate Professor, Microbiology and

Immunology, Medical School

University of Michigan

Ann Arbor, Michigan

Terry Gillespie

(Patient Representative)

Westmont, Illinois

James E.K. Hildreth Sr., MD, PhD

President and Chief Executive Officer

Professor, Internal Medicine

Meharry Medical College

Nashville, Tennessee

Daniel B. Horton, MD, MSCE

Assistant Professor of Pediatrics and Epidemiology

Department of Pediatrics

Rutgers Robert Wood Johnson Medical School

Rutgers Center for Pharmacoepidemiology and

Treatment Science

Institute for Health, Health Care Policy and

Aging Research

Rutgers School of Public Health

New Brunswick, New Jersey

Miriam C. Poirier, PhD

Scientist Emeritus

Laboratory of Cancer Biology and Genetics

Center for Cancer Research

National Cancer Institute

National Institutes of Health

Bethesda, Maryland

Uma M. Reddy, MD, MPH

Professor

Department of Obstetrics, Gynecology and

Reproductive Sciences

Section Chief, Maternal Fetal Medicine

Yale School of Medicine

New Haven, Connecticut

Rita S. Schoeny, PhD

Senior Science Advisor

U.S. Environmental Protection Agency (retired)

Consultant in Risk Assessment and Science Policy

Rita Schoeny LLC

Washington, District of Columbia

FDA PARTICIPANTS (Non-Voting)

Peter Stein, MD

Director

Office of New Drugs (OND), CDER, FDA

John Farley, MD, MPH

Director

Office of Infectious Diseases (OID)

OND, CDER, FDA

Debra Birnkrant, MD

Director

Division of Antivirals (DAV)

OID, OND, CDER, FDA

Robert H. Heflich, PhD

Director

Division of Genetic and Molecular Toxicology

National Center for Toxicological Research

Office of the Chief Scientist

Office of the Commissioner, FDA

Patrick R. Harrington, PhD

Senior Clinical Virology Reviewer

DAV, OID, OND, CDER, FDA

Aimee Hodowanec, MD

Senior Medical Officer

DAV, OID, OND, CDER, FDA

Mark Seaton, PhD, DABT

CAPT, U.S. Public Health Service

Research Officer

Division of Pharmacology/Toxicology-Infectious Diseases

OID, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

DR. BADEN: Good morning and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email and phone number are currently displayed.

My name is Lindsey Baden, and I will be chairing this meeting. I will now call the November 30, 2021 Antimicrobial Drugs Advisory Committee to order. Dr. Joyce Yu is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. YU: Good morning. My name is Joyce Yu, and I am the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Baden?

DR. BADEN: Dr. Lindsey Baden. I'm an infectious diseases physician and investigator at Brigham and Women's Hospital, Dana-Farber Cancer Institute, Harvard Medical School in Boston, Massachusetts.

DR. YU: Dr. Burgess?

CAPT BURGESS: I'm Timothy Burgess. I'm an adult infectious disease physician and a research program director and faculty member at the Hebert School of Medicine at Uniformed Services University, U.S. Department of Defense, Bethesda, Maryland.

DR. YU: Thank you.

Dr. Chandra?

DR. CHANDRA: Hello?

DR. YU: Yes, we can hear you.

DR. CHANDRA: I am Dr. Richa Chandra. I am clinical development head for Communicable Diseases at Novartis Pharmaceuticals, and I am representing the pharmaceutical industry on this advisory committee, and I'm a non-voting member. Thank you.

DR. YU: Dr. Green?

DR. GREEN: Hi. I'm Michael Green. I'm a pediatric infectious disease physician and research investigator at the UPMC Children's Hospital Pittsburgh and the University of Pittsburgh School of Medicine. Thank you.

DR. YU: Dr. Hardy?

DR. HARDY: Good morning. My name is David Hardy. I'm an adult infectious disease trained physician, and I'm a clinical investigator at the Charles Drew University School of Medicine and Science in Los Angeles, California.

DR. YU: Dr. Hunsberger?

DR. HUNSBERGER: Good morning. I'm Sally Hunsberger. I'm a biostatistician at the National Allergy and Infectious Disease Institute, NIH. Thank you.

DR. YU: Dr. Le?

DR. LE: Good morning. My name is Jennifer Le. I am professor at the University of California San Diego in California. My expertise is clinical pharmacy, pharmacology, and pediatric infectious diseases.

DR. YU: Dr. Murphy?

(No response.)

DR. YU: Dr. Murphy, you may be muted on Adobe Connect.

DR. MURPHY: Good morning. My name is Dr. Richard Murphy. I'm an infectious disease physician and researcher at the VA Medical Center in White River Junction, Vermont.

DR. YU: Dr. Perez?

DR. PEREZ: Good morning. I am Federico Perez. I'm a physician in infectious diseases at the Cleveland VA Medical Center and Case Western Reserve University in Cleveland, Ohio.

DR. YU: Dr. Siberry?

DR. SIBERRY: Good morning. This is George Siberry. I'm a pediatric infectious diseases physician and medical officer at the Office of HIV/AIDS at USAID in Washington, DC.

DR. YU: Dr. Swaminathan?

DR. SWAMINATHAN: I'm Sankar Swaminathan. I'm an infectious diseases physician and professor and chief of the ID division at University of Utah

School of Medicine. I'm a herpes virologist at university in Salt Lake City, Utah.

DR. YU: Dr. Walker?

DR. WALKER: Good morning. I'm Dr. Roblena Walker, research scientist for EMAGAHA, INC., located in Atlanta, Georgia, and I also serve as the consumer representative.

DR. YU: Dr. Weina?

DR. WEINA: Good morning. I'm Peter Weina. I'm an adult infectious disease physician and the director of the Office of Research Protections at the Defense Health Agency in Washington, DC.

DR. YU: Thank you.

Dr. Coffin?

DR. COFFIN: Good morning. I'm John Coffin. I run the Department of Molecular Biology and Microbiology at Tufts Medical School in Boston. I specialize in retroviruses and fundamental virology, and particularly focused on HIV evolution and drug resistance.

DR. YU: Dr. Cragan?

DR. CRAGAN: Hi. I'm Jan Cragan. I'm a

pediatrician in the Birth Defects Monitoring and Research branch in the National Center on Birth Defects and Developmental Disabilities at CDC in Atlanta, Georgia.

DR. YU: Dr. Dublin?

DR. DUBLIN: Good morning. I'm Dr. Sasha Dublin from Kaiser Permanente Washington in Seattle, Washington. I'm trained as a general internal medicine physician, and I'm a pharmacoepidemiologist. My work focuses on using electronic health records to understand the safety of medications and vulnerable populations, including pregnant women.

DR. YU: Dr. Eastmond?

DR. EASTMOND: Good morning. I'm Dave Eastmond. I'm a professor emeritus and genetic toxicologist at the University of California, Riverside.

DR. YU: Dr. Fuller?

DR. FULLER: Good morning. I'm Dr. Oveta Fuller. I'm a virologist at the University of Michigan Medical School and a member of the African

Studies Center. In microbiology and immunology, I studied viruses and now do community implementation science.

DR. YU: Ms. Gillespie?

MS. GILLESPIE: Hi. My name is Terry Gillespie. I'm an 18-year lung cancer survivor, and I'm a patient representative in Illinois.

DR. YU: Dr. Hildreth?

DR. HILDRETH: Good morning. I'm James Hildreth. I'm the president and chief executive officer of Meharry Medical College. I'm also a professor of internal medicine. For many years, I was professor of pharmacology at Johns Hopkins School of Medicine. Thank you.

DR. YU: Dr. Horton?

DR. HORTON: Good morning. I'm Daniel Horton, pediatric rheumatology physician and pharmacoepidemiologist from Rutgers Robert Wood Johnson Medical School in New Brunswick, New Jersey.

DR. YU: Dr. Poirier?

DR. POIRIER: Good morning. I'm Miriam

Poirier. I am scientist emeritus from the National Cancer Institute. For the last 20 years of my career, I've worked on the nucleoside reverse transcriptase inhibitors and nucleoside analogs used for HIV.

DR. YU: Dr. Reddy?

DR. REDDY: Good morning. I'm Uma Reddy. I'm a maternal-fetal medicine physician and clinical researcher, professor of OB-GYN at Yale School of Medicine.

DR. YU: And Dr. Schoeny?

DR. SCHOENY: Hi. This is Rita Schoeny. I'm currently an independent consultant on risk assessment in humans and science policy. I was at U.S. EPA for 30 years, working in the area of human health risk assessment.

DR. YU: Thank you.

We'll now move on to our FDA participants, starting with Dr. Stein.

DR. STEIN: Peter Stein, director of the Office of New Drugs, CDER.

DR. YU: Dr. Farley?

DR. FARLEY: Good morning. John Farley, director of the Office of Infectious Diseases in the Office of New Drugs, CDER, FDA.

DR. YU: Dr. Birnkrant?

DR. BIRNKRANT: Good morning. Debbie Birnkrant. I'm the director of the Division of Antivirals, CDER, FDA.

DR. YU: Dr. Heflich?

DR. HEFLICH: Hello. I'm Robert Heflich. I'm the director of the Division of Genetic and Molecular Toxicology at FDA's National Center for Toxicological Research.

DR. YU: Thank you.

Dr. Harrington?

DR. HARRINGTON: Good morning. I'm Patrick Harrington. I'm a senior clinical virology reviewer in the Division of Antivirals in CDER, FDA.

DR. YU: Dr. Hodowanec?

DR. HODOWANEC: Good morning. I'm Aimee Hodowanec. I'm a senior medical officer in the Division of Antivirals at CDER, FDA.

DR. YU: And Dr. Seaton?

DR. SEATON: Good morning. I'm Mark Seaton, pharmacology/toxicology reviewer in the Division of Pharmacology/Toxicology for Infectious Diseases, FDA, CDER.

DR. YU: Thank you.

Back to you, Dr. Baden.

DR. BADEN: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic

at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Back to you, Dr. Yu.

Conflict of Interest Statement

DR. YU: Thank you. I will now read the Conflict of Interest Statement for the meeting.

The Food and Drug Administration, FDA, is convening today's meeting of the Antimicrobial Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of

this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves the discussion of Emergency Use Authorization, EUA, 000108, submitted by Merck & Company, Incorporated, for emergency use of molnupiravir oral capsules for treatment of mild to moderate COVID-19 in adults who are at risk for progressing to severe COVID-19 and/or hospitalization.

This is a particular matters meeting during which specific matters related to Merck's EUA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in

connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Rita Chandra is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Chandra's role at this meeting is to represent industry in general and not any particular company. Dr. Chandra is employed by Novartis Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial

relationships that they may have with the firm at issue. Thank you.

DR. BADEN: Thank you, Dr. Yu.

We will proceed with the FDA introductory remarks from Dr. Farley.

Dr. Farley?

FDA Introductory Remarks – John Farley

DR. FARLEY: Good morning. Molnupiravir is an oral prodrug of the antiviral ribonucleoside analog N-hydroxycytidine. Molnupiravir inhibits viral replication by causing an accumulation of errors in the viral genome, leading to inhibition of replication.

The sponsor, Merck & Company, Incorporated, has submitted a request for emergency use authorization of molnupiravir. The emergency use currently under consideration is treatment of mild to moderate COVID-19 in adults with a positive result of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death. The proposed oral dosage regimen is 800 milligrams,

4 200-milligram capsules every 12 hours for 5 days.

The FDA Emergency Use Authorization authority to authorize an unapproved product, or unapproved uses of an approved product for emergency use, exists during a public health emergency after declaration by the Secretary of the Department of Health and Human Services. The Secretary has determined that a public health emergency exists that involves the virus, SARS-CoV-2, that causes COVID-19, and declared that the circumstances exist, justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic. Based on this declaration, FDA may issue an EUA after determining statutory requirements are met.

The requirements for an EUA under statute are as follows. SARS-CoV-2, the biological agent referred to in the EUA declaration by the secretary, can cause a serious or life-threatening disease or condition. Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available,

it is reasonable to believe that the product may be effective in treating a serious or life-threatening disease or condition that can be caused by SARS-CoV-2.

In addition, the known and potential benefits of the product when used to treat the identified serious or life-threatening disease or condition outweigh the known and potential risks of the product, and there is no adequate FDA-approved and available alternative to the product for treating the disease or condition.

There are certain considerations with respect to an EUA. FDA's authorization of a medical product under EUA is not the same as the agency's approval or licensure of a product. Those statutory requirements are different and include substantial evidence of effectiveness from adequate and well-controlled trials, among other requirements.

For an EUA, the agency authorizes a healthcare provider fact sheet and patient fact sheet. These are similar to prescribing

information and patient labeling or a medication guide for approved products. The authorized use statement included in the healthcare provider fact sheet and the letter of authorization issued to the EUA sponsor specifies the patient population and clinical condition for which the product is authorized.

As part of its authorization, FDA will establish, to the extent practicable, conditions in the EUA that it finds necessary to protect the public health. FDA may establish requirements for healthcare providers or the sponsor, such as requiring in the letter of authorization that the sponsor collect and report certain data.

FDA will periodically review the circumstances and appropriateness of the EUA. FDA's review may result in revisions to the authorization, including the authorized fact sheet or revocation of the EUA; for example, if the criteria for an EUA are no longer met.

There are no FDA-approved therapies for the treatment of mild to moderate COVID-19, however,

three anti-SARS-CoV-2 monoclonal antibody regimens administered intravenously, or for one product with a subcutaneous administration option, are currently authorized with a similar authorization as that under discussion for molnupiravir. These include casirivimab and imdevimab administered together, bamlanivimab and etesevimab administered together, and sotrovimab.

This is an example of an authorized use statement based on the healthcare provider fact sheet for the anti-SARS-CoV-2 monoclonal antibody products. We are presenting this as an example so that the advisory committee will have a point of reference as they opine on the appropriate patient population for this authorization. Note that there is additional information providing criteria for identifying high-risk individuals, which we will present as an example during the FDA presentation later this morning.

The agency has identified several review issues which will be discussed today. These are issues which are important to consider as one seeks

to ensure that the known and potential benefits outweigh the known and potential risks. The review issues include the patient selection for authorized use; bone/cartilage formation-related findings; reproductive toxicology findings; mutagenicity; and the effect of molnupiravir on SARS-CoV-2 spike protein sequences in clinical trials.

The agency looks forward to the committee's consideration of these issues, the appropriate authorized population, the adequacy of proposed risk mitigation strategies, and the overall benefit-risk assessment.

Thank you very much, Dr. Baden.

DR. BADEN: Thank you, Dr. Farley.

We will now move to the sponsor's presentations.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships they may have with the sponsor such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Merck's presentations. I will pass the floor to Dr. Curtis to introduce and guide us through the sponsor's presentations.

Sponsor Presentation – Sean Curtis

DR. CURTIS: Thank you, Dr. Baden.

Good morning. My name is Sean Curtis. I

lead Merck's Global Regulatory Affairs and Clinical Safety organization. On behalf of Merck and Ridgeback Biotherapeutics, I'd like to thank the FDA and the Antimicrobial Drugs Advisory Committee for the opportunity to discuss our Emergency Use Authorization application for molnupiravir.

COVID-19, caused by the SARS-CoV-2 coronavirus, has spread worldwide since the first case was identified in December of 2019 and the declaration of a public health emergency by the U.S. Secretary of Health and Human Services in February of 2020.

As of mid-November of this year, globally, more than 250 million confirmed cases of SARS-CoV-2 infection and more than 5 million COVID-19-related deaths have been reported. In the United States, over 46 million cases and 750,000 deaths have been reported through the same time period, with approximately 75,000 confirmed cases and over a thousand deaths occurring daily.

A significant unmet medical need exists for safe and effective therapeutics for COVID-19. Many

Americans remain at high risk for infection, severe illness, and death, including unvaccinated individuals, who are comprising the majority of new cases, and vaccinated individuals experiencing breakthrough infections.

The unmet need necessitates treatment options across the spectrum of COVID-19 disease. SARS-CoV-2 replication leads directly to many of the early clinical manifestations of COVID-19. Antivirals that inhibit viral replication and monoclonal antibodies that inhibit viral entry are particularly effective when administered early in the course of illness, and symptoms are mild to moderate, and before the disease progresses to a hyperinflammatory state that characterizes later in more severe stages of disease.

Monoclonal antibodies have demonstrated benefit in patients with mild and moderate disease who are at increased risk for progressing to severe COVID-19 or hospitalization and are currently authorized for use. These therapies have limitations, however. They must be administered

parenterally by qualified healthcare providers who have immediate access to emergency medical services and medications in the event of a severe infusion-related hypersensitivity reaction. Patients must be monitored clinically during and for at least one hour following administration.

In addition, as new variants emerge, some monoclonal antibodies may become less effective due to mutations in the spike protein which may alter the antibody binding site. The antiviral remdesivir requires intravenous administration and is only approved for the treatment of COVID-19 in hospitalized patients. There are currently no adequate approved oral antiviral agents available for the treatment of patients with COVID-19.

Molnupiravir is an oral ribonucleoside analog that inhibits SARS-CoV-2 replication by introducing errors into the viral RNA genome. Molnupiravir, more specifically its active metabolite, has demonstrated potent in vitro activity against SARS-CoV-2 and has a high barrier to the development of resistance. In addition,

molnupiravir retains activity in variance associated with changes in the viral spike protein, such as the Delta variant.

The pivotal phase 3 trial, PROTOCOL 002, enrolled non-hospitalized adults with mild to moderate COVID-19, with at least one risk factor associated with poor outcomes and symptom onset within 5 days. Protocol design and endpoints were agreed to by the FDA prior to trial initiation.

At a planned interim analysis of this trial, molnupiravir was shown to significantly reduce the risk of hospitalization or death by approximately 50 percent. 7.3 percent of patients who received molnupiravir were hospitalized or died through day 29 following randomization compared with 14.1 percent of placebo-treated patients, a clinically meaningful and statistically significant difference.

Through day 29, no deaths were reported in patients who received molnupiravir as compared to 8 deaths in patients who received placebo. At the recommendation of the independent data monitoring

committee, and in consultation with the FDA, further enrollment in the trial was stopped due to the overwhelming efficacy demonstrated, and plans were made to submit the data as part of the already ongoing rolling submission for emergency use authorization.

Results from the all randomized population, which includes those patients enrolled before and after the interim analysis, are now available and support the benefit and the safety profile observed at the interim analysis.

The proposed intended use for molnupiravir is for the treatment of mild to moderate COVID-19 in adults with positive results of a direct SARS-CoV-2 viral test and who are at high-risk for progressing to severe COVID-19, including hospitalization or death.

With regard to dosage administration, the proposed dose is 800 milligrams every 12 hours with or without food for 5 days. Molnupiravir can be administered to patients with acute or chronic renal or hepatic impairment without the need for

dose adjustment. No drug-drug interactions have been identified. Treatment should be initiated within 5 days of symptom onset.

The following consultants are attending today's advisory committee meeting and are available to participate in the discussion; Dr. David Kirkland, independent genetic toxicology consultant from the United Kingdom, and Dr. Anthony Scialli, director of the Reproductive Toxicology Center and a faculty member at George Washington University and Georgetown University, Departments of Obstetrics and Gynecology.

The agenda for the rest of the sponsor presentation consists of mechanism of action by Dr. Daria Hazuda; nonclinical safety by Dr. Kerry Blanchard; clinical efficacy, safety, and benefit-risk by Dr. Nicholas Kartsonis.

I will now turn the presentation over to Dr. Hazuda. Thank you very much.

Sponsor Presentation – Daria Hazuda

DR. HAZUDA: Thank you, Dr. Curtis, and good morning, everyone. My name is Daria Hazuda. I

lead Infectious Disease and Vaccine Discovery Research at Merck. As Dr. Curtis noted, I will now briefly review the mechanism of action of molnupiravir.

Molnupiravir is an oral prodrug which is rapidly metabolized to N-hydroxycytidine, or NHC, by esterases in vivo. NHC is converted to NHC-triphosphate, or NHC-TP, in cells. NHC-triphosphate is a substrate for the SARS-CoV-2 RNA polymerase and is incorporated into the viral RNA genome. The incorporation of NHC results in errors in the CoV-2 RNA. The accumulation of errors impacts the ability of SARS-CoV-2 to replicate in cell culture models, animal models, and in infected patients.

NHC and NHC-triphosphate can adopt either of two different forms, the oxime and the hydroxylamine form, which behave either like UTP or CTP, respectively. The interconversion between these two forms misdirects the viral RNA polymerase to incorporate either guanosine or adenosine into the viral RNA. This results in the introduction of

transition errors. Transition errors are defined as the replacement of one purine for another or one pyrimidine for another, as listed here. NHC does not lead to transversion errors or to nucleotide insertions or deletions.

The accumulation of improper substitutions impairs viral replication, resulting in fewer viruses and viruses which are also less infectious. The antiviral activity and mechanism of NHC has been demonstrated both in vitro and in vivo.

In cell culture and in animal models, NHC is active against multiple RNA viruses, including SARS-CoV-2, CoV-2 variants of concern, as well as other coronaviruses. Note that the antiviral activity is similar across CoV-2 variants of concern, including, alpha, beta, gamma, delta, lambda, as well as mu. Given the sequence conservation of the polymerase, it is anticipated that NHC will have similar activity against any new variants.

The conservation of the activity of NHC across coronaviruses is consistent with the

conserved nature of the SARS-CoV-2 RNA polymerase and suggests a favorable resistance profile, which is consistent with the clinical experience to date. A high barrier to the development of resistance has been demonstrated in cell culture for a number of RNA viruses, including influenza, Venezuelan equine encephalitis virus, as well as coronaviruses, including MHV and MERS.

Consistent with the mechanism of action that is selective incorporation into viral RNA, NHC has no activity against DNA viruses or viruses which use dNTPs as substrates such as HIV. In cell culture models of coronavirus infection, the antiviral activity of NHC is also consistent with the mechanism of action as described. In the presence of NHC, errors are shown to accumulate in the coronavirus genome. Fewer viruses are produced with a greater overall impact on the total number of infectious viruses.

In addition, the effect of NHC on infectious virus titer is proportional to the increase in error rate. For example, in this particular study,

a 6-fold increase in the error rate resulted in a greater than 5-log decrease in infectious virus titer.

These observations have been reproduced in animal models of SARS-CoV-2 infection. For example, studies in hamster, as shown here, have shown robust antiviral activity against several CoV-2 variants of concern. Treatment of SARS-CoV-2 infected hamsters with molnupiravir results in a dose-dependent increase in the number of transition errors, which is consistent with the mechanism of action of NHC.

This increase in the number of transition errors is associated with a dramatic decrease in infectious virus titers in the lungs, and the impact of molnupiravir on infectious virus titer is greater than the impact observed on total viral RNA.

The clinical experience with molnupiravir is also consistent with these preclinical data and the mechanism of action. In placebo- and molnupiravir-treated patients, we have analyzed

changes from the baseline virus sequence at day 5. Consistent with the mechanism of action of NHC, there was specifically an increase in transition errors observed, which is as expected; whereas transversions and deletion errors were similar in both the placebo- and molnupiravir-treated groups.

Importantly, these transition errors were randomly distributed throughout the viral RNA with no evidence of selection bias in any of the replicase genes or in spike. Finally, the average number of errors observed for SARS-CoV-2 RNA genome exceeded the threshold, which has been shown to substantially impact production of infectious virus.

We looked in greater detail, in particular, at substitutions in spike. This table lists all amino acid changes that were observed in the interim analysis of our phase 3 study. Treatment-emergent changes in spike were detected in both the placebo- and in molnupiravir-treated patients. All spike substitutions detected in this phase 3 study our present in currently circulating

strains.

Most treatment-emergent changes in spike resulted from transversions and other mutations, and therefore not a direct consequence of the mechanism of action of NHC. Importantly, molnupiravir treatment led to a more rapid decline in infectious virus. No infectious virus was recovered from molnupiravir-treated subjects at the end of treatment on day 5, decreasing the likelihood that any such variant would be transmitted.

To summarize, molnupiravir is an oral prodrug which is rapidly converted to NHC. NHC-triphosphate is a substrate for the SARS-CoV-2 RNA polymerase. Incorporation of NHC by the SARS-CoV-2 RNA polymerase introduces transition errors into the SARS-CoV-2 viral RNA. Accumulation of errors in the viral RNA impacts SARS-CoV-2 replication, resulting in fewer viruses and viruses which are less infectious.

Molnupiravir and NHC are active against SARS-CoV-2 variants of concern in vitro and in

animal models. In patients, molnupiravir treatment resulted in a random distribution of transition errors in the SARS-CoV-2 viral RNA with no evidence for an increased rate of transition errors at any specific position or gene, including replicase and spike.

Now I will turn it over to Dr. Kerry Blanchard, who will discuss the preclinical safety.

Sponsor Presentation – Kerry Blanchard

DR. BLANCHARD: Thank you, Daria.

My name is Kerry Blanchard, and I'm the head of Preclinical Development at Merck Research Labs. I'm here to provide you with an overview of our nonclinical safety program and the key findings to consider.

As you can see from this slide, we conducted a comprehensive nonclinical safety program, which followed applicable regulatory guidelines. This included not only a standard battery of genotoxicity studies, but also additional in vivo mutagenicity studies, repeat-dose studies that extended beyond clinical dosing, and a

comprehensive development and reproductive toxicology program. These data collectively support the short-term use of molnupiravir in the treatment of COVID-19 adults.

I'll now go into more detail on the four key nonclinical findings identified and addressed during this nonclinical safety program. First I'll describe the comprehensive genotoxicity assessment; then I'll go through a dog hematopoietic finding; next I'll go through an effect on the bone growth plate of rapidly growing rats; and finally I'll end with our development and reproductive toxicology assessment.

The first I'd like to draw your attention to is our genotoxicity assessment, which identifies in vitro mutagenicity and why we describe a low risk of genotoxicity in vivo. When developing any new drug, we follow a progressive testing strategy defined in regulatory guidelines, which starts with an in vitro mutagenicity assay using bacterial cells, otherwise known as the Ames assay, and as many of you know, molnupiravir was positive in the

Ames assay. We also look for chromosomal damage in the micronucleus assay using human TK6 cells, and this was negative.

Now, earlier this year, an external publication by Zhou, et al. also suggested a positive result in vitro. Though we have a number of questions about the conduct and design of the reported assay by Zhou and the biological significance of these data, nevertheless we considered this in vitro result; and in summary, these lab assays identified a potential mutagenicity hazard that needed extensive in vivo follow-up.

In vivo geno-tox tests have the added benefit of including mammalian metabolic processes, which are key components of human risk assessment not present in the in vitro assays. As you can see in this slide, the rat micronucleus study detected no chromosomal damage in erythroid cells from bone marrow. Now, usually we limit this testing to just the in vivo micronucleus, but given the in vitro mutagenicity data, we tested the compound in two

additional in vivo mutation assays, specifically the Pig-a and the Big Blue transgenic rodent.

This slide presents the equivocal Pig-a data, meaning it's not clearly positive nor clearly negative. Pig-a is a gene involved in synthesizing a protein called GPI that tethers other proteins to a cell surface. Mutations in the Pig-a gene prevents this tethering, and we can monitor this as a marker of increased mutagenicity.

The Y-axis identifies the mutation frequency and the X-axis includes the various treatment or control groups, first the historic negative controls, then the increasing molnupiravir doses, and finally the positive control on study. Reticulocytes are on the left and red cells are on the right.

We follow OECD recommended prospective criteria when interpreting data for all our gene-tox studies, and in the blue box on this slide, this summarizes those criteria. As you can see, this study met one of the three criteria. It revealed that some of the molnupiravir-treated

groups were statistically different than the concurrent control. However, it did not achieve a statistical trend analysis, and data stayed within the lab's 95 percent historic confidence intervals. Thus, it cannot be called a clear positive or negative, and the biological relevance of these results remains questionable.

The Pig-a provided a result that we could not use to inform our clinical risk. This was further complicated because we received this information in the summer of 2020 when we were all beginning to realize the true nature of the brood impact of this pandemic, and we needed a reliable perspective on the in vitro mutagenicity finding. Therefore, we decided to further evaluate the biological relevance of these results by repeating the in vivo mutagenicity assessment in a different assay, the transgenic rat, which is the gold standard in vivo mutagenicity assay.

These are the results of the transgenic rat in vivo mutagenicity assay, which provided that clear perspective on risk. The transgenic rodent

model is a more involved in vivo mutation assay to enable, and it requires a longer lead time to execute. But we were convinced that we needed to go to this established assay, as it provided greater confidence in delivering a clear interpretable result.

The Big Blue rat is a transgenic animal with numerous copies of a reporter gene target for mutagenesis present in all cells, and these reporter gene targets are readily isolated after drug treatment and can be measured as an indication of in vivo mutation frequency.

The transgenic rat has a well-established OECD guideline, and this is the gold standard assay, as it has high predictive value towards mutagenic carcinogens in rodents and humans, and it is the assay by which the performance of the Pig-a is defined. And as you can see from this slide, the Big Blue rat assay confirmed a clear lack of in vivo mutagenicity in both rapidly proliferating bone marrow cells, as well as highly metabolic liver cells, so all three prospective criteria were

met for a clear negative.

In summary, while we have an in vitro finding, we see a lack of in vivo genotoxicity or mutagenicity. Based on the totality of data, molnupiravir had low risk for in vivo genotoxicity.

I'll now switch to our hematopoietic finding in dogs, which is not translating to clinical trials. With NHC exposures at and below clinical exposure, we observed hematologic changes in the dog. These findings were mild at 7 days and became severe after 2 weeks, primarily affecting reticulocytes, platelets, and neutrophils. These findings were the result of bone marrow toxicity, and began to rapidly reverse within days following treatment and cessation.

Similar hematologic findings were not observed in other nonclinical species tested, and for perspective, on this slide I've listed the fold above clinical exposure and the duration of those studies for those other species. Now, this was all considered in the careful design of clinical studies, and as you will see later during the

clinical section of this presentation, similar hematologic findings are not observed in humans.

Now I'll switch to describing an effect on bone growth plate in the rat and why this is not relevant to adult humans. We observed effects on the growth plates in rats, and this needs further investigation before administering the drug to pediatrics.

In the 3-month rat study, there was an effect on cartilage associated with decreased bone formation at the growth plate. This was limited to the growth plate area and no effects were seen on cortical bone or articular cartilage. It's important to note that these animals are rapidly growing and basically double their body weight during the study.

These findings required dosing well beyond the 5-day clinical indication and impacting a growth plate tissue bed no longer present in adult humans. However, these growth plates are present in children and important in determining the future length of mature bones, therefore, we started a

juvenile rat study to further characterize this effect, for example, to assess broader tissue beds and reversibility before potential treatment to younger populations.

My last presentation topic is to describe the comprehensive developmental and reproductive toxicology package and to highlight an effect observed in the developing fetus that needs to be considered for women of childbearing potential.

As a visual, I'm presenting this figure so you can see where our studies fit into the reproductive cycle. If you follow the center of this circle, starting at 12 o'clock and go clockwise, you'll see the progression from the beginning of gamete production, all the way through sexual maturity.

On the outside of this circle, I've highlighted the three development and reproductive toxicology studies. Starting with the fertility and early embryonic development studies in rats, we saw no effect on reproductive performance and fertility. We did encounter facts in the

embryo-fetal development study, which focused on the pregnant females and impacts on developing embryos and fetuses. I'll come back to this on the next slide because these effects are worth discussing.

The final study we did was the pre- and postnatal development study in rats where we saw no adverse impact of the drug on pregnant and lactating females and no effects on the development of offspring. Of note, we did detect NHC in nursing pups, indicating lactational transfer occurred during that study.

Let me bring you back to the effect on the developing fetus we observed in rats. This table in the slide indicates data from two rat studies, a preliminary study and the GOP definitive study. When initiating an embryo-fetal assessment, we first conducted a preliminary study to explore appropriate dose selection and tolerability. In this first study, we found the high dose to 1000 mgs per kg per day resulted in NHC exposures 8-fold above clinical studies and exceeded a

maximally tolerated dose; so 1000 mgs per kg per day is a maternally toxic dose level. However, in the surviving animals at this dose is where we observed post-implantation loss and fetal malformations.

At the next dose down of 500 mgs per kg per day, a maternally tolerated dose, we observed reduced fetal weight but did not see post-implantation loss nor malformations at NHC level 3-fold above clinical exposure. When studying molnupiravir in the second species, the rabbit, we saw no post-implantation loss nor malformations at any dose, even with the higher NHC exposures 18-fold that of the clinical exposure.

Let me also point out that although not depicted in this slide, we similarly conducted a preliminary rabbit study at 1000 mgs per kg per day, which also exceeded the maximally tolerated dose and still no signs of post-implantation loss nor malformations.

In summary, the critical finding in these studies were the post-implantation loss and fetal

malformations. This only occurred in the rat at a dose level that produced maternal toxicity and did not recapitulate in a second species, making it difficult to clearly define a direct risk to the fetus. Nevertheless, these findings still need to be considered when administering molnupiravir to women of childbearing potential, and we are not recommending use during pregnancy.

In summary, these are the highlights of a comprehensive, nonclinical safety program, which are used to support the development of molnupiravir. The risk of in vivo genotoxicity is low. The hematopoietic toxicity is not presenting clinically. The growth plate finding is not relevant to adult humans and needs further assessment prior to pediatric use, and we are not recommending use during pregnancy based on the reproductive findings.

I'll now introduce Dr. Nick Kartsonis as the next speaker to address our clinical data.

Sponsor Presentation – Nicholas Kartsonis

DR. KARTSONIS: Good morning. I'm

Dr. Nicholas Kartsonis, and I oversee the Infectious Disease and Vaccine Clinical Research departments at Merck Research Laboratories. For the remainder of this presentation, I'm planning to discuss the efficacy and safety profile of molnupiravir as demonstrated in our clinical development program.

A clinical development plan for molnupiravir was designed to identify a safe and effective dose, and then to formally evaluate the safety and efficacy of that selected dose. To this end, the clinical development program includes six clinical trials: one phase 1 study, three phase 2 studies, and two phase 2/3 studies. Let me take a moment to introduce these.

The phase 1 study, PROTOCOL 004, which was conducted by our partner Ridgeback Biopharmaceutics, was a single and multiple ascending-dose trial in healthy volunteers, which explored doses up to 1600 milligrams as a single dose and 800 milligrams twice daily every 12 hours for 5 and a half days. One phase 2 study, PROTOCOL

006, which was also conducted by Ridgeback, was performed in outpatients with COVID-19. That trial is now complete. There are two ongoing phase 2 studies, one in inpatients run by Ridgeback, known as PROTOCOL 007, and the other in outpatients that's being run in the United Kingdom under the AGILE platform known as PROTOCOL 005.

Finally, Merck conducted two phase 2/3 studies, PROTOCOL 001 in hospitalized inpatients, also known as the MOVe-IN study, and PROTOCOL 002 in non-hospitalized outpatients with mild to moderate COVID-19, also known as the MOVe-OUT study. Most of the data I will show today comes from PROTOCOL 002, the large phase 2/3 outpatient trial.

The early preclinical and clinical work defined the key pharmacokinetic, or PK, properties of molnupiravir, which are now well understood. Molnupiravir is a prodrug that is rapidly and completely absorbed and then immediately cleaved to form the nucleoside and hydroxycytidine, or NHC, which circulates in the plasma. And as you heard

from Dr. Hazuda, NHC is then taken up into cells and phosphorylated to the active form, NHC-triphosphate. NHC is then eliminated by metabolism to either uridine or cytidine.

As molnupiravir is cleared through the normal endogenous pyrimidine metabolic processes, no drug-drug interactions are expected, and the presence of renal and hepatic impairment are not anticipated to affect the PK of NHC.

The PK of NHC was characterized in the single phase 1 study, PROTOCOL 004, and in the various phase 2 studies. NHC increases dose proportionally with little accumulation, limited renal elimination, and no meaningful effect of food on the PK. Demographic factors, included the presence of COVID-19 19 infection, had less than a 2-fold effect on the PK. Hence, molnupiravir is well suited to serve as an oral option to treat COVID-19.

Both of the two phase 2/3 studies conducted by Merck, Protocols 001 and 002, were designed in two parts. First, the phase 2 dose ranging part

which enrolled approximately 300 participants and studied 200, 400, and 800 milligrams of molnupiravir given every 12 hours for 5 days versus placebo, this was used to inform the dose selection and study design of the phase 3 component.

Following phase 2, a final dose -- as you'll see in here, 800 milligrams -- was selected that was taken into the larger phase 3 part of the outpatient study, which was intended to independently demonstrate the efficacy and safety of that final selected dose; but first let's discuss the phase 2 design and results.

The phase 2 portion of the outpatient study, PROTOCOL 002, enrolled adults with confirmed mild or moderate COVID-19 who had less than 7 days of symptoms at the time of enrollment. Participants with mild disease had to have a risk factor for progression to severe COVID, but risk factors were not required for those with moderate COVID.

The study evaluated 3 doses of molnupiravir versus placebo to facilitate the dose selection for the phase 3 portion. The primary endpoint was

hospitalization or death through day 29, but additional virological markers were assessed to assist in the dose selection. The study was conducted broadly, including here in the United States.

Incidentally, the sister phase 2/3 inpatient study, PROTOCOL 001, enrolled adults who were hospitalized, mostly with moderate or severe COVID-19 infection and who had less than 10 days of symptoms at the time of enrollment. The study was identically designed in terms of the study therapy groups and sample size as it was for PROTOCOL 002. In PROTOCOL 001, however, the primary endpoint was time to sustained recovery, which is defined as either not being hospitalized or being hospitalized but not requiring oxygen or medical care.

The decision on which dose to bring into phase 3 was based on virologic, clinical, and PK data from the various phase 1 and phase 2 studies. In the next few slides, I will be showing the key results that supported the choice of the 800-milligram dose.

Let's start with the virological markers. The virologic data included viral RNA reduction after treatment, infectivity assays, and viral substitution analyses. On this slide we're shown the viral RNA reduction across the 4 doses in the phase 2 portion of PROTOCOL 001 and 002 separated out by the time of symptom onset. And as you might anticipate, the viral load kinetics were impacted by the time from symptom onset, with those who were treated within 5 days, shown on the left, having the largest viral load decline.

As per the natural course of COVID-19 infection, viral load reductions were observed across time, across all groups, including placebo; yet, the 800-milligram dose, shown by the solid dark green line, led to the largest viral load reduction in those who were treated within 5 days. Now, as shown on the right in those treated more than 5 days after symptom onset, the overall decline in viral RNA was lower across all groups, and no evident dose effect was seen with molnupiravir.

In addition to reduction in viral load, treatment with molnupiravir in patients with COVID-19 leads to a rapid decline in infectious virus, a finding also previously described in animal models. This was best evaluated in the phase 2 Ridgeback outpatient study, PROTOCOL 006, and at day 3 in PROTOCOL 006, the percentage of participants with infectious virus was lower in the molnupiravir 800-milligram group relative to placebo.

No infectious virus was recovered at day 5 with either the 400-milligram or the 800-milligram dose of molnupiravir. Similar results are seen in the infectivity assessments performed in the phase 2 portion of the Merck outpatient trial, PROTOCOL 002.

In both PROTOCOL 001 and 002, we also collected virus from nasal swabs at baseline and during treatment and performed next-generation sequencing analyses for the frequency of substitutions in the SARS-CoV-2 genome.

In the outpatient PROTOCOL 002 study, a

dose-response relationship between the molnupiravir dose and a number of substitutions in the SARS-CoV-2 genome were observed at the end of treatment on day 5. The most substitutions were seen at the 800-milligram dose.

Please note the log scale on the Y-axis, as the difference from baseline in the molnupiravir dose group is substantial. These clinical data strongly support the mechanism of action of molnupiravir, whereby the drug induces a large number of viral errors in the SARS-CoV-2 genome, ultimately leading to a virus incapable of further replication.

Now let's turn to the clinical outcomes from the phase 2 program. An assessment of clinical effect was limited in the phase 2 portion of the trial, PROTOCOL 002, given the small sample size and the small number of primary endpoint events. That said, numerically fewer participants in the molnupiravir group versus placebo were hospitalized or died through day 29, especially in those who initiated treatment within 5 days of symptom onset

and in the presence of risk factors for disease progression.

Certain risks factors, such as age over 60 years, demonstrated an even more pronounced effect. In this study, only one death occurred, and it was on placebo. Finally, exposure-response analyses were performed on the virology and clinical data from the phase 2 studies, and as noted in the background document, these analyses, along with the favorable safety profile at all doses in phase 2, supported the 800-milligram dose. Taken altogether, Merck selected 800 milligrams every 12 hours for 5 days as the molnupiravir dose and duration for the phase 3 portion of PROTOCOL 002.

Given the phase 2 results, we modified our phase 3 plans for PROTOCOL 002 to focus on at-risk outpatients who are early in the course of their disease. Those key modifications are shown in red font on this slide; first, the limited recruitment to those who had symptoms within 5 days of randomization. In addition, all participants, both

those with mild or moderate disease, had to be at increased risk of progression to severe disease. Samples of risk are shown on this slide.

As in the phase 2 portion, we did not include SARS-CoV-2 vaccinated individuals in order to be able to enrich for the primary endpoint rapidly to evaluate the benefit of molnupiravir. The sample size was set at 1550 to ensure a proper assessment of both efficacy and safety.

Randomization was stratified by the time from symptom onset less than or equal to 3 days versus 4 to 5 days. The selected phase 3 molnupiravir dose was 800 milligrams every 12 hours for 5 days. Participants were randomized 1 to 1 to receive either molnupiravir or placebo. Finally, it should be noted that we stopped recruitment in the hospitalized study PROTOCOL 001, as no treatment effect was seen at the end of the phase 2 portion of that trial; so going forward, all the data I will show you comes from the phase 3 portion of PROTOCOL 002, our outpatient trial.

The primary endpoint for the phase 3 portion

of PROTOCOL 002 was a clinically relevant composite one, the percentage of participants who are hospitalized or died through day 29. One of the two secondary endpoints focused on either the improvement or progression of 15 different signs and symptoms through day 29. The other secondary endpoint focused on responses through day 29 on the WHO ordinal scale, an 11-point scale that measures COVID-19 severity. This same scale has been routinely used for the treatment trials of COVID-19.

All analyses were conducted using a modified intention-to-treat or mITT analysis, which included all participants who received study therapy and were not hospitalized prior to the onset of this therapy. Interim analysis was predefined to be conducted when 775 participants, or 50 percent of the plan 3 enrollment, had reached the day 29 time point. The interim analysis evaluated the potential for an early efficacy signal, but it also evaluated for the potential of futility. We controlled the type 1 error at a one-sided alpha of

0.025, and a criterion for early efficacy was set at a p-value of less than 0.0092.

As we will see in the coming slide, the external data monitoring committee, or eDMC, recommended stopping enrollment early following this interim analysis, as the test for statistical significance was met, thereby demonstrating superior efficacy of molnupiravir. Now, at that time, a total of 1433 of the 1550 intended participants, or 92 percent of the protocol defined sample size, had been randomized into the trial.

Now, before I walk through the phase 3 data, I need to inform the committee that I'll be showing the data from both the interim analysis population, which was the definitive assessment when the statistical criterion for early efficacy was met, as well as the all randomized population, which support the interim analysis.

Importantly, it's the data from the first 775 participants included in the interim analysis that led to the early stopping of the trial by the eDMC and the basis for the EUA submission.

The study began recruitment in May of this year. The last participant included in the interim analysis was enrolled in early August, and they completed their day 29 visit in September. In the face of the recommendation to halt recruitment, the last participant was enrolled October 2nd, the day we announced the trial's early termination, and their last visit was in early November.

Approximately 20 percent of the subjects were still in the day 29 efficacy period at the time of that announcement, and as the database from the all available -- hereafter referred to as the all randomized population -- of the 1433 participants only became unblinded to us in the last 10 days, the backgrounder for this meeting was focused on the interim analysis. However, an addendum was written with the data from the all randomized population.

I'll start by sharing important demographic data and baseline characteristics. As you can see here, the study was balanced in terms of gender with slightly more females enrolled in the trial.

The participants' age ranged from 18 to 88 years with a mean of approximately 44 years and a median of 43 years. Overall, 35 percent of the participants were over the age of 50 years.

Two groups were also balanced in terms of race and ethnicity. Individuals in this trial were screened in over 100 sites, in 20 countries, on 5 continents. Enrollment was highest in the countries of Russia and Colombia, followed by South Africa and Mexico. To this end, more than 43 percent of the participants were non-white and half were Hispanic or Latino.

As the study required participants not to be vaccinated against SARS-CoV-2, it's not surprising that most enrollment for the phase 3 portion of this trial took part outside of the United States despite our best effort to include a large number of trial centers in the United States. In total, approximately 6 percent of the participants were enrolled in the U.S. in the phase 3 portion compared to about 40 percent during the phase 2 portion.

Baseline characteristics pertaining to COVID-19 were similar across the two groups. Overall, 52 percent of the participants were enrolled more than 3 days after COVID-19 symptom onset. Obesity was the most common risk factor for severe illness from COVID-19, but older age, defined as being over 60 years of age, diabetes mellitus, and serious heart conditions were risk factors in at least 10 percent of the participants.

In this trial, 45 percent had moderate disease at study entry. The most common symptoms at entry, each identified in approximately two-thirds of the participants, or at least two-thirds of the participants, included cough, fatigue, headache, and muscle ache.

Baseline SARS-CoV-2 virological status was collected from all participants, and as of November 19th, we have sequence data from approximately 55 percent of the participants. These data confirm the most common viral variants were the delta, mu, and gamma strains. Together, these three variants comprise nearly 90 percent of

the available population.

Detectable virus, defined as an RNA titer of greater than or equal to 500 copies per mL, was confirmed in 86 percent of the participants. And finally, the study did not prohibit the inclusion of individuals if they had a prior SARS-CoV-2 infection, and about 20 percent of the participants had a positive SARS-CoV-2 baseline antibody status, which is based on the assessment of the presence of antibodies against the nucleocapsid protein. Overall, these characteristics are generally balanced across the two groups.

Nearly all randomized participants were assessed for both efficacy and safety. In the interim analysis population, of the 775 participants randomized, more than 98 percent were included in the efficacy analysis for the primary efficacy endpoint; and of those 775, 10 were excluded because they weren't treated and another three were already hospitalized at the time of initiation study therapy. So you end up with 762 participants, 385 on molnupiravir and 377 on

placebo, who are counted in the efficacy mITT population. Finally, as shown below, nearly all randomized participants completed study medication and were followed through the day 29 visit.

Now, in the all randomized population, the disposition of participants showed similar results. Overall, among the 1433 participants recruited in the entire trial, 1411 are included in the safety population and 1408 are counted in the efficacy ITT population.

Here are the compelling results for the primary efficacy endpoint, and we will start first with the interim analysis. Treatment with molnupiravir reduces the risk of hospitalization or death through day 29.

In the study cohort, 7.3 percent of those on molnupiravir were hospitalized or died through day 29 versus 14.1 percent for placebo. This represents a 6.8 percentage point reduction between the two groups, and this difference, which corresponds to an approximately 50 percent reduction, was associated with a significant p-

value of 0.0012. As that number was lower than the 0.0092 criterion defined in the protocol for early efficacy success, the eDMC recommended that further recruitment be stopped.

As we discussed, the primary endpoint is a composite one comprised of both hospitalizations or death. The slide shows the number of participants meeting the composite endpoint for each individual component at the interim analysis. Hospitalization was the predominant reason participants counted towards the primary endpoint.

Death occurred in 8 participants in the interim analysis. Importantly, all eight of those participants who died through day 29 were in the placebo group. That's a difference of 2.1 percentage points and was associated with a nominal p-value of 0.002. All 8 participants who died had been hospitalized before their death, so they're counted in both categories for hospitalization and death.

As we discussed, the primary endpoint is all-cause hospitalizations or deaths through

day 29. Here you can see, on the right side of the figure, the results of a predefined sensitivity analysis of the primary endpoint looking at those hospitalizations or deaths that were considered COVID related by the investigator. The analysis provides consistent results with the primary analysis, with three less events in each group as compared with the primary endpoint. In the molnupiravir group, all three of these hospitalizations were caused by other infections.

Here are the efficacy data from the all randomized population which recently became available. It's important to remind the committee that the formal evaluation of efficacy is considered complete at the planned interim analysis, at which time hypothesis testing of the primary efficacy endpoint was undertaking and statistical criterion for success was met. Hence, the data for the all randomized population are considered important but supportive.

Nevertheless, these are important to consider as we evaluate the full efficacy and the

estimate of efficacy for molnupiravir. The efficacy results from the all randomized population confirm that treatment with molnupiravir reduces the risk of hospitalization or death through day 29. A 3 percentage point difference favoring molnupiravir is observed, which corresponds to a nominal p-value of 0.0218.

This slide shows the corresponding number of participants meeting each of the individual components of the composite endpoint in the all randomized population. Strong survival benefit was maintained for molnupiravir at the day 29 time point. Of the 10 deaths reported, all but one occurred on placebo, a difference of 1.1 percentage points between the two groups. The nominal p-value for the mortality difference is 0.0052.

The one death in the molnupiravir group occurred in an 81-year old participant with underlying metastatic liver cancer, who initially responded to therapy but then died on day 26 following complications of community-acquired bacterial pneumonia.

The sensitivity analysis for COVID-related deaths in the all randomized population are also supported. As shown in the right, there were 3 and 4 participants in the molnupiravir and placebo group, respectively, who were removed because their hospitalizations were not considered COVID related by the investigator.

Now, for the remainder of the efficacy section of this presentation, as well as the safety data to follow, including the discussion of subgroup data, the secondary objectives, and virological assessment, I will focus on the all randomized population.

Overall, the trial enriched for a group at risk of progression to severe disease. What I'm sharing on this bar graph are the rates of the primary endpoint of hospitalization and death at day 29 in the placebo group only for various subgroups. As you can see, a variety of risk factors at baseline predisposed participants to the progress of this endpoint. Particularly, moderate COVID, age over 60 years, and the presence of

diabetes mellitus are associated with the highest rates of hospitalization or death.

Now, when we add in the molnupiravir arm for each of these factors, we can appreciate the noticeable impact of active treatment. It's interesting to note that molnupiravir was not negatively impacted by certain risk factors that one might predict could lead to lower efficacy, such as the presence of moderate COVID, treatment initiation after day 3 of symptom onset, or even the Delta variant. These data speak to the robustness of the efficacy response with molnupiravir.

Another way to look at the subgroup analyses is using a forest plot. This figure displays the risk differences between the two groups. Points to the left of the dotted line favor molnupiravir and points to the right favor placebo. This representation also allows us to look at the efficacy in those groups potentially associated with corresponding lower risk such as younger age, mild COVID-19, and early treatment relative to

symptom onset. All in all, the results of subgroup analyses of the primary endpoint are consistent with the results of the main endpoint. In this slide, we have also included region of trial conduct, and once again, consistent efficacy was observed regardless of geographical location.

Finally, we should note one subgroup, namely the group who was SARS-CoV-2 antibody positive at baseline. The assay used for this antibody testing is a qualitative system that does not discern whether the positive antibody level is indicative of a prior infection or an emerging immune response in the setting of the current infection. That said, those with pre-existing antibodies were at low risk for poor outcomes in both groups. In fact, incidence in the placebo group was a mere 1.5 percent.

Now let's turn our attention to the two secondary efficacy analyses included in PROTOCOL 002, starting with an assessment of self-reported signs and symptoms. We looked at a list of 15 signs and symptoms that were

self-reported daily in a diary by the participants through the course of the study from day 1 through day 29, and as you can see in this forest plot, where the dots to the right show result in favor of molnupiravir, sustained improvement or resolution was more likely for participants treated with molnupiravir for most of their COVID-19 signs and symptoms as compared to placebo.

Now, as noted at the top of the forest plot, these include some that have profound impact on patients with COVID-19, such as fatigue, difficulty breathing, and even loss of smell and loss of taste.

In addition, we looked at the progression or worsening of signs and symptoms. Hence, here the dots on the left of the dotted line show results that favor molnupiravir. And again, as you can see from most signs and symptoms, regression was less likely for the participants treated with molnupiravir. This was particularly notable for cough and loss of smell.

We also look at outcomes by the WHO 11-point

ordinal scale. For those who might be unfamiliar with this scale, a lower number represents a better outcome. Essentially, a 1 score corresponds to asymptomatic disease; a 2 signifies symptomatic outpatient disease without any need for assistance; and a 3 corresponds to outpatient disease but now requiring some assistance. Scores at 4 or higher signify requiring hospitalized care of increasing intensity.

This graph shows those with a WHO score of 3 or greater, and as you can see in this figure, a lower percentage of those for molnupiravir showed worse outcomes on this ordinal scale compared to those who received placebo. The largest difference occurred at days 10 and 15. For instance, when the WHO scores were grouped by category at day 15, the odds of an improved outcome were one and a half times higher following treatment with molnupiravir versus placebo, and that corresponded with a nominal p-value of 0.0065.

Turning to virological parameters, we looked at the mean change in SARS-CoV-2 RNA from baseline.

Recall that 86 percent of all subjects had detectable viral RNA at baseline. Treatment with molnupiravir was associated with a greater decrease in mean SARS-CoV-2 RNA at days 3 and 5 compared to placebo. At days 3 and 5, there's a 0.24 log and 0.33 log reduction, respectively, in the molnupiravir group relative to placebo, and this of course presents a 53 percent relative reduction from molnupiravir compared to placebo.

Differences were seen irrespective of the viral load at baseline, but in those with higher viral load at baseline, that is greater than 10 to the 6 copies per milliliter, the greatest difference is seen at day 5, and in those with lower viral loads, the greatest difference was seen earlier, at day 3.

In summary, a 5-day oral treatment course with molnupiravir in outpatients with mild to moderate COVID-19 treatment led to a significant reduction in the risk of hospitalization or death through day 29 versus 9 of the 10 participants who died through day 29 who were in the placebo group.

Molnupiravir also improved clinical outcomes based on self-reported COVID-19 signs and symptoms. In addition, participants receiving molnupiravir also had better outcomes on the WHO 11-point ordinal scale.

Molnupiravir was also associated with a greater decrease in mean RNA from baseline of the virus as compared with placebo. Finally, the phase 2 results demonstrate molnupiravir reduces the percentage of participants with infectious virus compared with placebo, and that molnupiravir treatment leads to an increase in errors in the viral genome consistent with the proposed mechanism of action. Similar infectivity in viral substitution data from the phase 3 portion of the trial are currently being evaluated and are pending.

Let's now turn our attention to the safety data. This table shows the total exposure to molnupiravir participants. Approximately 1400 individuals have received any dose of molnupiravir in a clinical program and 917 individuals have

received molnupiravir at the proposed dose and duration of 800 milligrams every 12 hours for 5 days. Importantly, this does not include participants in ongoing treatment-blinded studies, including the two ongoing phase 2 studies, PROTOCOL 005 and 007. For the sake of completeness, we will focus on the safety from the all randomized population in PROTOCOL 002 for the upcoming slides.

As for the safety data from PROTOCOL 002, let me first remind you that a total of 1411 participants were randomized and received at least one dose of study therapy in this trial, so that's the number that's counted in the safety analysis.

As you can see in the summary table, the percentage of participants who have had at least one adverse event, or AE, were comparable between the two. Moreover, the incidence of any serious adverse event, an AE leading to discontinuation, or a serious adverse event leading to discontinuation was lower in the molnupiravir group versus placebo.

The difference in death is noteworthy. Importantly, four more participants, all who died after day 29, are included in the safety population but not in the efficacy population. They are included because their AEs leading to death started within the reporting period. Notably, three of these four fatal outcomes were on participants receiving placebo; that a number of deaths that we have are 12 versus 2 in favor of molnupiravir.

This table shows those AEs that occurred in at least one and a half percent of the participants in either group. Not surprisingly, worsening COVID and COVID-19 pneumonia are the most common AEs, so on both of these AEs, the percentage of participants with these events are lower on molnupiravir versus placebo. Other reported AEs, such as diarrhea, nausea, bacterial pneumonia, and an increase in ALT, or alanine aminotransferase, were infrequent and imbalanced between the groups.

I'd like to now turn to adverse events reported as related to study therapy based on the assessment of the study investigators. This table

shows those drug-related AEs in at least 1 percent of participants in the molnupiravir group. You can appreciate that the incidence of specific drug-related AEs are very low and well balanced between the groups.

Another measure to carefully assess is the incidence of serious adverse events or SAES. This table shows those SAEs that occurred in at least 2 participants in either group. Again, the most common SAEs were related to COVID-19 and were actually more common in the placebo arm. There was only one drug-related SAE in the trial, and it also occurred on a participant receiving placebo.

Given the preclinical findings in the toxicology studies in dogs, hematological parameters were closely monitored in the molnupiravir clinical program, including this trial, PROTOCOL 002. As you can see here, no hematological toxicity was observed in participants who received molnupiravir in the phase 3 portion of the trial.

Although not shown, the percentage of

participants with grade 3 or grad 4 lab values for serum chemistry parameters, such as liver function tests, renal function tests, serum electrolytes, and even amylase and lipase, were all low and generally comparable between the groups.

In summary, in PROTOCOL 002, the incidence of adverse events was comparable to placebo and the incidence of any individual event was low. Rates of serious adverse events and deaths were low in recipients of molnupiravir than placebo, and importantly, the hematological toxicity that was seen preclinically in that one species, the dog, has not been seen in people.

Today I focused on the safety results from the all randomized population for more than 1400 participants included in PROTOCOL 002. It should be noted that the unblinded safety results in the other completed trials for the proposed intended use under consideration are generally similar to those shown here. Overall, the totality of the safety database supports molnupiravir for the proposed intended use.

Now I'd like to turn to a discussion of benefit-risk for molnupiravir. Overall, the data reviewed today demonstrates that the benefit-risk profile for molnupiravir is highly favorable and supports the use of the drug for the treatment of COVID-19 in the proposed intended use.

COVID-19 continues to rage in the United States, as well as around the world, despite the rollout of effective vaccines against SARS-CoV-2. The cumulative number of cases we've seen over time are simply staggering. Even now, we're seeing more than 75,000 new cases daily of this infection, and sadly, more than a thousand Americans continue to lose their life every day to this devastating disease.

Our hospitals currently have more than 50,000 Americans struggling with this disease. As we enter the winter months, another surge is imminent, potentially in the setting of emerging new variants of concern. And although monoclonal antibody therapies work and address mild to moderate COVID in the ambulatory setting, these

agents are often not used for a variety of reasons we've highlighted today. We remain in dire need of novel, effective, well-tolerated and conveniently administered therapies to treat COVID-19 in the outpatient community [inaudible].

As we've shown today, molnupiravir is a novel oral therapy for outpatients with COVID-19. Molnupiravir has demonstrated a clinically meaningful reduction in the risk of hospitalization or death in adults with mild to moderate COVID-19 and who have risk factors for progression to severe disease.

In particular, a substantive mortality benefit was seen in favor of molnupiravir. This result was generally consistent across subgroups, including various underlying medical conditions, those treated later in the course of their disease, and viral clade, including the currently circulating variants of concern. Molnupiravir also demonstrated the potential for improvement in patient-reported outcomes for signs and symptoms of COVID-19.

Finally, this novel oral agent can be taken without consideration of food intake, or for concomitant therapies associated with drug-drug interactions, or the need for drug modifications in special patient populations, such as those with renal or hepatic insufficiency. Its high barrier of resistance is also noteworthy considering the unsettling future of a rapidly evolving virus. Altogether, molnupiravir offers an attractive option for use in the outpatient setting.

As you've heard today, the safety profile of molnupiravir has been comprehensively evaluated and supports the proposed intended use. We started with a comprehensive nonclinical assessment, as was described by Dr. Blanchard. Preclinical findings were assessed in a rigorous step-wise approach supporting execution of the phase 3 clinical program. Providing a description of these findings from these evaluations in the patient and provider fact sheet will help inform appropriate clinical use.

The preclinical program was followed by a

robust clinical development program in which approximately 1400 individuals received molnupiravir, including 917 at the proposed dose of 800 milligrams every 12 hours for 5 days. In the pivotal phase 3 trial, PROTOCOL 002, molnupiravir was well tolerated with comparable rates of AE events, or adverse events, relative to placebo. Rates of serious adverse events were lower than placebo, and no new safety signals were identified during any of the clinical trials.

As a testimony to these compelling results, the external data monitoring committee had recommended that the trial be stopped following the interim analysis readout, as they did not believe it was ethical or appropriate for additional patients to be randomized to placebo.

Based on the preclinical evaluation and the lack of clinical experience in certain populations, we propose that molnupiravir is not recommended for use in pregnant or lactating adults. Contraception is recommended for women of childbearing potential while exposed to molnupiravir, yet Merck does not

feel a contraindication in pregnancy is warranted, as there may be scenarios where the benefit of treatment may outweigh the potential risk.

We will initiate a pregnancy surveillance program too closely monitor for pregnancy outcomes in women exposed to molnupiravir during pregnancy and will request that patients or their healthcare providers report these exposures to Merck. Finally, it should be noted that we are also not seeking intended use in pediatric patients at this time. Overall, the totality of the data supports a 5-day treatment course of molnupiravir in the intended adult population.

This concludes our presentation. In closing, the data demonstrate that the benefit-risk for molnupiravir is highly favorable for the proposed intended use. We urge the rapid approval of the Emergency Use Authorization for molnupiravir so that another crucial treatment option can be added to our limited armamentarium in the fight against COVID-19. Thank you for your attention, and I now pass it back to the advisory committee

and Dr. Baden.

DR. BADEN: I would like to thank the applicant for an incredibly clear and comprehensive presentation of the data establishing how this therapy may benefit our community. We will now take a 12-minute break till 10:45, and then we will proceed with the agency's presentations. Please return at 10:45 sharp. Thank you.

(Whereupon, at 10:33 a.m., a recess was taken.)

DR. BADEN: It is now 10:45, and we shall resume the committee meeting. We will now proceed with the FDA presentations, starting with Dr. Hodowanec.

Dr. Hodowanec?

FDA Presentation – Aimee Hodowanec

DR. HODOWANEC: Good morning. My name is Aimee Hodowanec. I am a senior FDA medical officer in the Division of Antivirals, Office of Infectious Diseases in the Center for Drug Evaluation and Research. We will now begin the FDA's presentations on the data submitted in support of

Merck's Emergency Use Authorization request for molnupiravir.

At this time, the proposed authorized use under consideration is for the treatment of mild to moderate COVID-19 in adults with a positive result of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death.

The purpose of this meeting is to seek the committee's assessment of the known and potential benefits and the known and potential risks of molnupiravir for the proposed authorized use. The agency is specifically seeking advice based on the patient population and risk mitigation strategies for a potential authorization.

To inform this discussion, the agency will present its assessment of the available nonclinical and clinical data, followed by a discussion of identified review issues and proposed risk mitigation strategies. The agency asks the advisory committee to consider the mechanism of action, proposed risk mitigation strategies,

existing authorizations for intravenously and subcutaneously administered monoclonal antibodies, and the oral route of administration of molnupiravir in its deliberations.

Over the next hour, the agency will give several presentations. First, Dr. Mark Seaton will provide a summary of the agency's assessment of key nonclinical findings. Next, Dr. Robert Heflich will provide a detailed presentation of the available mutagenicity data. I will then provide a brief overview of the clinical development program, and then Dr. Patrick Harrington will report on clinical virology findings. And last, I will discuss the five review issues that the agency has identified and will describe the proposed patient population and risk mitigation strategies.

I now turn the presentation over to Dr. Mark Seaton.

FDA Presentation – Mark Seaton

DR. SEATON: Thank you Dr. Hodowanec.

As we heard earlier, the nonclinical toxicology findings from studies with molnupiravir

are associated with four general areas of toxicology. Those are bone marrow toxicity, bone and cartilage abnormalities, embryo-fetal developmental toxicity, and mutagenicity. Whereas potential effects on bone marrow cellularity have been monitored in clinical trials, bone effects, reproductive toxicology, and mutagenicity continue to be nonclinical review issues.

I will provide details about bone and cartilage findings and embryo-fetal findings, and Dr. Heflich will discuss the genotoxicity data in the next presentation.

Significant findings in dogs administered molnupiravir for 28 days included decreased bone marrow cellularity leading to severe thrombocytopenia with subsequent hemorrhage in multiple tissues. These effects occurred in NHC exposures less than the mean clinical exposure at the recommended human dose.

Platelet levels in treated dogs tended to show recovery when measured 28 days after dosing was stopped. Bone marrow toxicity is not a

nonclinical review issue, as hematology parameters are being monitored in clinical trials.

In terms of mutagenicity, molnupiravir and NHC were positive for mutagenicity in in vitro Ames tests, but molnupiravir was negative for mutagenicity in a follow-up in vivo study in male transgenic rats. Given the weight of evidence and the 5-day treatment duration with molnupiravir, the risk of mutagenicity is considered to be low. As I said, Dr. Heflich will discuss the genotoxicity data in the next presentation.

Regarding bone and cartilage findings, abnormal growth plate formation of both bone and cartilage was noted in rats following 3 months of daily dosing. Also, incomplete ossification was noted in rabbit fetuses and delayed ossification and skeletal malformations were noted in rat fetuses. As was noted in the previous presentation, the bone and cartilage effects are not thought to be relevant to adults.

In an embryo-fetal development study in rats, developmental findings included reduced fetal

body weight, increased post-implantation loss, and external visceral and skeletal malformations. In rabbits, findings included reduced fetal body weights and incomplete ossification that was possibly test-article related given the bone effects noted previously. I will provide more detailed information about bone and cartilage findings and embryo-fetal development findings in the following slides.

Starting with bone and cartilage findings, molnupiravir was administered in rats once-daily by oral gavage at doses up to 1000 milligram per kilogram for approximately 3 months. The high dose resulted in exposures 9 and 15 times the mean clinical NHC exposures in female and male rats, respectively. At greater than or equal to 500 milligram per kilogram, test-article-related findings included increased growth plate thickness in all high-dose males and/or cartilage changes in all mid-dose and high-dose males and all high-dose females.

There was also altered cartilage of the

trachea in 6 of 10 mid-dose and all high-dose males. The bone and cartilage effects are not thought to be relevant to adults since in humans, growth plates are typically closed at the end of puberty.

Mild to marked increased thickness of the growth plate of the femur and tibia of male rats dosed at 1000 milligram per kilogram was characterized by irregularly widened growth plates involving the zone of hypertrophic chondrocytes and occasional disruption of the growth plate itself.

According to the study pathologist, the changes observed in the bone were indicative of an alteration in the normal progression of hypertrophic chondrocytes towards osteogenesis, resulting in impaired transformation of cartilage into new bone.

Growth plate-related bone and/or cartilage findings were noted at systemic exposures approximately 5-fold higher in males and 9-fold higher in females than the mean clinical NHC exposures at the recommended human dose. There

were no significant findings in a one-month study in rats at similar exposures possibly because animals were 8 to 9 weeks old at the start of dosing compared to 5 weeks old at the start of dosing in the 3-month study.

There were also bone-related findings in rat fetuses from dams dosed with molnupiravir, including skeletal malformations, variations, and delays in ossification at 1000 milligram per kilogram. Systemic exposures of NHC in pregnant rats were approximately 8 times the mean clinical exposure.

When molnupiravir was administered to pregnant rabbits, incomplete ossification was present in more litters at the middle and high dose than in controls. Although the incidence does not appear to increase with dose, this finding is noteworthy, given the effects on bone and cartilage described previously in rats. Systemic exposures in pregnant rabbits at 400 and 750 milligram per kilogram were approximately 7 and 18 times the mean clinical NHC exposure.

Moving to embryo-fetal developmental findings, in a preliminary study, molnupiravir was administered orally to pregnant rats at up to 1000 milligram per kilogram from gestation day 6 to 17. In the pivotal study, molnupiravir was administered up to 500 milligram per kilogram over the same period of gestation.

Developmental toxicities associated with molnupiravir included post-implantation losses, malformations of the eye, kidney, axial skeleton, and rib variations at 1000 milligram per kilogram. That dose resulted in systemic exposures 8 times the NHC exposure at the recommended human dose. Decreased fetal body weights and delayed ossification were noted at 3 times the mean clinical NHC exposure, and there were no developmental toxicities when exposures in pregnant rats were roughly equivalent to clinical exposures.

Maternal toxicities included decreased food consumption and body weight losses, resulting in the early sacrifice of 2 animals at 1000 milligram per kilogram and decreased body weight gain at

500 milligram per kilogram.

With respect to maternal toxicity, decreased body weight gain in females administered 1000 milligram per kilogram dose not appear to account for the malformations noted in fetuses from that group. For example, coronal malformations, including small eye and missing eye, were noted in the litter from a dam with normal body weight gain, whereas no coronal malformations were noted in a litter from a dam that lost body weight.

In an embryo-fetal development study in rabbits, molnupiravir was administered orally to pregnant rabbits at doses up to 750 milligram per kilogram from gestation day 7 to 19. Developmental toxicity included reduced fetal body weights at the high dose. Earlier I mentioned incomplete ossification that was possibly test-article related. Maternal toxicity in rabbits were related to reduced food consumption at the high dose.

To summarize, embryo-fetal effects were seen in rats and rabbits at the exposure multiples listed here. The benefit-risk assessment should

consider these exposure margins while also accounting for the unknown susceptibility of humans to the toxicity findings in nonclinical studies.

In conclusion, bone and cartilage changes, embryo-fetal toxicity, and mutagenicity continue to be review issues. Regarding bone and cartilage, abnormal growth plate formation was noted in rats following 3 months, but not one month, of daily dosing. A study of molnupiravir toxicity in juvenile rats is ongoing and pediatric trials will wait until that study is reviewed.

Finally, embryo-fetal lethality and malformations of the eye, kidney, and axial skeleton in rat fetuses suggest that molnupiravir may cause fetal harm when administered to pregnant individuals.

Thank you for your attention. Our next presentation is Dr. Heflich, who will discuss the genotoxicity data.

FDA Presentation – Robert Heflich

DR. HEFLICH: Thank you, Dr. Seaton.

Good morning, everyone. My name is Bob

Heflich from the FDA's National Center for Toxicological Research. My job is to describe the genotoxicity data on molnupiravir, and this will be the same data presented earlier by Dr. Blanchard. I will try to explain FDA's interpretation of these data as clearly as I can.

As we have been told, mutagenicity is the basis for the antiviral action of molnupiravir. Shown here is how that mutagenicity is targeted to RNA molecules. A concern for the safe use of molnupiravir is whether or not the drug is also mutagenic for the treated patients' DNA. Shown here is one of the possibilities of how that could happen; through conversion of the N4-hydroxycytidine ribonucleotide precursor to deoxyribonucleotide, followed by incorporation into the patient's genomic DNA, resulting in mutation with the possibility that mutation could eventually cause cancer and genetic disease.

Here is a summary of the major genetic toxicology data on molnupiravir. CDER follows the International Council for Harmonization S2(R1)

safety guidelines for testing drugs for mutagenic potential. I have circled the assays that address one of the ICH recommended testing batteries referred to as option 1: Ames test with the prodrug molnupiravir and with the active pharmaceutical ingredient N4-hydroxycytidine; an in vitro micronucleus assay in human lymphoblastoid cells; and an in vivo micronucleus assay in rat bone marrow. Both micronucleus assays were negative, but the Ames tests were positive.

To look at these bacterial gene mutation data a little more closely, the Ames test measures mutations that affect a specific small target, often a single base-pair, and the types of mutations detected are limited. As a result, the panel of tester strains are used that cover different targets and mechanisms of mutation.

Six different tester strains were used in assaying molnupiravir and N4-hydroxycytidine. Molnupiravir did not induce mutations in any of the strains that detect mutation at G:C base pairs, the top 4 strains in this table here, but it was

positive in 2 tester strains that detect base-pair substitution, affecting single A:T base pairs at salmonella strain TA102 and in E. coli strain WP2uvrA. So molnupiravir is Ames positive both with and without exogenous activation by rat liver S9, and it appears to specifically induce base-pair substitutions at A:T in this assay.

This finding was followed up with two in vivo gene mutation assays to evaluate if the positive response in vitro could be seen in vivo. This testing addresses the weight of the evidence determination of risk that is expressed in S2(R1). To quote from the guideline, "Negative results in appropriate in vivo assays, with adequate justification for the endpoints measured and demonstration of exposure, are considered sufficient to demonstrate absence of significant genotoxic risk." In this case, the appropriate follow-up in vivo assay to an Ames positive would be an in vivo gene mutation assay.

I have circled here the two in vivo gene mutation assays that were conducted as follow-up.

Both these assays have gone through an extensive validation process to establish their positive and negative predictive value for identifying in vivo mutagenicity. The first assay I'll cover will be the Pig-a assay.

The Pig-a assay measures gene mutation in the endogenous Pig-a gene, which is necessary for the biosynthesis of glycosylphosphatidylinositol cell-surface anchors, shown in this cartoon of the wild-type cell on the left as these structures protruding from the cell surface, with their associated surface protein shown here as gray circles. Pig-a wild-type cells have these structures, while Pig-a mutant cells, like the cell on the right, do not.

Pig-a wild-type cells can be distinguished from the mutant cells by using fluorescent antibodies to proteins associated with the anchors. Pig-a wild-type cells will fluoresce while Pig-a mutant cells do not, and the two can be distinguished and counted using flow cytometry.

You can see the antibodies recognizing these

GPI-anchored structures on the surface of the wild-type cell in the figure. The assay specifically measures mutations using peripheral blood in two cohorts of erythrocytes: both in mature red blood cells and immature reticulocytes.

Here are the Pig-a data with molnupiravir. Doses were 50, 150, and 500 milligrams per kilogram per day, 500 being the MTD. Dosing was done for 28 consecutive days. A positive control was included in the assay, ethylnitrosourea, a potent in Vivo mutagen. Note that the frequency of both total red blood cell mutants and reticulocyte mutants appears to increase with dose, and some molnupiravir treatments produce statistically significant increases in mutant frequency, marked here with asterisks.

International guidelines recommend evaluating genetic toxicology results using three criteria. By pairwise comparisons to the control, there were significant increases to mutant reticulocytes in red blood cells for those groups, consistent with a positive response.

In evaluation of the data for a trend, the sponsor found no trend using a Cochran-Armitage one-sided linear trend test in comparison of the responses to the distribution of the historic pro-negative control, which is considered a test for biological relevance. All the responses were within the 95 percent confidence limit of the negative control, indicating that none of the responses from dosed rats could be distinguished from the background mutant frequency.

There is a hint of a mutagenic response in this data. There were significant increases, but there were also negative results with the assay. This was concluded by the sponsor as being an equivocal response, neither clearly positive nor clearly negative.

When an equivocal result is found, the usual procedure is to make an attempt at resolving the equivocal to either a positive or negative. In this case, rather than doing anything further with the Pig-a endpoint, the resolution involved performing a second in vivo mutagenicity assay, the

transgenic rodent mutation assay.

Although this choice leaves a loose thread about the Pig-a response, there is logic to switching assays. The TGR assay is recommended specifically for follow-up of an in vitro gene mutation positive in ICH S2(R1), and because of this, it is considered by CDER to be the primary assay for evaluating the in vivo genotoxicity of drugs.

This slide shows schematically how the TGR assay is conducted. The steps involved are in the numbered boxes. The assay uses transgenic rats or mice carrying a bacterial transgene integrated into the DNA of every cell. In the case of molnupiravir, Big Blue rats were used that have a lambda phage cassette as the transgene and the assays used a lambda C2 gene as the reporter of mutation.

The in-life design was similar to that of the Pig-a assay. Treatment was carried out by dosing the animals for 28 consecutive days with the same 3 doses of molnupiravir used for the Pig-a

assay. Following the treatment, the tissues of interest were collected; in this case, 2 tissues -- liver, a metabolically active tissue, and bone marrow -- in which cells continued to divide relatively rapidly during the treatment period to promote mutation fixation were collected. Also, bone marrow is the source of the mutations that were measured in the Pig-a assay. DNA is extracted from the tissues, and the lambda transgenes recovered and packaged into infectious phages, 3 and 4 here. The phages were next plated to generate mutant frequencies for each tissue.

The mutant frequencies in both tissues were mainly between 30 and 40 per 10 to the 6th recovered infectious phage for the vehicle control and all the treatment groups; no apparent increase with dose and no asterisks this time. A positive control with ethylnitrosourea demonstrated the system could detect a mutagenic response should it exist.

Applying the same rules as were used for evaluating the Pig-a data, all the results are now

pointing in the same direction, no significant pairwise comparisons to the control, no trend, and all responses for the molnupiravir-treated groups were within that 95 percent control bounds for the historical control distribution. In addition, other experiments conducted with molnupiravir in rats indicated sufficient levels of exposure for the target tissues. Our FDA PK experts tell me the high dose resulted in blood levels for the N4-hydroxycytidine that were 9.3-fold clinical levels. These data then fulfill the requirements for a strong data set supporting a negative in vivo mutagenicity assay.

The CDER Genetic Toxicology Subcommittee was asked to evaluate the molnupiravir genotoxicity data. The results from that analysis is summarized on this slide. After consulting with colleagues from the Pharmacology/Toxicology Genotoxicity Subcommittee -- myself and my colleague, Mugimane Manjanatha at NCTR -- Dr. Robison, who is the chair of the committee, provided the following conclusions.

First of all, the in vitro bacterial reverse mutation assay would be considered positive based upon the response to the E. coli strain. A transgenic rodent study, not the Pig-a assay, is the primary assay for follow-up of an Ames-positive active pharmaceutical ingredient. Thirdly, the results of the Big Blue assay study suggests that the compound is not an in vivo mutagen. And finally, given the negative response in the Big Blue rat assay, it would seem that neither parent prodrug nor the initial metabolite NHC are in vivo mutagens, suggesting the level of concern for mutagenicity in the clinical setting would be low.

Since this review was conducted, we became aware of some further data evaluating the mutagenicity of molnupiravir in mammalian cells in vitro. The study has gained some attention, and we take a look at it here in terms of its effect on the genetic toxicology subcommittee conclusions.

Zhou et al. have recently published a non-guideline study indicating that molnupiravir is mutagenic in CHO cells following 32 days of

treatment. The study differed significantly from the regulatory guidelines studies used to evaluate mutagenic potential, and the assay design did not permit calculating mutant frequencies. However, there was little doubt that molnupiravir is mutagenic under the conditions of these assays.

Our analysis of the report was that it doesn't change the fact that molnupiravir is an in vitro mutagen. This was already established by the Ames test data. The difference here is that the assay being done is with a rodent cell line. It also doesn't change the conclusion from the TGR assay that molnupiravir is not an in vivo mutagen in rodents. So the bottom line is that these data are not sufficiently compelling to change the conclusions reached by the Genetic Toxicology Subcommittee.

To summarize, molnupiravir is certainly an in vitro mutagen, but its mutagenic potential in vivo appears to be low, whether that be due to a specific mechanism or structural preference for DNA polymerases or due to any of the myriad ways

in vivo conditions modulate the effects of chemical toxicants. Thus, based upon our analysis of the data, we conclude that the concern for molnupiravir mutagenicity in a clinical setting appears to be low.

I'll stop here, and thank you for your attention. Our next presentation will be by Dr. Hodowanec.

FDA Presentation – Aimee Hodowanec

DR. HODOWANEC: We'll now turn our focus to the clinical development program for molnupiravir.

Trial MK-4482-002, henceforth referred to as P002, is an ongoing, randomized, placebo-controlled trial of molnupiravir versus placebo in outpatient adults with mild to moderate COVID-19. The part 1 phase 2 portion of the trial is a dose-ranging trial. The part 2 phase 3 portion of the trial is the primary source of data in support of this EUA request.

Additionally, a phase 2/3 trial, MK-4482-001, or P001, was conducted in hospitalized patients. This trial was stopped after part 1 of

the trial and part 2 was not initiated because the sponsor concluded that treatment with molnupiravir is likely to have the greatest benefit when initiated early in the COVID-19 disease course.

We will now focus on trial P002 in outpatients with mild to moderate COVID-19. Part 1 is a dose-ranging trial in which approximately 300 participants were randomized 1 to 1 to 1 to 1, to receive molnupiravir 200 milligrams, 400 milligrams, 800 milligrams, or placebo, every 12 hours for a 5-day treatment course.

Based on the results from part 1 of this trial, combined with additional supportive data from other trials, the 800-milligram molnupiravir dose was chosen for part 2. In part 2, a planned total of 1550 participants were to be randomized 1 to 1 to either molnupiravir 800 milligrams or placebo every 12 ours for 5 days. The primary endpoint is the proportion of participants with all-cause hospitalization or death by day 29.

This trial is ongoing and patients are being followed through month 7. Of note, this trial was

conducted at sites in Latin America, Europe, Africa, North America, and Asia, with the majority of participants coming from Latin America and Europe and approximately 6 percent from North America.

The data included and the original EUA request came from an interim analysis conducted when approximately 50 percent of the planned part 2 population had reached day 29. Based on the results of the interim analysis, the trial was stopped early for efficacy, at which time a total of 1433 participants had been enrolled. On November 22, 2021, the agency was made aware of top-line safety and efficacy results from all 1433 randomized participants.

The following are key eligibility criteria for part 2 of trial P002. All participants were outpatient adults with mild or moderate COVID-19. Laboratory confirmation of SARS-CoV-2 infection, as well as the initial onset of COVID-19 signs and symptoms, were required to have occurred within 5 days prior to randomization.

Of note, in the original protocol, participants were required to be within 7 days of symptom onset, however, based on the viral kinetics and the mechanism of action of molnupiravir, the sponsor concluded that molnupiravir is likely to have the greatest benefit when started early. This eligibility criterion was therefore changed from within 7 days to within 5 days of symptom onset between parts 1 and 2 of the trial.

All part 2 participants had at least one condition that placed them at increased risk for severe illness from COVID-19. Qualifying conditions included age greater than 60 years; active cancer; chronic kidney disease; chronic obstructive pulmonary disease; obesity; serious heart condition such as coronary heart disease or heart failure; and diabetes. Persons who had previously received a COVID-19 vaccine were excluded. Pregnant individuals were also excluded from the trial and contraception use was required for all male and female participants of childbearing potential.

The agency has conducted an independent benefit-risk assessment based on the available efficacy and safety data submitted by the sponsor. Our initial review, as presented in the briefing document, focused on the P002 interim analysis data from 775 participants. A review of data from the full P002 part 2 population from all 1433 randomized participants is currently ongoing.

The agency generally agrees with the sponsor's top-line safety and primary efficacy analyses. However, we note that a number of secondary endpoints, such as the sustained improvement or resolution of COVID-19 signs and symptoms, are still under review. The agency's presentations will highlight selected topics that are thought to warrant further discussion.

Here, we present the primary efficacy analysis comparing the findings in the interim population to those in the full population. On the left side of the figure is the primary endpoint analysis in the originally submitted trial P002 part 2 interim analysis population. As shown,

molnupiravir was associated with a 6.8 percentage point reduction and the risk of hospitalization or death through day 29. This equates to a 48 percent relative risk reduction.

The right side of the figure shows the primary endpoint analysis in the trial P002 part 2 full population, including the post-interim analysis participants. Here, molnupiravir was associated with a 3 percentage point reduction in the risk of hospitalization or death, which equates to a 30 percent relative risk reduction. As noted, formal statistical testing was not performed for the full population assessment because statistical significance was demonstrated at the interim analysis.

We will now break down the primary efficacy analysis further, showing the results for the interim analysis population, the post-interim analysis population, and the full population. As you can see, the rate of hospitalization or death in the molnupiravir arm remained relatively constant over the course of the trial. However,

for reasons that remain unclear, the rate of hospitalization or death in the placebo arm was lower in the second half of the trial at 4.7 percent compared to the first half of the trial at 14.1 percent.

In the post-interim analysis population, consisting of those participants who had not reached day 29 by the interim analysis data cutoff, the rate of hospitalization or death by day 29 was 6.2 percent in the molnupiravir arm and 4.7 percent in the placebo arm, showing no apparent treatment effect.

This table displays the total molnupiravir clinical safety database. As shown, a total of 917 participants have been exposed to molnupiravir for the proposed dose and duration; 710 of these participants come from part 2 of the outpatient trial P002 with 386 participants coming from the interim analysis and an additional 324 participants in the full population.

The safety database is supplemented with additional outpatients, as well as hospitalized

patients and a small number of healthy volunteers from other completed and ongoing trials. This is comparable to the initial safety databases for the monoclonal antibodies, which are authorized for similar intended use.

Based on our review of the safety results provided by the sponsor, no notable safety concerns were identified in part 2 of trial P002. We have not verified the sponsor's analyses. Given the report of bone marrow toxicity in dogs, hematologic laboratory parameters are being carefully assessed in clinical trial participants.

Clinically meaningful abnormalities in leukocyte, lymphocyte, platelet, and hemoglobin values were rare and occurred at a comparable rate between arms. The agency's evaluation of the safety data from all randomized participants through day 29, particularly the post-interim analysis participants, is ongoing.

I will now turn the presentation over to Dr. Patrick Harrington, who will present the agency's clinical virology assessments.

FDA Presentation – Patrick Harrington

DR. HARRINGTON: Thank you.

Good morning. My name is Patrick Harrington. I am the primary clinical virology reviewer for this application, and I am presenting on behalf of the virology review team, which also includes Dr. Eric Donaldson and Dr. Jules O'Rear. For this presentation, I will be focusing on our assessment of molnupiravir-associated SARS-CoV-2 genetic changes in clinical trials, and in particular focusing on changes observed in the viral spike protein.

First, as a reminder, molnupiravir is a prodrug of NHC, which is a nucleoside analog that inhibits SARS-CoV-2 replication by causing the accumulation of nucleotide errors in the RNA genome. Molnupiravir-associated mutagenesis of the viral RNA can occur anywhere in the viral genome, which could, in theory, lead to amino acid changes in proteins targeted by therapeutics or the immune response.

The SARS-CoV-2 spike protein is of

particular interest, as it is the major functional target for antibody responses to infection, and it is also the target of vaccines and anti-SARS-CoV-2 monoclonal antibodies. So we conducted analyses to explore whether molnupiravir treatment is associated with changes in the viral spike protein, and I will present these results, and at the end discuss some of the conclusions, as well as the numerous uncertainties with our findings.

To investigate SARS-CoV-2 genetic changes in clinical trials, the sponsor isolated viral RNA from NP and OP swab samples collected from study participants mostly between baseline and day 5, and subjected the samples to RT-PCR and full genome sequencing using a next-generation sequencing assay based on Ion Torrent platform.

Nucleotide and amino acid coding changes were identified and reported relative to a prototypic reference isolate, and the sponsor calculated nucleotide mutation rates across the entire viral genome to quantify and characterize molnupiravir-associated mutagenesis.

We conducted an independent analyses of the amino acid changes reported by the sponsor, and we also analyzed raw NGS fastq data for a subset of participants. Our analyses primarily focused on treatment-emergent amino acid changes from baseline based on a 5 percent variant sensitivity cutoff. We analyzed the viral spike protein, as well as the replicase proteins to investigate possible molnupiravir resistance, although this presentation is focused on the spike protein analyses.

The analyses of treatment-emergent amino acid changes were conducted for the phase 2 studies, MK-4482-002 part 1 and MK-4482-001, as only limited data were available at the time of the EUA submission from the phase 3 portion of PROTOCOL 002.

First, we'll look at the SARS-CoV-2 nucleotide mutation rates across the viral genome, and these results are from a subset of participants in the phase 3 trial 002 part 2. As shown in the top table, when you compare the numbers of mutations detected at day 5 relative to each

individual participant's baseline viral sequences, the mutation rates were significantly higher in molnupiravir-treated participants compared to those who received placebo. So these results confirm clinically that molnupiravir increases the numbers of nucleotide mutations in SARS-CoV-2 genomes, supporting its mechanism of action.

The second table summarizes the types of nucleotide changes observed in molnupiravir and placebo-treated participants. The mechanism of action of molnupiravir directly leads to the accumulation of C:U and G:A transition mutations, as the NHC monophosphate is incorporated into viral RNA in place of cytidine or uridine, and then is subsequently copied.

As you can see, most viral genome changes observed in molnupiravir-treated participants were transition mutations, but I will note that other types of changes, including transversion mutations and insertions and deletions, were also observed. The precise molecular mechanisms of these other types of nucleotide changes are unclear, but the

bottom line is molnupiravir treatment was associated with increases in all of these types of nucleotide changes.

Similar results were also observed for MK-4482-002 part 1, the phase 2 part, and I will also note that any assessment of mutation rates likely underestimates the viral mutagenic effects of molnupiravir, as replication defective genomes may not be detected.

Next, we will look specifically at changes in the viral spike protein, and these data come from the phase 2 outpatient trial 002 part 1. And for this analysis, we pulled results from all three molnupiravir dosing groups in which participants received dose levels of 200, 400, or 800 milligrams every 12 hours for 5 days. As you can see from the table, compared to placebo, a greater proportion of participants who received molnupiravir had at least one treatment-emergent amino acid change detected in the viral spike protein.

We conducted additional analyses for 7 participants who had the treatment-emergent

changes highlighted in green, including the substitutions, deletions, and an insertion in the spike N-terminal domain, spanning amino acids 139 to 145, detected among 5 participants, as well as substitution E484K and P681H.

These particular spike changes caught our attention because they occurred in regions of the spike protein that are under immune selective pressure and also where variability has been reported in some important SARS-CoV-2 variants. These changes were detected as minority variants, and we confirmed that the N-terminal domain changes were clearly detected in the raw NGS reads and not obviously attributed to any NGS artifacts.

I'll come back to these 7 participants in a subsequent slide, but it's important to note that several other emergent spike amino acid changes of unknown significance were detected in individual participants, both in the molnupiravir arms, as well as in the placebo arm.

A similar analysis was conducted for the phase 2 trial, MK-4482-001, and again we see a

greater rate of treatment-emergent spike changes in molnupiravir-treated participants, and, again, including at positions or regions that are under evolutionary pressure.

Now, coming back to those 7 participants from PROTOCOL 002 part 1, who had some of the more notable spike protein changes, we explored whether these changes had any obvious impact on clinical or virologic outcomes. As you can see in the figure on the right, the trends in viral RNA shedding for these 7 participants did not appear to differ from other molnupiravir-treated participants without these spike changes. Again, I will note we do not have sequencing data beyond day 5 to know if any changes are emerging or persisting after treatment.

None of the 7 participants had cell culture infectious virus detected in any post-baseline sample, although I will add that even among those who received placebo, only 2 to 4 percent of participants in the trial had a positive infectivity result on day 3 or day 5 in this assay; so I do question the sensitivity of this assay for

detecting potentially infectious virus.

Nevertheless, there was no indication from the available data that these 7 participants had the emergence of a transmissible neutralization resistant virus. Also, none of the 7 participants reached the clinical endpoint of hospitalization or death, and when we expanded these analyses to those with any spike amino acid change, the results were comparable.

In conclusion, molnupiravir treatment may increase the rate of detection in SARS-CoV-2 populations with amino acid changes in the viral spike protein, which is consistent with this viral mutagenic mechanism of action; and we do agree with the sponsor that changes can occur anywhere in the SARS-CoV-2 genome and are not specific to the viral spike protein.

Based on the data analyzed thus far, there is no evidence that the emergence of spike protein amino acid changes affected virologic or clinical outcomes in outpatients with COVID-19 in the phase 2 trial, MK-4482-002 part 1.

Now, unfortunately, there are many more questions on this issue than there are answers, and here I've tried to outline some of the key questions and uncertainties that remain. First of all, we have to ask whether all spike protein changes that were detected were clearly attributed to molnupiravir.

We know that as a direct result of its mechanism of action, molnupiravir causes transition mutations, but not all of the spike protein changes that emerged were actually due to transition mutations. However, as shown previously, molnupiravir treatment was associated with increases not just in transition mutations, but also in transversions, insertions, and deletions. And even if other types of nucleotide changes are relatively uncommon, at least in theory they could be enriched in the viral population if they confer a selective advantage.

It is also unclear if molnupiravir-associated changes in the viral spike protein could substantially affect SARS-CoV-2 evolution in a

broader context. Of course, we all know that the spike protein is already under evolutionary pressure with or without molnupiravir, and we do see some spike protein changes also emerging in participants who received placebo in clinical trials. This evolution can be facilitated by a variety of other factors such as natural immunity, vaccines, and other treatments, so it is unclear to us if molnupiravir would have a substantial impact on the evolutionary patterns that are already happening with SARS-CoV-2.

Now, for molnupiravir to affect SARS-CoV-2 evolution beyond a treated individual, the variants would also have to be transmissible; and at this time, we do not know if this is possible to a significant degree. Most spike changes that we found were detected as minority variants, and only in one post-baseline sample or one time point.

Viral RNA levels in respiratory samples were declining rapidly in nearly all participants during the treatment period regardless of treatment arm, indicating that virus was being cleared from the

upper respiratory tract, and that the risk of SARS-CoV-2 transmission was likely quite low by the time the spike changes emerged to a detectable level.

Furthermore, molnupiravir antiviral activity is linked directly to its mutagenicity and that if the drug is truly active, it's going to cause mutations in the viral genome, which may or may not involve the viral spike protein. But as these changes accumulate, the virus should eventually become less fit, and thus less transmissible.

One final point, it is certainly possible that the transmissibility of any SARS-CoV-2 variants that may emerge with molnupiravir treatment will depend on other factors such as the immune status of the treated individual and whether they are able to effectively clear the virus infection and prevent spread to close contacts.

Now, this is one of the key topics for discussion this afternoon, and given all of these uncertainties, we do look forward to the perspectives of the committee on this issue. Thank

you for your attention, and I will turn the microphone back to Dr. Hodowanec to close out the FDA presentation.

FDA Presentation – Aimee Hodowanec

DR. HODOWANEC: Thank you, Dr. Harrington.

Based on the available nonclinical and clinical data that have been presented, the agency has identified several key review issues. The main overarching review issue is the proposed patient population for authorized use. It is important to identify patients likely to receive the greatest benefit from molnupiravir in order to offset the known and potential risks of molnupiravir.

In addition, the agency will propose risk mitigation strategies for the known and potential risks. The agency looks forward to the committee's deliberations on the use of molnupiravir in specific populations, as well as the acceptability of the proposed risk mitigation strategies.

The following are the five primary review issues identified: the patient population for authorized use; bone and cartilage toxicity;

embryo-fetal toxicity; the potential for mutagenicity; and the potential for enhanced viral evolution.

As noted, we consider patient selection to be an overarching review issue. The identified risks should be taken into consideration when defining the patient population for authorized use. Additional specific patient selection factors that we ask the committee to consider include the time from symptom onset, criteria to be used to identify patients at high risk for progression to severe COVID-19, and the potential for vaccinated adults who are at high risk for progression to severe COVID-19 to benefit from treatment with molnupiravir.

The first review issue to be discussed is bone and cartilage toxicity. Molnupiravir will not be authorized for use in patients less than 18 years of age due to an absence of clinical data from pediatric patients and the bone and cartilage findings in animals, which may be relevant for pediatric patients.

These animal findings may also be relevant to the unborn fetus. Results from a juvenile toxicity study are forthcoming and are hoped to further inform these potential risks. To convey the currently available nonclinical data to prescribers, the agency proposes a warning and precaution in the fact sheet describing the bone and cartilage toxicity and noting the potential relevance to pediatric patients.

Next, given the findings of embryo-fetal toxicity and bone and cartilage toxicity in animals, molnupiravir use during pregnancy requires careful consideration. The agency is considering the following two approaches to the authorization. Under the first approach, molnupiravir is not authorized for use during pregnancy. This approach would be appropriate if there are no scenarios in which the benefit of molnupiravir is thought to outweigh the risk of molnupiravir during pregnancy.

Under the second potential approach, molnupiravir is not recommended for use in pregnancy, but pregnancy will not be considered a

limitation of the authorized use. Therefore, the second approach would allow for the use of molnupiravir under the EUA during pregnancy in certain clinical scenarios in which the clinician determined that the benefit of molnupiravir outweighs the risk.

Both approaches to molnupiravir use during pregnancy would involve the inclusion of a warning and precaution in the fact sheet based on the findings from animal reproductive toxicology studies and indicating that molnupiravir may cause fetal harm if administered to a pregnant individual. Lastly, the sponsor is establishing a pregnancy surveillance program to collect information on pregnancy outcomes in individuals who are exposed to molnupiravir during pregnancy.

The observed embryo-fetal toxicity in animal studies also has implications for individuals of childbearing potential. The agency proposes the following requirements for use in individuals of childbearing potential. First, prescribers should verify that a patient is not pregnant based on the

first day of the last menstrual period in individuals who have regular menstrual cycles; are using a reliable method of contraception correctly and consistently; or have had a negative pregnancy test.

A pregnancy test is recommended if the individual has irregular menstrual cycles, is unsure of the first day of the last menstrual period, or is not using effective contraception. Verification that an individual is not pregnant is not needed in patients who have undergone permanent sterilization, are currently using an intrauterine system or contraceptive implant, or in whom pregnancy is not possible.

Second, prescribers should recommend that individuals of childbearing potential use an effective method of contraception for the duration of treatment with molnupiravir and for 4 days after the final dose. Four days was chosen, as this will cover more than 5 half-lives of the drug and its metabolites.

The next review issue is mutagenicity. The

overall risk of mutagenicity in humans is considered low. The risk is further reduced by the short 5-day treatment course. The agency proposes that the fact sheets stipulate that molnupiravir not be authorized for use for more than 5 consecutive days and that molnupiravir be dispensed in the original container as a single treatment course to further mitigate the risk of mutagenicity.

The potential for enhanced viral evolution in association with the use of molnupiravir is currently a theoretical risk. It is unclear that any restrictions on the authorized population could meaningfully impact this trajectory should this theoretical concern be realized. One additional theoretical concern for consideration is that the potential for enhanced viral evolution may be greater in immunocompromised patients who may have more prolonged viral shedding.

We will now discuss the issues pertinent to patient selection. Many of the review issues already described will impact patient selection.

The agency proposes that the use of molnupiravir be limited to individuals who are at least 18 years of age; have a positive result of direct SARS-CoV-2 viral testing; are within 5 days of symptom onset at the time of treatment; are at high risk for progression to severe COVID-19, including hospitalization and death; and are not already hospitalized due to COVID-19. As previously discussed, a molnupiravir authorization may also be limited to non-pregnant individuals.

The next several slides will be devoted to three patient selection factors for further consideration. We will first discuss the maximum time from symptom onset to treatment.

As previously described in part 1 of trial P002, participants were required to be within 7 days of symptom onset at randomization. Based on molnupiravir's mechanism of action and findings in part 1 of the trial, it was concluded that individuals earlier in the course of their illness were more likely to benefit from molnupiravir. Therefore, eligibility in part 2 of P002 was

restricted to participants within 5 days of symptom onset. Randomization in part 2 was stratified by less than or equal to 3 days from symptom onset versus 4 to 5 days from symptom onset.

As previously presented by the sponsor, the treatment effect was relatively constant in the less than or equal to 3 days from symptom onset subgroup and the 4 to 5 days from symptom onset subgroup. While it is important that molnupiravir be administered when it is most likely to be effective, it is also important to have a treatment window within which patients can feasibly access molnupiravir.

As a frame of reference, the authorized monoclonal antibodies all require that patients be within 10 days of symptom onset at the time of treatment, though in the case of molnupiravir, there are no data demonstrating benefit in participants who are beyond 5 days from symptom onset.

We also seek the committee's advice regarding how to best identify patients at high

risk for progression to severe COVID-19. One potential approach would be to use criteria similar to those used for the authorized monoclonal antibodies.

As you may be familiar with, the fact sheets for the monoclonal antibodies provide examples of conditions that place patients at high risk for severe COVID-19 and refer to the CDC website for a complete up-to-date listing of high-risk considerations. This approach would have the advantage of providing prescribers with a consistent approach to identifying high-risk patients eligible for receipt of an authorized product for the treatment of mild to moderate COVID-19.

Alternatively, a more restrictive list of criteria, such as those used in trial P002, could be used to identify patients at high risk for severe COVID-19 to determine eligibility for receipt of molnupiravir under an EUA. This approach would ensure that the authorized population reflects the population from which data

are available to support the effectiveness of molnupiravir for its proposed use.

This slide shows a proposal of how to define high risk in the fact sheet that has been modeled off the authorized monoclonal antibody fact sheets. As you can see, this example fact sheet lists several of the most common and important high-risk criteria and provides a web address for the CDC website, where a complete listing of high-risk considerations can be found.

As a refresher, this slide displays the specific criteria used to identify patients at high risk for severe COVID-19 to determine eligibility for participation in part 2 of trial P002. These criteria are more limited than those provided by the CDC.

The final patient selection factor for consideration is COVID-19 vaccination status. As previously described, vaccinated individuals were excluded from trial 2002. However, approximately 20 percent of participants enrolled in part 2 of the trial were positive for anti-SARS-CoV-2

nucleocapsid antibody at baseline. The presence of antibody at baseline could have either been from a prior SARS-CoV-2 infection or from the current infection.

This table shows the incidence of hospitalization or death through day 29 by baseline antibody status in the full P002 part 2 population. As shown, the rate of hospitalization or death through day 29 was nominally higher in the molnupiravir seropositive subgroup than the placebo seropositive subgroup. However, given the small number of events observed in these subgroups, these findings must be interpreted cautiously.

As is the case with molnupiravir, vaccinated individuals were not represented in the trial supporting the authorizations of the monoclonal antibodies for similar intended uses. Despite this, the monoclonal antibodies are authorized for use in patients with mild to moderate COVID-19 who are at high risk for progression to severe COVID-19 regardless of vaccination status.

There are data available regarding efficacy

by baseline serostatus from some of the monoclonal antibody clinical trials. As shown here, amongst seropositive participants in the phase 3 trial of the monoclonal antibody combination casirivimab and imdevimab, the primary endpoint of COVID-19-related hospitalization, or all-cause mortality through day 29, was met by 0.6 percent of casirivimab and imdevimab participants and 3.7 percent of placebo participants. The observed relative risk reduction was similar in the seropositive and seronegative subgroups. For this particular monoclonal antibody product, the treatment benefit appears relatively consistent regardless of baseline serostatus.

Ascertainment of serostatus prior to the initiation of treatment for COVID-19 is not currently feasible in clinical practice given the available assays and the turnaround time for results. Therefore, it is not practical to consider baseline serostatus as a potential patient selection factor for molnupiravir authorization. However, in the absence of data from vaccinated individuals, data from seropositive individuals may

provide some insight into the potential efficacy of molnupiravir in vaccinated individuals.

It remains unclear how applicable the findings in individuals with positive baseline nucleocapsid antibodies from natural immunity from a current or prior infection are to individuals with immunity from prior COVID-19 vaccination.

To further explore the potential for molnupiravir to reduce the rate of hospitalization or death among fully vaccinated individuals, a literature review was undertaken. Data regarding the incidence of breakthrough infections, defined as infections occurring in fully vaccinated individuals, and the characteristics of patients experiencing breakthrough infections are just now emerging.

Data reflective of the Delta variant experience are particularly limited, however, available literature suggests that most breakthrough infections leading to hospitalization or death occur in patients with advanced age and in those with medical comorbidities. The

comorbidities recorded in association with breakthrough infection leading to hospitalization or death appear to overlap with the CDC risk factors for severe COVID-19.

In conclusion, molnupiravir has been shown to reduce the risk of hospitalization and death among adults with mild to moderate COVID-19 and who are at high risk for progression to severe COVID-19.

Molnupiravir appeared generally safe in adults with mild to moderate COVID-19. Several safety issues were identified based on nonclinical findings that impact the patient population for authorized use and require the implementation of risk mitigation strategies.

We look forward to the committee's discussions on these complex benefit-risk considerations. Through your deliberations, we hope to gain a better understanding of the appropriate patient population for authorized use and what risk mitigation strategies should be mandated in a potential authorization.

Before we move on to clarifying questions, I would like to thank the many colleagues in the Division of Antivirals, as well as across other CDER review divisions, who have contributed greatly to this work. Thank you.

Clarifying Questions for Presenters

DR. BADEN: Thank you, Dr. Hodowanec. And I would like to thank all of the FDA presenters for, again, covering a lot of ground of very complex data to allow us to better understand the issues at hand that need to be deliberated and put into context as we move forward as a community; so thank you.

I did not thank earlier our Merck colleagues, the applicant, for providing the second half of the P002 part 2 data. It is clear that they were available very late in the process, but it is appreciated that all available data have been shared so that we as a community can weigh their meaning.

We will now take clarifying questions for all presenters thus far. To the panel members,

please use the raised-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raised-hand icon again after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you, and the end of any follow-up questions with, "That is all for my questions," so we can move to the next panel member.

As we discussed previously among the panel members, if you would like to chime in to add your thoughts on what another panel number is stating, please use the green check mark icon. When you are done chiming in, please remember to clear the check mark. This will allow us to build on key themes that have been raised so that we can have as in-depth a discussion as possible.

I would like to ask the panel members to please raise your hands with questions, and we will start the clarifying questions, and we will be asking questions to both the applicant and the agency. I will happily ask the first question while we get our panel members to raise their hands. As I already mentioned, a terrific amount of data has been shared, and I'd like to ask this question of the applicant.

In understanding some of the key findings, one of the key findings was the mortality benefit, particularly in the first half of the MOVe-OUT part 1. My question to the applicant is, part 2 of MOVe-OUT, it was really pronounced in part 1 but not the second half, the mortality benefit. And in fact, the clinical benefit seemed to be inverted in the second half of the MOVe-OUT study.

In addition, in the hospitalized study, the P001 study, the mortality seemed to go in the wrong direction with 14 out of 218 individuals, or 6.4 percent, in the molnupiravir treated, or 2 out of 75 individuals in the placebo, 2.7 percent.

So help me understand why the mortality benefit is concentrated in one-half of those studies, not in the second half, and then inverted in the inpatient study. Can you help me understand that?

DR. KARTSONIS: Dr. Baden, this is Dr. Kartsonis. Just for the record, I will be serving as the applicant's moderator for today's session and will happily call on others to address different issues.

With regard to your first part of your question about the inversion -- or the decrease I guess I would say in the mortality benefit, or the number of deaths that occurred in the second part of the study -- we've obviously carefully looked at the first part of the study relative to the second part of the study. We did not identify a specific factor that is driving not only the efficacy effect, but the diminution of mortality that was seen.

Now, mind you, one of the things we carefully did was obviously look at the baseline

characteristics of the patients enrolled in the study. We looked at virological components and other factors to see if there were any driving forces.

It's interesting because on one side of the equation, the second part of the study after the interim analysis enrolled an older population, enrolled patients with older age and more diabetes, so one would have thought, indeed, that that would be the case; that you would see more mortality.

However, there were also more women in the second part of the study, and that's been associated, for what we can see, with less risk, as well as more patients who are antibody positive. So we may be in the situation where we're catching people later in the course of the disease in terms of that.

It's interesting because when you look at the second part of the study, the effect that we're seeing is almost entirely in the last 20 percent of the recruitment in the trial. In fact, if you look at recruitment between 50 to 80 percent of the

study, we're still seeing some evidence of efficacy.

It's really in that last part that you'll see this massive drop in the placebo rate, and it doesn't really add up to us. Obviously, we expected to some potential regression to the mean, but we didn't expect that we would see this absolute reduction, as the FDA noted, in the placebo rate without a corresponding drop in the molnupiravir arm. So there's no clear explanation I can give you for the lower mortality.

Now mind you, as I mentioned, some of the baseline demographics has changed. The study did recruit more in Europe in the second portion, and whether or not some of these factors taken together might have played a role.

The second part of the study, I should finally note, tended to be almost all Delta variant. And we know the drug works against Delta not because only that we showed you the clinical data, but we've even looked at RNA reductions in the Delta, and there's some improvement there. So

I don't have a satisfying answer to your question, but at least that's the totality of the data that we have now.

Now, I did want to get to the second part of your question about PROTOCOL 001 and the mortality benefit that was seen there. Obviously, you are right; when we look at the total safety database in that study, there were 14 deaths in molnupiravir versus 2 in placebo. But I do want to remind folks, this is a 3 to 1 randomized trial, so you would have expected it to be numerically at least more on molnupiravir. So honestly, to see only 2 deaths on the placebo was an interesting finding.

We obviously started by looking at the safety data to make sure that there wasn't a safety concern in hospitalized patients. If I could put the slide up, please, you can see here that safety-wise in this study, there really was no evidence of concern. If anything, there were fewer adverse experiences and drug-related adverse experiences in molnupiravir versus placebo, and even serious adverse events were generally similar

across the board. The difference is really the 14 versus 2 that you look at.

So of course, immediately the next thing we did was to look at those deaths and see what was the particular factor and anything we could appreciate there, and clearly almost all these people died of COVID-19. We carefully evaluated that.

Slide up, please. What you can see here are the deaths from the different groups, and appreciably most of them are due to COVID-19. It is interesting -- we've included some of the characteristics here just for you to see -- this was a particularly high-risk portion of the study; 75 percent of the patients had severe disease, 75 percent of them got treated pretty late in the symptom standpoint, and more than 80 percent of them were over the age of 60 or had underlying comorbidities.

Now, mind you, obviously we took all of this together and then thought about a little bit more. We also compared it relative to what we know about

the public domain in these hospitalized studies. As many of you know -- and if I could put the next slide up, please -- we know that the event rate in placebo tends to be higher. What I've included here on the left-hand side are some of the studies that have looked at the death rate in the placebo arm. This data is in people before they've been ventilated, so we tried to be as consistent as we can with the PROTOCOL 001 study.

You can see that the rate of placebo is much lower at 2 percent than we had seen in this study, but the rate of molnupiravir in terms of mortality was pretty much on par with what we've seen with some of the other studies that have been done. Ultimately, we can't explain that particular issue.

Finally, and probably the most important question is, we're not looking for this drug to be used in hospitalized patients, but we have carefully looked at those patients on molnupiravir who did get hospitalized and continued therapy to see if there was any continued benefit, and indeed there is continued benefit.

If I can just show one last slide -- slide up, please -- this is the data that we have of people who got admitted to the hospital. Now, this is from the all randomized population, so this is data right off the press, so to speak. You can see there are 34 people that got included here, 12 on molnupiravir and 22 on placebo. You see some notable benefits even for the patients who got hospitalized on molnupiravir: the rate of oxygen, the rate of ventilation use, and particularly the mean durations of hospitalization are lower.

I know I've given you a very long-winded question, but it was a complex question, so I apologize for the very detailed response. But I wanted to make sure that I gave you the full slate of information there.

DR. BADEN: Dr. Kartsonis, thank you. The mortality issue is such an important one and central to what many of us believe is key benefit.

There are many hands and many questions, so I would ask the panel members and the respondents to be as pointed as possible so we can cover much

ground. There are several panel members who have follow-on questions, starting with Dr. Hardy.

(No response.)

DR. BADEN: Dr. Hardy, you're on mute if you are talking.

DR. HARDY: I think I just unmuted myself, correct?

DR. BADEN: Yes, you have.

DR. HARDY: Great. This is David Hardy from Los Angeles, adult infectious disease trained physician and researcher.

I just had a question for you about whether or not, as the trial was going on, and since about 75 percent of it was done in Latin America and in Europe, it looked like, vaccine rollout was later than in the U.S., and due to the short entry period for enrollment, did the entry criteria for your clinical trial involve an antibody test to demonstrate persons had not been vaccinated?

DR. KARTSONIS: No, we did not. We didn't mandate -- I imagined, Dr. Hardy, you wanted that to be addressed to me as the applicant or us as the

applicant?

DR. HARDY: Correct. Sorry. I didn't indicate that.

DR. KARTSONIS: No problem.

No, we didn't require that people have an antibody test. We had a specific exclusion criteria outlined that patients were not to have been vaccinated with SARS-CoV-2 vaccine either prior to entry or at any time through the 29-day period, but we didn't mandate the test.

The antibody test that we look at -- and I should take a second and explain that test -- it's a Roche Elecsys assay. It basically looked at -- you know, it's a qualitative test. It doesn't differentiate. It doesn't give you a value in terms of what the antibody level it is. And because it measures nucleocapsid, it's probably more of a reflection of natural infection versus vaccination because, as you know, most vaccines are targeted against the spike region.

It also doesn't measure the differentiation between IgG and IgM, so we don't know how much of

this is really an effect of a prior infection versus did we catch people at a point where they were already demonstrating an immune response to the current infection.

Obviously, as you heard from us, as well as from the FDA, there's a very low event rate in that group that got the antibody test, but the long answer to your question is we didn't require that antibody test.

DR. HARDY: I just posed that question as a potential explanation for why in the placebo group, the mortality rate was dropped so significantly, in that perhaps persons were coming in who were not unvaccinated, who were having breakthrough infection perhaps, and had an immune response as a result of the vaccine and got nothing in terms of treatment.

I think the thing that really is striking is how the second half of the PROTOCOL 002 mortality rate and hospitalization rate really dropped in the placebo group. There's something that seems to be very different in those participants than in the

ones enrolled earlier in the trial.

DR. KARTSONIS: You're right about that. But no, basically our study required that people not be vaccinated, and obviously we've done source document verification of the data, and we feel very confident that that's indeed the case.

You're right about the drop in the second half, and I particularly mentioned that last 20 percent. Interestingly, in that last 20 percent, the difference in antibody positivity was notable. It was 27 percent in the placebo group versus 19 percent on the molnupiravir group. So could that have played some role in the latter end? We don't know, but that's the data that we currently have.

DR. BADEN: Thank you. We have a lot of questions to go through, so thank you for clarifying.

Dr. Green, you have a follow-on question?

DR. GREEN: Yes. Thank you. This is Michael Green, and I think it qualifies as a foul line because Dr. Kartsonis in his initial response

to you identified the diabetic patient cohort, and I'm wondering if he has any thoughts as to why the study drug did not appear to have an impact on diabetes, either in the first part of the study or I think in the second part of the study. Thank you.

DR. KARTSONIS: Yes. Thank you for that question. Maybe we can go back to the subgroup plot that we showed so that I can present that first from the core presentation, CC-28, if we could start there.

So you're right. There were no differences --

(Audio feedback.)

DR. BADEN: Please mute your phone if you're not talking. Thank you.

DR. KARTSONIS: Sorry about that.

In the diabetic cohort, there were 17 cases in each arm that we're seeing, so there were no differences. Interestingly, there was a difference at the interim analysis, at least proportionally, favoring molnupiravir.

We have looked at these diabetic patients pretty closely, and there are some differences between the two groups. Interestingly -- and if I could just put the slide up, please -- these are some of the baseline characteristics in this group. I particularly call up -- slide up, please. The group was pretty well matched with regard to age and gender. The one place where we did see some differences were with regard to the risk factors. There was a tendency for more obesity and more serious heart conditions to occur on molnupiravir; small numbers.

One of the things that we found interesting is that those people who had diabetes and two other risk factors, the difference was 7 percentage points against molnupiravir. So could this have had an effect? We don't know.

I will tell you, we've looked also at the efficacy based on people having diabetes and other risk factors. Interestingly, if you had just diabetes and/or you had diabetes and one other risk factor, there were 11 cases on molnupiravir versus

16 persons on placebo. The real difference was in those people who had two or more risk factors.

If I could just put the slide up just to show you, you can appreciate -- here's the data. As you can see, as I mentioned, 11 had no additional risk factor or one additional risk factor on molnupiravir versus 16 on placebo. The real difference was in those people who had additional risk factors, and I can't explain how only 1 of 15 placebo subjects in that group didn't progress to hospitalization.

I mean, I think this is some of the discreteness of the data that makes it hard to look at. And then you look at people who had three additional risk factors or more, and there are no cases across the two groups.

I don't have a great answer for you, Dr. Green, other than the demographic data that I've highlighted in some of these issues you're seeing here.

DR. BADEN: Dr. Dublin, you had a follow-on question? Go ahead.

DR. DUBLIN: Thank you.

This is Dr. Dublin from Kaiser Permanente, Washington. I wanted to ask if the FDA presenters could show again the slide that focused on the second half of the enrolled patients in the outpatient study in P002, where it showed the difference in the death rates in the second half of the group versus the first half.

While they're getting the slide up, I had a follow-up question for the sponsor, again, hypothesizing about why you might have not seen a treatment benefit in the very tail end of the study. I wondered if you collected data on concomitant treatments participants might receive or if they were barred from receiving concomitant treatments such as oral steroids, or fluvoxamine, or other things that could have been given off label.

DR. KARTSONIS: Thank you for that question, Dr. Dublin. We've looked at that very carefully, concomitant therapies, obviously, those that received them through the interim analysis, those

that received them in the second half, and particularly in that last 20 percent cohort, and there really weren't any differences in terms of those therapies.

For the most part, people were not allowed to receive other concomitant COVID-19 therapies. There were some countries that did allow for steroid use, so in that situation that was permitted, but the numbers who actually received it was exceedingly low.

We also allowed for DVT prophylaxis with either a factor 10a, or heparin, or low molecular weight heparin, just to prevent that risk based on the evolving data in terms of that. But people weren't allowed to receive monoclonal antibodies or any other therapies that may or may not have impacted on that.

We've looked at the entire study of COVID-19 therapies, and -- slide up, please -- you'll see that, if anything, over the course of the study, there were fewer proportions of patients in molnupiravir --

DR. BADEN: Sorry. We're not in a position to vacillate between sponsor and applicant presentations. They pulled up the FDA's presentation --

DR. KARTSONIS: Okay. No problem.

(Crosstalk.)

DR. BADEN: -- so [indiscernible], Dr. Kartsonis.

DR. KARTSONIS: I'm sorry. The only point I will just say is that, proportionally, there were 10 percent of people on molnupiravir versus 12 percent on placebo that received any COVID therapy, but there weren't any differences -- those were mostly therapies that were received after people had already been hospitalized. So I'll stop there.

DR. BADEN: Dr. Dublin, they've pulled up slide 10 that you've asked for, from the agency's presentation.

DR. DUBLIN: Perfect. Thank you.

DR. BADEN: And your question to the agency on this?

DR. DUBLIN: I just wanted to review again the way the death rates looked different in the second half versus the first half; so I'm just perusing it.

DR. HODOWANEC: So as we can see here, there were zero deaths in the molnupiravir arm in the first half of the trial compared to eight in the placebo arm, for a 0 percent versus 2.1 percent death rate in that first half of the trial. And then if you look in the middle columns there, reflecting the second half of the trial, you can see there is one death in each arm; so less than 1 percent death rate in each arm in the second half of the trial.

DR. DUBLIN: Great. Thank you.

DR. BADEN: Dr. Le, you had a follow-on question.

(No response.)

DR. BADEN: You're on mute, Dr. Le.

DR. LE: Hi. Jennifer Le. I have a question related to the forest plot. I think it was slide CC-28, and kind of tying in to

Dr. Green's comment about mortality, when we've looked at the interim versus the full analysis, the absolute risk reduction also decreased. I think it was about minus 6 percent to minus 3 percent, encompassing both mortality and hospitalization.

I wanted the applicant's feedback in terms of why was there this difference, and particularly to see if there's any effect regionally, because when you look at the forest plot for North America, it differed a little bit with other countries.

DR. KARTSONIS: Sure. Thank you for that question. I tried already to answer the question earlier regarding the different effect that we saw in the post-IA period of the trial versus the interim analysis section. And as I indicated, there are some factors that might suggest to have driven it down a little bit, but there are also some factors that might have anticipated that it would have gone up. So again, we don't have a convincing explanation as to why the effect was lower.

Obviously, everybody who died in this study

had previously been hospitalized, so it's not like there's a difference in terms of those factors; it just was lower overall across the board in the second half of the study.

Now, your question about the region is an important one, and you do see here on this slide the breakout by continents. But continents are big places, and practices do differ at a country-by-country level. So we've also looked at the data at the individual country level, and I can show that to you.

Slide up, please. What you'll see is a pretty consistent effect for molnupiravir across the different countries that we've seen, for the most part. I'm obviously focusing on the difference here and for the negative numbers that we're looking for, which would favor molnupiravir versus placebo. Generally, you are seeing a consistent -- somewhere between a few percentage points up to a higher percentage point.

Brazil is an outlier in favor of molnupiravir and Guatemala is an outlier in favor

of placebo, but everything else sort of lines up with the estimates that we've seen across the board.

We think this is a pretty consistent result, and it makes sense because the way we defined hospitalization in this study was you had to be hospitalized for 24 hours, or at least 24 hours. So it eliminates those possibilities of people who just got hospitalized for a few hours or maybe got stuck in the emergency room and whathaveyou. So we think it is a more firm assessment of the hospitalization aspects. So I hope that answers your question, Dr. Le.

DR. LE: Thank you. That's all.

DR. BADEN: Dr. Hunsberger, you have a follow-on question?

DR. HUNSBERGER: They answered my question. I took my hand down, so thank you.

DR. BADEN: Thank you.

Now we can move to the next question. It's Dr. Coffin.

Dr. Coffin, do you have a question?

DR. COFFIN: Yes. Thank you. John Coffin, Tufts Medical School.

Actually, a lot of the topic of discussion is going to be, hence, the possibility of enhanced evolution of the escape mutations, and there's also a lot of what we've seen in the press and so on in the last few days. So I'd like to have the sponsor's view on that. We didn't hear much about that topic specifically.

DR. KARTSONIS: Yes. We didn't talk about Omicron at all in terms of what's happening around the world. As Dr. Hazuda shared earlier today, as new variants have been becoming available, we have been testing them for the activity of molnupiravir. She showed you the data earlier today regarding alpha through delta. We now have results for lambda and mu, which are both variants of concern, and we see consistent efficacy for molnupiravir.

We expect, based on what we know about the Omicron variant, that molnupiravir would be effective against this particular variant. When you look at the changes that are seen in Omicron,

the changes that are seen are changes that have been seen with other variants that have already been shown to be effective, at least in the non-spike region.

If I could put the slide up, please. Here is a slide that shows the original Wu variant, which was the wild type, relative to Delta, 21A Delta, and then the AY42, which is the 21J clade, and finally Omicron. You can see some of the changes that are seen in Omicron have already been seen in Delta in the polymerase at the 323 position, and in the 671 position, the change is consistent with what's been seen with Wu.

So we have every expectation that, based on the mechanism of action of molnupiravir, it should work against this particular variant. The same goes when you look at NSP14, which is the exonuclease. Similar changes have been seen before.

We haven't tested it yet. As you can imagine, we are feverishly working to collect samples and do that. It does take a little longer

to do this testing for us as opposed to a monoclonal antibody because we have to actually evaluate it across the entire genome. We need to collect the virus and evaluate it thoroughly, but we are committed to get those results out as soon as they're available. So thank you for the question, Dr. Coffin.

DR. COFFIN: Yes. Actually, that was a nice answer, but my question was a little different. I was concerned about the possibility that the drug, by being a mutagen, may in fact be enhancing the possibility of creation of yet even worse variants; that that's been raised by a number of people who have been interviewed on this topic that I've seen on the news.

DR. KARTSONIS: Thank you for that. I think Dr. Hazuda had covered that earlier today. And maybe what I can do is put up that slide, CA-8, where we talked about it, and maybe I can hand it over to Dr. Hazuda to provide a perspective on this issue.

DR. HAZUDA: Thank you, Dr. Kartsonis; Daria

Hazuda from Merck.

As we showed in the core presentation --

DR. KARTSONIS: Slide up, please.

DR. HAZUDA: This study here is the interim analysis from day 3. But in all of the studies to date, we have observed changes in spike in both the placebo- and molnupiravir-treated subjects. Also to date, all of the changes in spike that we've observed in all of the analyses are changes in spike that have been observed in circulating variants.

It's also important to note that although there did seem to be some imbalance in the number of mutations or substitutions in spike that were observed in some of the studies with the molnupiravir treatment group, if you look very carefully at where those errors reside, it's largely in a very small number of patients that seem to account for the large number of errors in spike.

Again, if you look very carefully at those particular samples, in general, most of those

samples in fact were in patients for whom the baseline clade that was assigned was different from the end-of-treatment clade. So these are changes from baseline, and the baseline clades were different, which suggests that at least for those small number of samples, there was either a sampling error or a contamination error that might have accounted for those large number of changes based on the fact that the clade assignments were very different.

So if you then discount or look at those patients where there were treatment-emergent mutations in spike in the placebo group versus the molnupiravir group, they are actually very similar in terms of the number of participants who have such changes.

Most of the changes are not transition mutations. They're either transversions, or insertions, or deletions. And again, if you look across all of our studies, the vast majority of changes that we observe with molnupiravir treatment are in fact transition errors, and this is true in

our clinical studies, and it's also true in animal models. Then last but not least, as Dr. Harrington also showed, in all cases where we had observed changes at end of treatment, no infectious virus could be recovered from those samples.

The last point I want to make with respect to the point about recovery of infectious virus in clinical studies, yes, we agree with the statement from Dr. Harrington that the sensitivity of recovery of virus for clinical studies is somewhat problematic, but I would note that in animal studies, this is not the case. There is a huge dynamic range when you sample -- can I have the slide up, please, for the infected mouse study?

The preclinical models don't suffer from that. There's a huge dynamic range in your ability to recover infectious virus, from tissues as well as nasal samples. And as shown here, this is one example of a study in a SARS-CoV-2 infected mouse model, which really demonstrates that end of treatment with just a few days of molnupiravir, the amount of infectious virus that you recover

post-treatment with MK-4482, or molnupiravir, is dramatically reduced by orders of magnitude compared to the vehicle control.

So while we agree that there are limitations to sampling infectious virus in clinical samples, you can do this very easily in preclinical models. And I think this data, as well as many published studies, demonstrate that there are orders of magnitude reductions in infectious virus titers upon treatment with molnupiravir.

DR. COFFIN: Did you sample for virus genome -- I'm getting an echo --

(Audio feedback.)

DR. COFFIN: -- at a time when -- I'm sorry; the echo is confusing.

Did you sample for infectious virus at a time when the -- or sample permutations at a time when there was infectious virus, before 5 days in the case of the high-level treatment?

DR. HAZUDA: I don't have that data from that particular study, but we did do it in one of the early clinical studies where we did dose

ranging. Or at earlier time points where we did recover infectious virus, we didn't see spike mutations. In the only sample where we recovered infectious virus where there was spike mutations, it was actually a placebo sample.

DR. COFFIN: Okay. Thank you.

DR. BADEN: Just a follow-on to Dr. Coffin's question, and there are a few others.

Part of the clearance when you treat individuals who have COVID is their immune system clears the virus. How do you think about the risk of this mutagenesis in the virus where you have an immunocompromised host who can clear the virus? And we've seen immunocompromised hosts have virus that are culturable for months. How do you assess that risk given the mutagenesis to the pathogen, to the applicant, Dr. Kartsonis?

DR. KARTSONIS: Yes. Thank you for that, Dr. Baden. Obviously, this is something that we've considered carefully. We did include immunocompromised individuals within our clinical program. About 4 percent of them either had

cancer, or HIV infection, or transplant individuals. In general, we didn't see -- obviously, we're still evaluating the genomic substitution data from the phase 3 portion of the trial, and we're still looking at the infectivity data from the trial but, in general, we are seeing good clinical outcomes in these individuals.

So we're not seeing an increased rate of hospitalization or other complications in that particular regard, particularly the cancer population. Cancer patients are a very diverse group. But of the 39 people that were in this trial who had an underlying active cancer, the event rate was half what it was in placebo. So yes, there were 4 cases on placebo versus only 2 cases on molnupiravir.

Obviously, it's something that we will continue to assess, and that's obviously one of the things we can continue to do as we look at our own data, and as I mentioned, the genomic data and the infectivity data; and obviously something in the

real-world setting that we can collect as part of standard surveillance to see if there are any particular concerns that might arise.

DR. BADEN: Dr. Fuller, you have a follow-on question?

(No response.)

DR. BADEN: You're on mute, Dr. Fuller.

(No response.)

DR. BADEN: You're still on mute.

Is that Dr. Fuller? If not, Dr. Hildreth has a follow-on while Dr. Fuller works out the audio.

DR. HILDRETH: Thank you, Dr. Baden. This is James Hildreth from Meharry Medical College. I wanted to follow on to the question about our evolution and escape mutants. Even if the probability is very low -- 1 in 10,000 or 1 in 100,000 that this drug would induce an escape mutant for which the vaccines we have do not cover -- that could be catastrophic to the whole world, actually.

So do you have data that you can properly

estimate the likelihood of this happening? And since we know that both transversions, as well as transitions, are possible, there's clearly a real possibility that that could happen. So do you have sufficient data to estimate the likelihood of that event happening in your data set, or can you comment about that, please?

DR. KARTSONIS: So we don't, but what we've been able to share with you earlier today is that at least proportionally we're not seeing increased rate in the phase 3 population in terms of unusual spike variants being formed relative to placebo. Obviously, we will continue to collect -- I think the data that's going to be most valuable is the full data set from this trial because we have samples that we'll be able to look at longitudinally, both from molnupiravir as well as placebo, and not only to evaluate how people do in that, but then we can also assess infectivity to see if there are any particular differences.

Theoretically, I can't answer that question because we don't feel that there's a notable

difference. But as the FDA also alluded to, this is the same risk that could happen as a result of vaccines or monoclonal antibody therapies as well, nor do I think there's data available there either.

DR. HILDRETH: I'm sorry. With all respect, the mechanism of action of your drug is to drive mutagenesis, so it's not the same as a vaccine. It's not the same as monoclonal antibodies. You're purposely mutagenizing the virus, which means that the likelihood of escape mutants is considerably stronger than it would be with those other kinds of treatments.

So with all respect, I think it's incumbent upon you to make some effort to make an estimate of what is the likelihood of escape mutants occurring as a result of your drug. Thank you.

DR. BADEN: Thank you, Dr. Hildreth.

Just to build off Dr. Hildreth's point, Dr. Kartsonis, are there strategies to decrease the risk of escape mutants occurring, such as completing the duration of therapy as recommended, or short courses, or inadequate treatment, a

differential risk; and then in certain patient populations, will the risk be enhanced?

What strategies are you thinking on that can decrease this concern that Dr. Hildreth raised?

DR. KARTSONIS: Yes. Thank you for that question, and we appreciate Dr. Hildreth's perspective on the issue. In terms of actual completion of course, indeed we will be recommending in the fact sheets that people complete their treatment course. And we feel confident, based on the data we've seen in the clinical program, that people will do that.

Ninety-five percent of the patients received at least 9 doses in this trial, so adherence was very high. And the fact that we have a very well-tolerated agent I think will facilitate that people work towards completing their course. But we do agree that there should be emphasis that people do work to complete their full course, as you would with any anti-infective that might be available.

Now strategies-wise, I mentioned what we're

doing to look at the data from our clinical study, which I think will be very informative. We are exploring the feasibility of using currently available public SARS-CoV-2 sequence databases to monitor for the emergence of these novel variants in the replicase complex, as well as the spike proteins. Obviously, that's one way we're working towards that, then obviously we can then see how that correlates over time.

With that, we will continue to work with the agency and mitigation strategies to help address this theoretical concern.

DR. BADEN: Thank you.

Moving to another line of questioning, Dr. Swaminathan, you have a question?

DR. SWAMINATHAN: Yes. Can you hear me ok?

DR. BADEN: Yes, we can.

DR. SWAMINATHAN: Hi. This is Sankar Swaminathan from the University of Utah.

I would ask you to look at the addendum that the agency sent out today to the FDA briefing document. In figure 1, there's a comparison of the

incidence of hospitalization or death in the full population broken down by various risk factors and other characteristics. What was most striking to me is that there is quite a remarkable difference in the efficacy of the treatment among the various clades that were described. Of the 22 excess cases in placebo compared to molnupiravir, of those 22 cases, 18 of them occur in variants other than Delta, particularly gamma, but also mu and others, so the percentage difference in the confidence intervals are at least significant in the Delta variant.

Just looking at those numbers, my ability to do p-values in my head has declined considerably, but I would assume that those are quite significant differences that are clade dependent. And a quick comparison to the interim population that I believe was in the applicant briefing document suggests that that difference in clade percentage would have been even greater in the first half of the study.

This raises the question in my mind as to whether there is, in fact, a clade-dependent

efficacy, particularly considering that Delta is now the overwhelmingly predominant strain in the United States.

I'll stop there, and this question is for the applicant.

DR. KARTSONIS: Thank you for that question. We have looked at that. You are right. When you look at the data by different variants, the difference is least with Delta relative to other variants. Now keep in mind, the second part of the study was almost entirely with Delta variants, so that probably explains it.

Maybe I can put this slide up, please. You don't have to do the p-values. We don't do p-values, even on subgroups because these are not things that -- we're not adjusting for multiplicity on any of these subgroups. And it's not surprising that some subgroups will invariably go one way versus another and/or show different treatment effects, as one might expect. But I am showing we have 95 percent confidence intervals for all of the different variants, and this is the most up-to-date

data we have, and we're still testing clades on a weekly basis.

You mentioned that in the Delta, the difference was minus 2 as opposed to in other clades. We've looked at this, and one of the things we've done is we've actually looked at what's the viral RNA reduction in Delta versus other clades, and it doesn't differ. The latest data we have from Delta is that at day 5, there's a 0.47 log drop, a minus 0.47 log difference, in titers at day 5 relative to placebo.

So we're still seeing that same consistent effect, but I think a lot of this goes back to what we discussed earlier with Dr. Baden's question in terms of what we saw in the second half of the study. And recognizing most of it was Delta, it's not surprising that the efficacy difference closed between the interim analysis and the all randomized population.

DR. BADEN: Thank you.

I think Dr. Fuller has reconnected, and please ask your question related to the prior

discussion, Dr. Fuller.

DR. FULLER: Thank you. Can you hear me this time?

DR. BADEN: Yes.

DR. FULLER: Alright. This is Dr. Oveta Fuller from University of Michigan. I wanted to clarify about the evolutionary impact of the drug, and I think some of my questions were answered. But we know that drugs notoriously can cause resistant mutants and viruses to occur, and here you are asking people, or allowing people, or proposing that people take this for only 5 days. If I understand the data, the drug reduces virus shedding to the point that you cannot isolate infectious virus after the 5-day regimen.

Have you a recommendation of what those people will do to make sure that anything that might have slipped through, any virus that may be lingering, is not communicated to somebody else or that there's some sort of follow-up?

I think some of this question was addressed by the subsequent questions when I could not be

heard, but what will be the recommendation for people, if this is approved as an EUA, who take this regimen for 5 days, and only 5 days? You can't go back and get more, would be my understanding. Is that correct?

DR. KARTSONIS: That is correct. Our recommendation would be that people take the full 5-day treatment course irrespective of their situation. I think the adherence data speak to the fact that we believe people can do that, and obviously we will encourage that. Obviously in our conversations we'll have with the agency, we want to make sure that we encourage that the full completion course is attained.

I will, though, make one point, is that at least to date, through all of our phase 2 studies we've done and our phase 3 program we've done, if you do treat people with 5 days, we have yet to identify a single case of infectious virus at day 5. I think that that's a very positive sign.

We do take the points around the infectivity assay not being a perfect assay and whathaveyou,

but on the same time point we even saw that with the 400-milligram dose in the studies that I showed earlier this morning. And even at 400 milligrams, at half the dose -- if I can go back to the infectivity results, CC-9 -- you'll see that even at the 400-milligram dose, by day 5, people had fully completed their treatment course. By day 5 in the 400-milligram group, nobody had infectious virus either at 400 milligram or 800 milligrams, and by day 3, we could only identify one situation where a person had infectious virus at that time point.

I think it does speak exactly to the point we're trying to make as well, that people do need to finish their treatment course, but it's not just to prevent evolution; we think that's the right thing to do to give people the full benefit of this therapy.

DR. FULLER: Yes. So what you're saying is that you really have found no infectious virus at the end of the 5-day treatment. And in the messaging that needs to go out, it should be

absolutely emphasized the need to complete the treatment as prescribed with, one, the reduction of disease possibility but, two, making sure that there are no viruses that will be generated from this that could possibly be passed on or shed, in even rare cases, to somebody else. This would be so critical in the messaging.

DR. KARTSONIS: We agree. Thank you, Dr. Fuller.

DR. BADEN: But these are immunocompetent individuals, so to some degree, you have not tested the question in individuals who can't have a meaningful immune response, which is a complicating feature that's been unassessed.

DR. KARTSONIS: Fair point, Dr. Baden. What we have is just the data that -- we've allowed for those patients to be included in our clinical trial, but we haven't done a separate evaluation of immunocompetent individuals; that is true.

DR. BADEN: I think there is follow-on.

Dr. Burgess?

(No response.)

DR. BADEN: You're on mute, Dr. Burgess.

CAPT BURGESS: Thanks, Dr. Baden. This is Tim Burgess from USUHS at Bethesda. The question for which I raised my hand was very similar to the question Dr. Swaminathan asked, and my follow-on question is on that theme for Dr. Kartsonis.

With respect to the clade-specific efficacy of molnupiravir, you said that there was similar proportional reduction from baseline regardless of clade. What about absolute reduction from baseline? Were there clade-specific differences there? In other words, if the baseline viral load, so to speak, from gamma was lower compared to individuals with Delta, is there a difference there? Thank you.

DR. KARTSONIS: We looked at that. Yes, thank you for that question.

We've looked at where people are starting in terms of that, and the latest data we have from Delta is that people are starting with a mean titer of over 7 logs, which is consistent with the overall data we're seeing. And we've looked at it

where we can. We've looked at mu, we've looked at delta, we've looked at gamma, which are three most common ones that we can look at and get a better evaluation of RNA, and we're not seeing any differences in terms of where people are beginning. So in that sense, when we're talking about the difference, I do think it's a little bit more of an apple-to-apple comparison.

CAPT BURGESS: Thanks. So just to be clear then, no difference in where they end up?

DR. KARTSONIS: Yes, really no difference in where they end up. Most people end up somewhere around 10 to the third log. Remember, this assay is pretty discreet. The limit is 500 copies per mL, but the means that we're looking at, for the most part, people end up, by day 10, at around 10 to the 3 logs.

CAPT BURGESS: Thank you.

DR. BADEN: Dr. Weina, you have a follow-on question?

DR. WEINA: Yes, I do. This is Pete Weina. Regarding the potential for active virus being

present, I was just wondering, as this is an outpatient therapy, was there any monitoring of family contacts for illnesses as well, or attempts to look at potential close-contact cases, or anything like that during the clinical trials? Thank you.

DR. KARTSONIS: Yes. Thank you, Dr. Weina, for that question. There wasn't any monitoring in that particular regard. I can't answer the question about did the virus spread to family members or whathaveyou.

I will tell you we are doing a post-exposure prophylaxis trial. That study is currently recruiting. It's a pretty large study, about as large as where PROTOCOL 002 ended up. I'm not sure that study enrolls people who already have an index case, and then follows the household contacts and treats those household contacts to prevent infection. In that study, we are doing a little bit more evaluation around the other members of the family but, no; at the end of the day, we don't have data from PROTOCOL 002 to support your

question.

DR. BADEN: Thank you.

Dr. Dublin, you have a follow-on question?

DR. DUBLIN: Thank you. I'm following up on Dr. Fuller's questions about the lack of detectable virus after 5 days. I was wondering if you have any data for days after day 5, after people had ceased treatment, if they could potentially have any infectious virus, if you had looked later.

DR. KARTSONIS: I don't believe we do. I think once people got negative at day 5, we didn't continue to do any further testing. And also, we know that, unfortunately, by day 5 your virus is already at a low titer, that by day 10, you're not -- the time points we looked at were day 1, 3, 5, and then day 10. So by that time point -- actually, we do have some data. Let me show you some data from our PROTOCOL 002 study that I've just been made aware of.

If you could put the slide up, please? What I showed you in today's presentation with the data from PROTOCOL 006, part of the reason we chose

PROTOCOL 006 is because the proportion of patients who had positive infective virus at baseline was higher and also because there was an equal distribution across the treatment groups.

Here, as you can see, there tend to be more patients who had infectious virus. This is the phase 2 portion of our outpatient study, PROTOCOL 002, and you can see that most individuals didn't have infectious virus. But when they did at baseline, it tends to be slightly higher on the molnupiravir arm versus placebo. But by day 5, as you can see, you still have participants in the placebo group who have positive virus, and they still do so out to day 1.

Your question about later time points, you can see at day 10 by that time point, even at a dose of 200 milligrams, nobody had infectious virus identified. Now, mind you again, we're starting with low N's across the board, but I think it's encouraging when you look at the totality of the data across the different [inaudible - audio fades].

DR. DUBLIN: This is Dr. Dublin to follow up. Was this also 5 days of treatment?

DR. KARTSONIS: Yes. This was the phase 2 portion of PROTOCOL 002. What I showed you earlier today was PROTOCOL 006, and in both those studies, the duration of therapy has been 5 days. In fact, in every patient we treated to date across our program, everyone has gotten 5 days of therapy. We have not looked at different durations of therapy beyond 5 days.

DR. DUBLIN: Thank you. This was very helpful to me.

DR. BADEN: Thank you.

It is now 12:46. We will take a 44-minute lunch break. We will then resume with the open public hearing session. When that concludes, we will continue with the Q&A with the applicant and the sponsor. So thank you all; back in 43 minutes, please.

(Whereupon, at 12:46 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

Open Public Hearing

DR. BADEN: It is now 1:30, and we shall resume. We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in the

meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please only speak when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected

now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. CAROME: I'm Dr. Michael Carome, director of Public Citizen's Health Research Group. I have no financial conflicts of interest.

With respect to the requirement that must be satisfied in order for the FDA to issue an EUA for molnupiravir for the treatment of mild to moderate COVID-19, the key question facing the FDA and this committee is whether the known and potential benefits of molnupiravir, when used to treat COVID-19, outweigh the known and potential risks of the drug; and if so, for which patients?

With respect to the known and potential benefits of molnupiravir, the updated fall population analysis of data from trial MK-4482-002, hereafter referred to as trial 002, for all 1433 randomized subjects revealed a modest, at best, reduction in the risk of all-cause hospitalization or death through day 29, 6.8 percent in the molnupiravir group versus 9.7 percent in the

placebo group, which represented an absolute risk reduction of molnupiravir comparable to placebo of minus 3 percent, with a 95 percent confidence interval of minus 5.9 percent to minus 0.1 percent and a relative risk reduction of 30 percent.

In addition, there was only one death in the molnupiravir group and 9 deaths in the placebo group. Notably, data from the post-interim analysis population for trial 002 -- which included 646 subjects enrolled during a period when the SARS-CoV-2 Delta variant became the predominant variant and causing COVID-19 cases -- found that the incidence of all-cause hospitalization or death through day 29 was 6.2 percent in the molnupiravir group versus 4.7 percent in the placebo group, with only one death less than 1 percent in each group.

Importantly, subgroup analyses of trial 002 and in vitro assessments of antiviral activity of the ribonucleoside analog N-hydroxycytidine, the major initial metabolite of the prodrug molnupiravir, suggest that the known and potential benefits of molnupiravir, at least at the proposed

dosage of 800 milligrams every 12 hours, may be substantially lower in patients infected with the SARS-CoV-2 Delta variant, which is currently responsible for more than 99 percent of COVID-19 cases in the U.S., compared with the known and potential benefits in patients affected with SARS-CoV-2 gamma or other variants.

In particular, as shown in figure 1 of the FDA's addendum to its briefing document, the absolute risk reduction of molnupiravir compared with placebo for all-cause hospitalization or death through day 29 was minus 19.1 percent with a 95 percent confidence interval minus 32.6 percent to minus 8.9 percent for patients infected with the gamma variant, but only minus 2.4 percent with a 95 percent confidence interval of minus 7.8 percent to plus 2.9 percent for patients infected with the Delta variant.

These clinical findings are consistent with data from in vitro studies of the antiviral activity of N-hydroxycytidine shown in figure 2 of the sponsor's briefing document, which revealed a

half maximal effect of concentration, or IC50, of 1.32 micromolar against the gamma variant and 1.68 micromolar against the Delta variant. Subgroup analyses also found no reduction in the risk of all-cause hospitalization or death through day 29 in subjects who tested positive for anti-SARS-CoV-2 antibodies at baseline.

The absolute risk reduction of molnupiravir compared with placebo for all-cause hospitalization or death through day 29 was positive 2.3 percent with a 95 percent confidence interval of minus 1.7 percent and positive 7.1 percent in subjects with positive baseline antibodies.

With respect to the known and potential risks of molnupiravir, although no major safety signals were identified in trial 002 or other clinical trials, several potential safety concerns pertaining to the drug were identified in preclinical studies, including embryo-fetal toxicity, bone and cartilage toxicity, and mutagenicity, including mutagenicity in vitro in mammalian cells and possibly in vivo in the Pig-a

assay.

There's also evidence that molnupiravir may increase the rate of mutations in the viral spike protein, which in theory could enhance SARS-CoV-2 spike protein evolution and accelerate the development of new variants that escape the immune protection provided by COVID-19 vaccines, or natural immunity following SARS-CoV-2 infection, or that are resistant to the currently authorized anti-SARS-CoV-2 monoclonal antibodies.

The risk of evolutionary viral mutations may be enhanced by tissue exposure to low N-hydroxycytidine concentrations, which is likely to occur given the proposed 12-hour dosing interval of molnupiravir and pharmacokinetics data that demonstrated amine and N-hydroxycytidine maximum plasma concentration, or Cmax, of 10.8 micromolar and an effective N-hydroxycytidine half-life of only 3.3 hours in subjects receiving 800 milligrams of the drug every 12 hours.

Based on the available clinical and preclinical data for molnupiravir, there is

significant uncertainty regarding whether the known and potential benefits of the drug for treating COVID-19 at the proposed dosage outweighs the known and potential risks of the drug.

If the FDA decides to issue an EUA for molnupiravir for certain adult patients who are at high risk of progression to severe COVID-19, we recommend the following.

One, the FDA should further assess whether the dosage of 800 milligrams every 12 hours is adequate to provide sustained and effective antiviral activity against the SARS-CoV-2 Delta variant in vivo.

Two, given, A) the robust protection provided by COVID-19 vaccines against severe disease that protect against hospitalization or death; B) the overall modest, at best, benefit of molnupiravir as the treatment for mild to COVID-19 in unvaccinated patient populations enrolled in trial 002; and C) the subgroup analyses showing no reduction in the risk of all-cause hospitalization or death through day 29 in subjects who tested

positive for SARS-CoV-2 antibodies at baseline, the FDA should exclude fully vaccinated individuals from the population of patients eligible to receive the drug, except perhaps vaccinated people who are immunocompromised.

Three, given, A) the substantial evidence of embryo-fetal toxicity found in preclinical animal studies; B) the modest benefit of molnupiravir as a treatment for mild to moderate COVID-19; and C) the availability of authorized anti-SARS-CoV-2 monoclonal antibody products for the treatment of mild to moderate COVID-19 in individuals who are at high risk for progressions to severe disease, the FDA should exclude pregnant women from the population of patients eligible to receive the drug.

Four, given the potential risk of embryo-fetal toxicity, the agency should require that prescribing healthcare professionals verify that an individual of childbearing potential is not pregnant. For all patients of childbearing potential verified to be not pregnant, the agency

should recommend the use of an effective method of contraception, which would include abstinence from sexual intercourse, for the duration of molnupiravir treatment and for 4 days after the final dose of the drug.

Five, given, A) the absence of data on the presence of molnupiravir or its metabolites in human milk; B) the detection of N-hydroxycytidine in plasma of nursing pups from lactating rats administered molnupiravir; and C) the substantial evidence of bone and cartilage toxicity in preclinical animal studies, the FDA should recommend that lactating individuals not breastfeed for the duration of molnupiravir treatment and for 4 days after the final dose of the drug.

And six, finally, if the FDA subsequently issues an EUA for another oral antiviral drug product for which the known and potential benefits appear to be greater than those for molnupiravir, and for which there are not safety concerns regarding embryo-fetal toxicity, bone and cartilage toxicity, mutagenicity, and acceleration of the

development of new SARS-CoV-2 variants, the agency should promptly consider whether the EUA for molnupiravir should be revoked. Thank you for your attention.

DR. BADEN: Thank you.

Speaker number 2, your audio is now connected. Will speaker number 2 begin and introduce yourself? Please state your name and any organization you're representing for the record.

DR. ISMAGILOV: My name is Rustem Ismagilov. I'm a professor at Caltech, however, opinions are my own. I'm very grateful for the work by the sponsor and the agency in developing and evaluating infectious disease therapies. I appreciate this opportunity to speak about the risks of emergence of new SARS-CoV-2 variants of concern driven by molnupiravir-induced mutagenesis. No conflicts of interest in this matter. My previously submitted written comments are publicly available.

Recent emergence of the highly mutated SARS-CoV-2 Omicron B.1.1.529 variant remind all of us that SARS-CoV-2 has not reached its evolutionary

limits and viral evolution is still a significant concern. How Omicron variant evolved with these numerous mutations is unknown.

Molnupiravir works by inducing mutations in the SARS-CoV-2 viral genome at high concentrations over a sufficiently long time. It leads to lethal mutagenesis and makes non-viable virus. However, lethal mutagenesis of a general approach can fail in some people for many reasons; for example, subtherapeutic concentrations of the drug or the treatment is too short, or the virus finds a refuge in body compartments with lower drug concentration, or some mutations the drug induces actually benefit the virus.

These coronaviruses have a low-based mutation rate, about 1 mutation per million copies and base pairs for SARS-CoV-1, so it's unlikely for numerous mutations to occur simultaneously during normal viral replication. Molnupiravir can induce numerous mutations simultaneously. After the treatment is complete, it can then be selected on the basis of the ability to escape the immune

response.

The FDA briefing document describes that, as expected in treated humans, molnupiravir induce mutations in SARS-CoV-2 genome, including mutations in the spike gene, which is targeted by the vaccine from the immune system, thus increasing mutations as observed on average and is concerning.

I emphasize that the concern with molnupiravir-induced mutagenesis is not only the increase in the average number of mutations per person but millions of patients potentially treated. Even rare -- 1 in 100,000 or 1 in 10,000 -- evolutionary events can become highly impactful if they lead to spread of any escaped variants.

We must look for evidence of such rare evolutionary events in molnupiravir-treated individuals. The FDA briefing document describes such evidence. In a few participants, numerous molnupiravir-induced mutations were found, including immune escape mutations in spike genes.

I'd like to make two key points. First, a

week ago, when this analysis was completed by the FDA, it was difficult to imagine that SARS-CoV-2 would produce such large evolutionary jumps with numerous and concerning mutations. This week, now that we know about the Omicron variant, we cannot dismiss this evidence. It's critical to resequence and reanalyze all these samples and compare the magnitude of the evolutionary change to that in the Omicron variant and make the data public.

Second, analyzing only a couple hundred individuals treated, where molnupiravir produced this evidence of extensively mutated virus with many concerning spike mutations, but millions of people are treated who would have tens of thousands times more evolutionary events.

Transmission of the molnupiravir-induced mutated virus is also of concern. Lethal mutagenesis can drive viral loads low, reducing probability of transmission. However, in a complex environment like a human body, this is not guaranteed. Elimination of transmission has not been proven, in general, for molnupiravir-treated

individuals. Aerosols are generated in the lungs, but we don't know the level of culturable virus in the lungs of treated individuals. Of particular concern is transmission during the treatment when culturable virus was detected in transmission from immunocompromised individuals during and after the treatment.

To summarize, antiviral drugs are important in this pandemic. However, data suggests that extensive SARS-CoV-2 evolution and selection may have already occurred in a few molnupiravir-treated individuals to produce highly mutated viruses of concern. Let's not assume that these are technical artifacts because the recent emergence of the highly mutated Omicron variant shows such extreme evolutionary events do occur and do have global impact.

Additional viral sequencing from these molnupiravir-treated individuals and public release of these data are urgently needed. In addition, it would be prudent to obtain and analyze viral sequencing data from the P001 inpatient trial in

which a numerically higher proportion of participants died in all three molnupiravir-treated groups compared to placebo. One should exclude the possibility that drug-induced viral evolution and immune escape played any role in these deaths.

The potential for transmission of SARS-CoV-2 events generated by molnupiravir treatment, especially during treatment and in immunocompromised patients, cannot be eliminated based on the current data. If molnupiravir is used in millions of people, even rare drug-induced viral evolution and transmission would reset all of the progress the world has made building immunity against the virus.

The sponsor, the advisory committee, and the FDA must take all possible steps to ensure that such molnupiravir-induced mutagenesis and production of new SARS-CoV-2 variants of concern does new not occur. Thank you.

DR. BADEN: Thank you.

Speaker number 3, your audio is now connected. Will speaker number 3 begin and

introduce yourself? Please state your name and any organization you're representing for the record.

DR. SEYMOUR: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Meg Seymour, a senior fellow at the center. The analyzed scientific data is to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

You're being asked to assess whether the known and potential benefits of molnupiravir outweigh the known and potential risks for those who are at high risk of severe COVID-19 infection. However, the balance of benefits and risks nay differ between different types of patients, and not all types of patients were studied.

Let's start by talking about vaccinations. All patients in the study were unvaccinated. To be approved for vaccinated patients as well, almost 60 percent of the U.S. population has been fully

vaccinated, and many of them still have antibodies to the virus.

The sponsor's data indicate that MOV patients with antibodies to the virus did no better than placebo. Without data on vaccinated patients, there's no way to know the safety and effectiveness of MOV for vaccinated patients, and yet you're being asked to vote on whether MOV should be authorized for all patients at risk, which includes the vaccinated.

The FDA proposed facts sheet for healthcare providers does not mention that the drug has only been tested on the unvaccinated. That limitation data needs to be noted and made clear to healthcare providers, who are otherwise likely to prescribe the drug to all patients, not just unvaccinated patients.

The study also only examined those with pre-existing conditions that are known to be risk factors for severe COVID-19. Drugs should not be used for populations that they're not tested on due to unknown safety and effectiveness in unstudied

populations. If authorized, what would FDA do to restrict the use of MOV only to the patients most likely to benefit? There are other patient groups that should be excluded from an EUA.

We agree with both the FDA and the sponsor that because of the potential developmental risks, MOV should only be used in those 18 or older. Given the findings from animal studies about the fetal toxicity of MOV, we are convinced that the known and potential benefits of MOV outweigh the known and potential risks of MOV in pregnant individuals. For that reason, if an EUA is granted today, it should not be authorized for pregnant patients. We also support the FDA's suggested protocol for lactating.

Finally, let's focus on the overall safety and effectiveness of MOV. Although the relative risk reduction for those taking the drug compared to placebo is described as 30 percent, there's only a 3 percent absolute difference in incidence of hospitalization or death between the two groups. Since the patients in the study were selected to be

the most at risk of severe COVID-19 due to their unvaccinated status and underlying health conditions, a 3 percent reduction in hospitalization or death seems to be a rather small benefit for any individual patients.

As noted in other data provided by the sponsor, the benefit may be even smaller for patients who are vaccinated, under 60, and/or who have no underlying conditions. Given that modest benefit, the unknown risk should be of greater concern.

FDA notes in the briefing document that the safety sample is relatively small compared with that of other COVID-19 treatments granted EUAs. Even with the additional data presented today, is the safety sample large enough to evaluate rare but serious side effects? Unfortunately, it's difficult to determine which adverse events in the studies were caused by the drug and which were probably a symptom of COVID-19 infection.

Given the modest benefit and much greater range of patients that may take MOV if it is

authorized, how confident are you of the proven benefits versus risks of the drug? There is a need for COVID-19 treatments, and especially those that can prevent hospitalization and death. However, the scientific standards should be authorizing and prescribing drugs only for the types of patients that have been studied. We urge you to consider these unknowns as you consider your recommendations today. Thank you.

DR. BADEN: Thank you.

Speaker number 4, your audio is now connected. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you're representing for the record.

DR. FREDERICK: My name is Clay Frederick. I'm a retired toxicologist with some experience in drug development. I don't think that I have any conflicts of interest.

It appears that the sponsor and the FDA have effectively either ignored or discarded the results of three different mutagenicity assays, and then selected a single mutagenicity assay as a basis for

saying that molnupiravir represents a low risk of mutagenicity for treating patients. I'm concerned about this decision.

I'd like to say up front that the Pig-a in vivo mammalian mutagenicity assay of molnupiravir is clearly screwed up. The biggest problem is the historical negative control database that is used as a basis of the interpretation of the study results. It's just not credible. Working groups of scientists with expertise in conducting the Pig-a assay have published guidelines on how to conduct it properly and how to interpret the results appropriately. The references are in my written comments on regulations.gov.

OECD and Hesse working groups that have provided these guidances on how to construct a credible database have also provided values in the published literature for what the database should look like. The historical control values cited by the sponsor for the Pig-a assay of molnupiravir are way too high relative to the published scientific

literature. The sponsor cites upper bound confidence values of around 6 mutations per million for red blood cells and around 12 for reticulocytes.

More appropriate values cited by the OECD and Hesse working groups are a mean of around 1 and an upper bound confidence interval somewhere around 3. This is important because comparisons to the historical control database were then used by the sponsor and the FDA to discredit the Pig-a study and to effectively discard the study results. The right answer would be to rerun the study at a laboratory with a more credible historical control database, however, the sponsor ran a Big Blue in vivo mutagenicity assay instead.

Both the sponsor and the FDA acknowledge there was a statistically significant increase in mutations in one or more treated groups relative to the concurrent control group in the Pig-a assay. Arguably, this is the most important comparison, and it suggests that molnupiravir is in fact mutagenic in mammals in vivo.

In summary, the in vivo Pig-a mutagenicity assay of molnupiravir is flawed, but aspects of it suggest it is mutagenic, and even the sponsor and the FDA describe it as equivocal.

The sponsor and the FDA have effectively chosen to only use the results of the negative Big Blue assay in its determination of the mutagenicity of molnupiravir. The sponsor described this Big Blue assay as a gold standard and suggested that it should take priority over the Pig-a study results. However, in the world of mutagenicity testing, there is no gold standard, and the Big Blue assay is definitely tarnished.

All the mutagenicity assays list some compounds that are mutagenic, and that is true of the Big Blue assay, too. A good example is provided in the 256-page review of the Pig-a assay that was conducted under the auspices of OECD, the organization that publishes standard test guidelines for the conduct of tox and mutagenicity studies. Dr. Heflich was a first author of this review and he participated in the data evaluation.

Comparisons were made in the OECD review between the Pig assay and the Big Blue assay. At one point, the review notes that the Big Blue assay did not detect -- did not detect -- the mutagenicity of diethylnitrosamine, DEN, in bone marrow. Note that diethylnitrosamine is a genotoxic carcinogen, and it is important to note that the Pig assay did detect diethylnitrosamine's mutagenicity in bone marrow.

This is noteworthy because as noted by the scientists at the University of North Carolina, the mutagenicity of molnupiravir would be expected to be most evident in fast turnover tissues like bone marrow and not in the slow turnover tissues like liver.

So the so-called gold standard Big Blue assay is not infallible, and the results of the Pig-a assay should not be summarily dismissed just because of a non-credible historical control database. In some cases, the Pig assay is more sensitive. The whole mutagenicity data set should be used for risk assessment.

It is important to note that the scientists at the University of North Carolina have detected the conversion of the active metabolite of molnupiravir NHC into its deoxyribonucleoside form. Incorporation of the deoxy form of NHC and the human DNA may well cause DNA sequence changes that are not repaired. This in fact may be the most likely way that molnupiravir causes mutations to DNA, and the sponsor does not discuss this pathway.

As the UNC scientists have noted, everybody who passes a biochemistry course learns about the reduction of ribonucleosides to deoxyribonucleotides to form the building blocks of DNA. Why isn't this pathway discussed by the sponsor, and why didn't the sponsor run metabolism studies to explore how effectively the reduction of NHC to its deoxy form occurs in human cells?

The studies are simple, and the sponsor certainly has the resources. The sponsor and the FDA have effectively discarded three mutagenicity assays that were positive, the bacterial assay, the in vitro mammalian cell assay, and the in vivo

Pig-a assay in their risk assessment. Instead, they selected the single in vivo mutagenicity assay in the Big Blue rat for their determination that there's a low risk of mutagenicity for human patients.

Based on the example of the genotoxic carcinogen diethylnitrosamine, the Big Blue assay that they selected may have just missed the potential mutagenicity of molnupiravir for clinical patients. This is a dangerous class of drugs. If you look at the mutagenicity and carcinogenicity results listed in table 10 in the back of the FDA briefing doc, you will see that most of the nucleoside analogs are mutagenic and/or carcinogenic. They're generally used for highly restricted patient populations, and they generally are used for dangerous diseases. The exception listed in table 10 is remdesivir, and for some reason, no mutagenicity or carcinogenicity studies are listed as being conducted for it.

Recommending oral dosing of molnupiravir for mild to moderate COVID patients targets much of

your patient population than any other nucleoside analog listed by the FDA. Mutations don't heal, and the consequences can show up years after exposure, much later than the short-term clinical studies that have been conducted with molnupiravir.

It wouldn't take a lot of mutagenicity to hurt a lot of people. The most obvious patients that may be at risk are those of childbearing age, both male and female, irrespective of pregnancy status. Let's not take a chance on hurting the future children of mild to moderate COVID-19 patients of today. I beg you to limit the use of molnupiravir to those who are past childbearing age. Thank you.

Clarifying Questions for Presenters (continued)

DR. BADEN: Thank you.

I'd like to thank all four open public hearing speakers. Your comments are greatly appreciated.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience. The committee

will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will continue with the clarifying questions that we did not complete from before lunch, and I will ask the panel members -- I have a list, but please put up your hand if you have a question or take down your hand if it's a residual from earlier.

We will start with Dr. Burgess, and please state your name and whether the question is to the agency or the applicant. Thank you.

CAPT BURGESS: Thank you. This is Timothy Burgess from Uniformed Services, University of Bethesda. My question is first to the applicant, and that is, when do you expect to have a complete assessment of the virologic outcomes from the all randomized data set?

DR. KARTSONIS: We are working through that data right now. Our intent would be to try to have it by sometime in the first quarter of 2022.

CAPT BURGESS: Thank you.

If I could ask a related question, Dr. Baden, to the agency.

DR. BADEN: Please.

CAPT BURGESS: Thank you.

The question to the agency virology reviewers -- first, a comment -- is I absolutely take the point about the sensitivity of the virus culture assay.

Do you have any recommendations or suggestions in terms of additional means to assess the presence of replication-competent virus, particularly in the context of concerns about alterations in spike, but also the potential for alterations elsewhere in the genome that might be expected to influence the likelihood of recovery in tissue culture? Thank you.

DR. HARRINGTON: Patrick Harrington, FDA. I think at this time we do not have any specific recommendations for a more sensitive assay. If one's available, we would certainly encourage the sponsor to use it. But I would also bounce the question back to the committee if they have any

other suggestions as far as other possible routes to investigate the potential infectivity and the concern of potential transmissibility of these viruses with the spike mutations. Thanks.

CAPT BURGESS: Thank you very much. I don't have a specific suggestion. I do think it's an important question. Thank you very much.

DR. BADEN: Thank you, Dr. Burgess.

Dr. Siberry?

DR. SIBERRY: Thanks, Dr. Baden. This question is for the sponsor.

Dr. Kartsonis, if I read it correctly, it looked like 15 percent of the participants were PCR negative. Did I read that correctly?

DR. KARTSONIS: In the study, we noted 86 percent of the people had detectable virus within that. Now, the remaining 14 percent weren't all not detectable; some of those were missing data. But yes, it is around 15 percent who we could not detect virus from.

DR. SIBERRY: Thank you. So I just want to understand, then, what the basis was for them being

included as proven COVID if they didn't have a PCR test that was positive.

DR. KARTSONIS: Sure. Their PCR test, as you know, could have been done within 5 days prior to inclusion into the trial, and obviously they had to have at least one symptom to be positive, to be included. So taking those two factors into consideration, they very well may have had detectable virus, and when you're catching the patients for recruitment into the trial, they may still be symptomatic, but they may no longer have detectable virus. All the data with regard to detection of the virus actually occurs on baseline samples on day 1.

DR. SIBERRY: If I can just then clarify, would that mean that, clinically, they had a PCR that was positive prior to coming into the study and having a negative baseline PCR or missing one?

DR. KARTSONIS: That is correct. They were done -- you're right. They came in with a PCR test that was done locally, and then we would retest it at day 1 so that we could have the information for

the purposes of our particular analyses.

DR. SIBERRY: Okay --

(Crosstalk.)

DR. KARTSONIS: And in doing that, that's where we found 15 percent of the people who had undetectable. And if I can just make one comment about that; those 15 percent with undetectable virus, it wasn't 15 percent. It was closer to 8 percent who had undetectable virus; 7 percent were missing. And none of those patients got hospitalized or died, which tells us that we did a pretty good job of identifying people and using an endpoint that could be used to evaluate that.

DR. SIBERRY: But they may have also been mostly antibody positives and had longer standing illness or prior illness.

DR. KARTSONIS: Not necessarily. We did look at that, and they didn't necessarily -- there were people that were still antibody negative.

DR. SIBERRY: Okay. Great.

Dr. Baden, I had one question for the FDA, but do you want me to wait and get back in line?

DR. BADEN: Dr. Green has a follow-on question.

DR. SIBERRY: Sure. I'll pass it to Dr. Green then. Thanks.

DR. BADEN: Dr. Green, your follow-on question?

DR. GREEN: Yes. It's a direct follow-on to Dr. Siberry's question, and I'm wondering if the sponsor happened to do an analysis, either excluding the 15 percent that had -- essentially almost a sensitivity analysis.

If you eliminate the 15 percent who were PCR negative or missing data on enrollment to study, and particularly if they were negative on entry but ended being positive, they may be less likely to benefit from the therapy, and it could have pointed the data in either direction in terms of the signal of benefit. So I'm interested in that question.

DR. KARTSONIS: Thank you for that, Dr. Green. Yes, we did do a subgroup analysis looking at what the efficacy was in the individuals

who were undetectable versus detectable viral load. We've also done it with lower high viral load. Let me show you the data first for detectable versus undetectable viral load, and we'll go from there. It's actually slide FF-11, please. Slide up, please.

So as I mentioned, 86 percent were detectable. That's the first row that you're seeing there, the 614 versus 613. You are seeing there that when it's detectable, you pretty much have the same efficacy difference that you see in the larger population.

As I mentioned to Dr. Siberry, when you look at undetectable virus, there's nobody in either group that was present. There are some people where the information was unknown, and clearly there were probably individuals there who did have detectable virus based on the fact that there were 10 cases in that subgroup as well.

I hope that answers your question.

Dr. Green.

DR. GREEN: Thank you. It does.

DR. BADEN: Thank you.

Dr. Eastmond?

(No response.)

DR. BADEN: You are on mute if you are talking, Dr. Eastmond.

(No response.)

DR. BADEN: I will continue with other questioners, and when --

DR. EASTMOND: This is Dave Eastmond. Can you hear me?

DR. BADEN: We can hear you now. Please ask your question.

DR. EASTMOND: Okay. Thank you.

My question's for Dr. Heflich from the FDA, and they're really two related questions related to mutagenicity.

I'm wondering if you can comment on the historical control and concurrent control values that we're seeing in both the Pig-a assay and the Big Blue assay. Are these values that are currently commonly seen, and if you know any more about those historical controls? Also, if you

could comment on the potency of the drug basically in the in vitro assays; were the effects seen at concentrations that are likely to be seen in human plasma? Thanks.

DR. HEFLICH: Well, I'm not in a position to answer the second question --

DR. EASTMOND: Okay.

DR. HEFLICH: -- but I can take a stab at the first question.

I would say the Pig-a assay that was performed on molnupiravir had some weaknesses associated with it. One was the negative control frequencies, which were a little high for the reticulocyte population.

The second was the nature of the historical control database that was collected by the laboratory. It was a small database, kind of on the bottom end of what's acceptable but in the range of what's acceptable, according to what we've indicated in the current guidance documents.

As it turns out, it has the highest control limits that I think I've seen associated with a

particular laboratory, so I'm sort of suspicious of it. But it is the laboratory's control database, and that's the basis for making a decision of how reliable the mutagenicity data is in any particular assay.

So you could say that the data is not very reliable, and that the sponsor's conclusion that the data is equivocal -- they really can't tell if it's positive or negative -- is probably well taken.

DR. EASTMOND: Thank you.

DR. BADEN: There are several follow-on questions.

Dr. Schoeny?

DR. SCHOENY: This is Rita Schoeny. This is a question also for Dr. Heflich.

Would you comment on the general study, the in vitro study with the rather long exposure of follow-up time? What was the value of information gained from that study?

DR. HEFLICH: Well, from my perspective, it confirmed the fact that molnupiravir is an in vitro

mutagen in a hazard ID type study that's sort of designed with the mode of action of the test substance in mind. The assay was conducted in a way that if it was mutagenic at all, it probably would be picked up in such a study.

So I think it was well designed for that purpose, and it did indicate that molnupiravir could be mutagenic in vitro, but recognize that the cells that are used are a cell line that has many deficiencies in DNA processing that probably make it more sensitive to mutagenesis than an in vivo system would. And that's essentially why you do in vivo assays, to see whether or not, in the real-world kind of situation, you will get the signal that you see in vitro. So I'll leave it there.

DR. SCHOENY: A related question, Dr. Heflich would you also comment on the value of information that may be gained, including the Pig-a assay?

DR. HEFLICH: I would not be surprised if the MOV, molnupiravir, is positive in Pig-a. But

given -- even though -- the data that we have in a notably flawed assay, the mutagenicity would be close to the limit of sensitivity of the assay.

Now, if that makes any difference, I'm not sure, but there have been two other nucleoside analogs that I'm aware of tested in that same Pig-a assay in rats, given 28-day doses to the MTD; and if you ran the same rat assay that was run on molnupiravir, on the two other, one of the nucleoside analogs -- one of which is CE:DU [ph], which I believe was a cancer chemotherapeutic agent at one time proposed -- they would have been detected as mutagens very easily.

So the assay was not perfect, but I think it was informative, as far as the level of mutagenicity that is potentially produced by molnupiravir.

DR. SCHOENY: Thank you.

DR. BADEN: Thank you.

Dr. Weina, a follow-on question?

DR. WEINA: Yes. This is Pete Weina, and just actually a follow-on to the sponsor.

The slide that you showed earlier showing the viral loads in which you had around 600 with the viral load and around 50 without a viral load, how does that relate to your slide CC-9 from your P006, in which, only at best, 50 percent of the individuals that you looked at had positive infectivity?

Is this a different measure than viral load? Are you measuring a different endpoint in that particular slide? Thank you.

DR. KARTSONIS: Yes. Thank you for that question. Obviously, what we're measuring here -- if you could put up the slide that I showed before, FF-11 -- and what we were doing here is this is a qualitative viral load assay basically looking for the presence of RNA or not. It doesn't differentiate infectious virus versus non-infectious virus.

The infectivity assays that are done actually look for evidence of the virus within cells, and there are different ways you can do it, and we've done it both ways. The study

PROTOCOL 006 actually looked at the quantitative PCR for supernatants so we could actually see whether or not you had evidence of active virus and virions that were being created. Then another way you look at it is obviously you do a plaque assay in virocells, and that's how we did it for PROTOCOL 002.

So we've looked at it both ways, the way, at least now, by which infectivity can be assessed, and in both situations we're seeing the exact same thing in terms of improvement in that.

Now, I will tell you, one of the things we have looked at carefully is, relative to the actual RNA level, when do you see infectious virus and when you do not see infectious virus. And at least in our hands, if your viral load is less than 10 to the 5th, you can't really pick up infectious virus. In fact, even as high as 10 to the 6th, there are very few cases where we actually pick up infectious virus.

Obviously, you have to look at both parts of the equation. You have to look at not just the

proportion of infectious virus, but we also did look at, obviously, viral RNA reductions, and in both cases, molnupiravir has an important effect.

DR. WEINA: Thank you. And just a quick follow-on to that for slide CC-9, that was for study 006.

DR. KARTSONIS: Yes.

DR. WEINA: Did you do the same type of analysis for the phase 3 study that we're actually looking at the data for hospitalizations and death, as well?

DR. KARTSONIS: Yes. If you could put up CC-9. This is the Ridgeback study, outpatient study. In this study, there was not a requirement that people had to be within 5 days of symptom onset. This was a study that was done relatively early. Also, it didn't require that everybody had a risk factor in the trial. I believe it was about 60 percent of the people who did have a risk factor in this trial. So it's more analogous to what we saw in our phase 2 trial.

There weren't many hospitalizations in this

trial. In fact, I think there was only one that was seen. So this was more of a study -- and the endpoint that we were looking at, particularly in this study, was around virological endpoints. The primary endpoint was the time to negative RNA, and it was statistically significant for the 800-milligram group versus placebo. But as part of that, we also looked at infectivity, and that's where we can make these assessments from.

DR. WEINA: And did you do the infectivity for P002 or not?

DR. KARTSONIS: In P002, we did do the infectivity data, and we showed it a little bit before. I could put it back up. That was the study that showed the data out to day 10 that had been asked previously by one of the investigators.

We can put it back up. Slide up, please. This is the data that we have from phase 2 that I had mentioned earlier, Dr. Weina.

DR. WEINA: Great. Okay. Thank you.

DR. KARTSONIS: You bet.

DR. BADEN: Dr. Swaminathan, you have a

follow-on question?

(No response.)

DR. BADEN: You're on mute, Dr. Swaminathan.

DR. SWAMINATHAN: Sorry. Can you hear me?

DR. BADEN: Yes, we can hear you now.

DR. SWAMINATHAN: Yes. This is Sankar Swaminathan from the University of Utah. I wanted to ask Dr. Heflich about the in vivo assays, toxicity assays -- mutagenicity assays.

If I follow you, one of the main concerns as to why the Pig-a assay was suboptimal is the choice of, perhaps, not the best historical control. But if I understand from your slides earlier today, at every dose, in comparison to the concurrent vehicle control, there was a significant increase in mutations in red cells with molnupiravir.

Is that correct?

DR. HEFLICH: That's right, for the red blood cells, the mature cells.

DR. SWAMINATHAN: I'm not sure I understand why this is really -- I mean, if something is equivocal because the controls that were chosen

weren't optimal, that doesn't seem to me to have a very high negative predictive value for the utility of that test.

DR. HEFLICH: Okay. I'm going to try to explain something about how these tests are used. I laid out the way that test data are evaluated. This has sort of come through a consensus of regulatory agencies, regulated industries, and academics, that to fairly evaluate the results of this test, you have to use not only statistical significance, but also biological relevance, and you can show that things are statistically significant.

In the Pig-a assay, you're looking at an N of 200 million in making that calculation for that increase in red blood cell mutant frequency, in some instances. We're talking about big numbers being analyzed. There are a lot of red blood cells in a drop of blood, as you probably know, and you can show statistical significance. But if the assay itself is not capable of that degree of decision, you've got to question that.

So what's been agreed upon is that three factors have been used to evaluate the data, one of which is pairwise comparisons to the control, which were significant. The other is a trend. Toxicology data often evaluates trends with dose. A trend test was performed, and it didn't show a trend, and I accept that. I didn't try it myself, but the eyeball test says there is a trend, but Cochran-Armitage says no.

The third test is this business about comparison to a historical database. If your laboratory is not capable of detecting a difference at that level of mutagenesis, any kind of data you generate at that low level of mutagenesis is probably not very meaningful.

So that's what happened in this case. The laboratory itself could not differentiate with that degree of precision to make a positive or negative call. And every laboratory does this that does testing on the GLP for regulatory submissions, and all tests are like this, the Ames test on up to the Pig-a assay and the transgenic assay. They're all

evaluated this way.

DR. SWAMINATHAN: And --

Go ahead. When things fall in the middle, then you start arguing about them, whether this is real or not, and that's what happened in this case. They fell in the middle.

DR. SWAMINATHAN: In the interest of time, with respect to the transgenic assay, one of the powerful aspects of such assays is that a variety of tissues can be examined that might have relevance to particular agents, or particular diseases, to look at tissue-specific differences in mutation rate.

I see that two, bone marrow and liver, were chosen for tissues that have different replicative rates, and this is particularly relevant in that we don't usually give potentially mutagenic agents to people in the midst of an ongoing severe infection where the replicating cells, the most rapidly replicating cells, are lymphocytes and other components of the immune response.

Given that this mutagenic agent is

particularly dependent on replication of DNA, do you have concerns of the limitations of this assay being confined to those two tissues, rather than tissues that might be more reflective of cells that would be liable to incur mutagenic damage from such an agent?

DR. HEFLICH: I'd like to answer this. I guess I am personally concerned about that, but the study that was conducted within the guideline, that's the study that has been validated for its predictive value and was what was conducted. And from that standpoint, it was an adequate study.

There are a lot of questions that could be asked about -- further questions that could be answered that might be addressed by looking at additional tissues, and it's a fair point to bring that up. That's all I can say.

DR. SWAMINATHAN: Thank you.

DR. BADEN: Thank you.

Dr. Coffin?

DR. KARTSONIS: Would it be possible, Dr. Baden, for the sponsor to provide a perspective

on that issue as well?

DR. BADEN: Yes.

DR. KARTSONIS: I'm going to ask my colleague, Dr. Blanchard, who spoke earlier today, to share it.

DR. BLANCHARD: This is Kerry from Merck. I would point out that the two tissues that we used in there, in addition, the bone marrow, that would be the target tissue if in fact something was happening in the Pig-a. So I think that's an important issue to look at. If that was an actual finding, which turned out equivocal, that would have been through mutations that occurred at the level of the bone marrow.

In the Big Blue or the transgenic rodent assay, we'd be looking specifically at mutations and not the downstream effects; so I think that's an important issue to understand in the sequence of events that we did here.

The other point I would say is that in the liver, this is the tissue bed that is getting a significant amount of drug when we administer the

compound to these animals. If you think of the characteristics of this compound, about 90 percent or more of the drug is absorbed, and we're only finding less than like 1 percent excreted, for example, in the feces.

So basically, an enormous amount of the drug actually gets into the first tissue bed being the liver. It's kind of like if you looked at a milligram per kilogram comparison to humans, it'd be like a person taking somewhere between 20 to 30 grams of the drug every day for a month.

So I think those are really relevant tissues to ask the question of whether or not it's capable of causing mutations in vivo.

(Audio feedback.)

DR. BADEN: Thank you.

Given the time, I'm going to ask everyone to be as pointed as possible, and please mute yourself if you're not talking, given the echo.

Dr. Coffin, you had a follow-on question.

(No response.)

DR. BADEN: You are on mute, Dr. Coffin.

(No response.)

DR. BADEN: You are still on mute.

Dr. Horton, you have a question, while Dr. Coffin works out the technology?

You have a follow-on, Dr. Horton?

DR. HORTON: Yes. Thank you. This is -- [inaudible – audio gap]

DR. BADEN: We lost you, Dr. Horton.

DR. HORTON: Sorry. May I speak?

DR. BADEN: Yes.

DR. HORTON: Okay.

This is Dan Horton from Rutgers. I had a follow-up question for Dr. Heflich regarding the Pig-a assay, and you mentioned what appeared to be a dose response that didn't meet statistical significance, and I'm just wondering if you think that experiment in 5 to 6 animals might be underpowered to detect what appeared to me as well to be a dose-dependent effect?

DR. HEFLICH: I'd say that was a typical hazard ID experimental design. If you wanted to characterize the dose response in any kind of

detailed way, you'd use more dose groups. But that wasn't the point of the assay. It was to determine whether there was a mutagenic hazard or not. It conformed to the guidelines in that 3 doses plus a control is the typical way that's evaluated, so I have no problem with that.

When you get a negative or a positive under a situation like that, where visually you can see an increase in frequency but your statistical test tells you there's not an increase -- the Cochran-Armitage test in this case, which is a test for linear increase in dose-response, commonly used to evaluate genetic toxicology data, I might add -- you might want to investigate that.

I'm not sure if that was done or not, but it was stated several times by the sponsor that the trend test was negative, period. I'll have to accept that.

DR. BADEN: Thank you.

DR. HORTON: And if I may ask one follow-up question?

DR. BADEN: Please.

DR. HORTON: You mentioned this could suggest kind of low-level mutagenicity, which in any given person may not have much of an impact. But I'm just wondering, in your opinion, what might be the public health impact for a low-level mutagenic compound given to millions of people; if you think that could lead to changes across the population or within the population? Thank you.

DR. HEFLICH: Well, I think you're losing sight of the patient selection process that will be involved in the EUA authorization as proposed. It will be only people at great risk and in populations that are perhaps less likely to be affected by mutation, assuming a cancer endpoint.

I think the mitigation strategies that have been used have been designed with low-level mutation or risk involved in mind to even decrease it further. So you're right; if you're exposed to any mutagen, even at low levels, there will be a risk unless there's a threshold involved, and that could very well be. We could only tell that by extensive experimentation, what that risk is.

DR. BADEN: Thank you.

DR. HORTON: Thank you.

DR. BADEN: Moving to new lines of questions? Sorry?

DR. COFFIN: Can you hear me now?

DR. BADEN: Is this Dr. Coffin?

DR. COFFIN: This is Dr. Coffin.

DR. BADEN: Yes, please. I can hear you now. Please ask your follow-on.

DR. COFFIN: My follow-on actually follows right along, and that is, at the level of sensitivity of, say, the Pig-a or either assay, what would be the mutational load over the whole genome? You're only looking at one small gene, and then only a few sites in that gene probably, for the most part, when you're doing these assays.

How does that expand over the whole genome? What is the total risk to the genome, and then what is the total risk to what the target might be for cancer, or what the target might be for mutations to pass on and infect the next generation?

DR. HEFLICH: If you're directing that

question to me, I'm sorry, I just can't give you an answer off the top of my head to that question.

DR. COFFIN: It should be possible to just look at the size of the target for mutation.

DR. HEFLICH: Yes, of course. It's simple multiplication, but it's known that the mutagenesis is not consistent among the genome. I mean, you have hot spots and cold spots in the genome, and I'm not sure what we're working with here.

DR. COFFIN: The use of the assay itself assumes that there is some correlation between the two.

DR. HEFLICH: Yes. It's an indicator of hazard.

(Crosstalk.)

DR. COFFIN: So it's a simple --

DR. HEFLICH: It's not a quantitative indication of hazard, the degree of hazard.

DR. COFFIN: But you can get kind of a family number out of it that I think would be very useful to have in mind.

DR. HEFLICH: Okay. It is possible to do.

DR. COFFIN: Has the sponsor thought about that?

DR. KARTSONIS: Yes. The sponsor's here. We'd be happy to provide a little perspective on that.

Dr. Blanchard?

DR. BLANCHARD: I might start back to your original question. I think you were talking about sensitivity and the impact to the whole genome and such. In the transgenic rodent that was used, I would point out this has multiple copies of this transgene for potential of the compound to induce those types of mutations, which we isolate and then can measure. So there are multiple copies of this present to enable that type of an assessment.

The other thing I might point out is we did invite David Kirkland to this meeting, and he has more subject-matter expertise in this area. Perhaps we can also invite him to share his perspective.

Dr. Kirkland?

DR. KIRKLAND: Yes. Thank you,

Dr. Blanchard.

I think the point that Dr. Blanchard just made about there being multiple copies of the transgene in every cell of the Big Blue is quite relevant. Also, the fact that the OECD guidelines specify that a very large number of mutant genes -- or target genes, I should say, need to be evaluated for mutation in every tissue, all of the relevant tissues of every animal.

That's quite a large genetic target that is being assessed in the transgenic assay. The assay has been around for quite a number of years. The OECD guideline was adopted, I think, 10 years ago. Lots of compounds have been tested in the TGR, and the sensitivity in terms of detecting not only human carcinogens is over 90 percent.

The sensitivity in detecting Ames-positive rodent carcinogens is also around 90 percent and, in fact, it could possibly be higher than that because some of the compounds, some of the Ames-positive carcinogens that were negative in the transgenic were actually tested over only a few

days of dosing, and we now know that we need to dose for 28 days in order to detect a number of Ames-positive carcinogens. So the target is very big, and the sensitivity is very good, certainly compared with all of the other gene tox assays that we use.

Just one quick comment on a point that Dr. Frederick made about the TGR being flawed because diethylnitrosamine was negative in bone marrow, it is clearly positive in liver. And one of the reasons that we tend to take more than one tissue in the transgenic assay is because of compounds like diethylnitrosamine, which are more easily detected as mutagenic in the liver than they are in the bone marrow.

So I think we're looking at an assay which is appropriately sensitive to detect mutations, and the data from that transgenic assay were very tight. This is clearly a laboratory that's got a lot of experience. The historical negative control ranges are nice and tight and, for me, the negative data is very credible. Thank you.

DR. BADEN: Thank you.

I'll ask everyone to be as pointed as possible, given the time and many more questions.

I think Dr. Robinson from the FDA has a comment.

DR. ROBINSON: I wanted to stress that the gene target assays are really done for hazard identification and that we have a clear in vitro mutagenic signal. But the follow-on in the transgenic rodent mutation assay was negative, suggesting that there's a low potential for in vivo mutagenic potential. Further, the treatment period is only 5 days. I think it was previously stated we think the mutagenic risk is relatively low over this short 5-day treatment period.

DR. BADEN: Great. Thank you.

We'll now move to another line of questioning.

Dr. Cragan, you have a question?

DR. CRAGAN: Yes. Thank you. This is Jan Cragan from CDC. I actually had two questions. The first one could be for the sponsor or for FDA,

I guess.

I wanted to know if there's any information to be gleaned from the animal reproductive studies that might look at whether there's a difference in the fetal effects of the drug, depending on the timing in pregnancy. One could speculate that use of the drug during the period of organogenesis might have different effects than use of the drug later in pregnancy when organogenesis is mostly complete.

So I wanted to see if there's any information on that from the animal studies, or are there additional studies that could be done that might shed some light on that, even after the drug is authorized, if it is.

My second question for the sponsor was, simply, can you elaborate on the methods to be used for the pregnancy surveillance activities that are proposed? I know there's a phone number that will be provided to report pregnancy exposures, but how are you exactly going to follow those until they deliver?

Are you going to interview the mothers about the outcome or will you get that from the mother's healthcare provider or also from the infant's health care provider? Will there be the possibility to assess the infant's health at a later time point after discharge from the hospital?

We know there are some adverse effects and even internal malformations that aren't apparent until several days or even weeks after birth. So I'm must wanting to understand better what was being proposed. Thanks.

DR. KARTSONIS: This is Dr. Kartsonis, Nick Kartsonis. I'll ask Dr. Blanchard to tackle the first question around the timing of the reproductive studies that were done preclinically.

DR. BLANCHARD: Kerry from Merck.

All the data that we have we've presented today, so there's no other studies ongoing that would address any more of the question that you're asking. As you see, we have not done specific types of studies that might tease out some of the timing. I think one could speculate to your point

about maybe more of an effect earlier rather than later, but like I said, we don't have data that would defend that either way. Thank you.

DR. KARTSONIS: With regard to the second question, I'm going to turn it over to Dr. Susan Kaplan from our clinical safety to provide a perspective.

DR. KAPLAN: Thank you, Nick.

This is Susan Kaplan, Clinical Safety Risk Management at Merck. As has been mentioned previously, if an EUA is granted for molnupiravir, we will establish a pregnancy surveillance program. Also as mentioned, there will be a phone number in the EUA fact sheet requesting reporting of all exposures to molnupiravir during pregnancy to the sponsor.

Following these reports, this then begins a process of structured active follow-up at specified time points throughout the prenatal period and following delivery. To obtain additional information on pregnancy outcome complications or adverse events, as asked, this would include

follow-up through the child's pediatrician for any birth outcomes that may not be evident at the time of delivery.

This is a voluntary reporting process that starts with a spontaneous report, but the key difference from our typical pharmacovigilance is the act of follow-up that ensues, and this is through telephone calls, structured questionnaires, as well as review of additional medical records or correspondence that are reported to the sponsor.

In most cases, pregnancy outcomes are reported by the patient's healthcare provider. We request that information if the patient is the reporter, so in most cases, this is the obstetrician. And as mentioned, we would also request contact information for the pediatrician to find out additional information about the health status of the baby. This complements our routine pharmacovigilance.

I will mention that all reports of exposure during pregnancy globally are entered into our safety database, with the more intense follow-up

occurring for patients who are enrolled in the surveillance program. We feel that this gives us the best chance of real-time, ongoing surveillance of pregnancy exposure because there is no lag in data availability, and this allows us to provide the most comprehensive summary of the safety profile of molnupiravir when exposures during pregnancy occur.

DR. KARTSONIS: Thank you, Dr. Kaplan.

DR. BADEN: Thank you.

Dr. Swaminathan, you have a follow-on question?

DR. SWAMINATHAN: Yes. Can you hear me ok?

DR. BADEN: Yes.

DR. SWAMINATHAN: This is something that could be mutagenic to replicating tissues, dividing cells. So with the embryo and a fetus, how to avoid exposure to the developing fetus is pretty clear, but the cycle of spermatogenesis in humans is a 64-day minimum. And if there were to be an effect on birth defects from exposure of the male, you would expect that to have a latency period of

anywhere from up to 2 months and beyond from viable spermatozoa that were generated during the period of exposure during the entire cycle of spermatogenesis, when DNA replication was occurring.

Have you considered -- and this is to the sponsor -- how you would mitigate against this likelihood, which would be a chronologically latent defect; and how you would advise the many, many, many men who would be taking this drug? And essentially all men of all ages would be potentially prone to this adverse effect.

DR. KARTSONIS: We've done some detailed evaluations on the males from our toxicology studies, and I'll pass that on back to Dr. Blanchard to share the data from those toxicology and fertility studies.

DR. BLANCHARD: Again, Kerry Blanchard from Merck. As pointed out in the presentation, we did do a fertility study, and that also includes looking at the performance of males, and we saw no effects. We obviously looked in the testes of the

animals on the tox studies, and we didn't see any signs of a drug-related disruption, spermatogenesis.

I know that the length from spermata [ph] go all the way to being released in the sperm; it's a lengthy process. But there are plenty of stages within the testes where you can actually identify adverse effects, and in shorter periods of time, we saw none. Thank you.

DR. SWAMINATHAN: Just to respond to that, the types of effects that you would see -- overt effects on fertility, loss of sperm count -- would be attributable to toxicity. The type of thing that one would be concerned about is, really, subtle mutation that does not rise to the level of -- we don't think this is a clastogenic agent; this is a potentially mutagenic agent. So the kind of things that we're talking about in terms of the propensity to cause birth defects would not be detected by morphologic exam or effects on overt fertility in rodents.

DR. KARTSONIS: Dr. Blanchard?

DR. BLANCHARD: Sure. I think I would also go back to the transgenic rodent assay where we're not seeing any signs of mutation on the somatic cells. And as I just recently pointed out, that in combination with a lack of obvious effect in the repeat-dose tox studies, no findings in the fertility studies that we did. It's general practice that that is used to indicate a lack of effect on germ cell mutations and, in fact, that's how it is written into ICHS S2(R1) guideline currently. Thanks.

DR. SWAMINATHAN: I would just respond again that when we use mutagenic agents in chemotherapy, there's an extended period of when either there's pretreatment sperm banking or avoidance of conception for a year even.

DR. BADEN: Thank --

DR. KARTSONIS: Go ahead. I'll give it back to you, Dr. Baden.

DR. BADEN: Yes.

Dr. Swaminathan, I think your point is well made. There are many other questions, and we have

very little time, so I want to make sure we have as many questions on the table; clarifying, not discussion. We'll be able to have discussion among the committee after.

Dr. Dublin, do you have a follow-on clarifying question for the applicant or agency?

(No response.)

DR. BADEN: We cannot hear you, Dr. Dublin, if you are talking.

DR. DUBLIN: Thank you. The double-mute problem strikes again. I have a follow-on question to Dr. Cragan's comment, and the question is for the applicant.

Considering the challenges with pregnancy registries and achieving goal enrollment, I'm wondering if you could comment on your past experiences with the kinds of sample sizes you've been able to achieve and the percent participation, and what your thoughts are about alternatives such as using real-world electronic medical records such as the kinds of data available through the Sentinel Initiative.

DR. KARTSONIS: I'm going to pass it back to Dr. Kaplan to address this question.

DR. KAPLAN: Thank you very much. This is Susan Kaplan, Clinical Safety Risk Management. I understand the question was about successful enrollment and follow-up in this type of pregnancy surveillance and have we considered other options.

Is that correct?

DR. DUBLIN: Yes.

DR. KAPLAN: Thank you for that.

First and foremost, I'll emphasize that we are not recommending the use of molnupiravir during pregnancy, although we understand where there are circumstances that this may occur. So we are initiating the pregnancy surveillance program in order to comprehensively collect this safety information and provide the most comprehensive safety profile that we can about use in this population.

We are considering other possible methods for assessing pregnancy outcomes, but at the present time we will move forward with the

surveillance program as described.

DR. BADEN: Thank you.

Dr. Gillespie, do you have a question in a new direction?

(No response.)

DR. BADEN: You're on -- we cannot --

MS. GILLESPIE: I'm sorry. I'm here.

DR. BADEN: Please, go ahead.

MS. GILLESPIE: I have a question about this whole conversation we were just having. I'm a consumer reviewer and patient advocate. My concern is you're giving the treatment for 29 days. How long after that does the treatment still stay with you? I mean, you're changing the DNA. Is it forever? And if so, treating people of childbearing ages, it could be a forever thing where they have a problem.

DR. KARTSONIS: This is Dr. Kartsonis. We know the half-life of this product pretty well, and the half-life of this product is on the order of an effective half-life of 3.3 hours, so it's relatively low. We've also looked at what's called

the terminal half-life to see how much of the drug sticks around over time, and it's on the order of about 14 to 16 hours.

So in terms of, for example, a woman of childbearing potential who was on contraception, what we're proposing is that people would -- if a person wants to stay abstinent or not get pregnant, it would not only be -- and by the way, it's only a 5-day treatment course; it's not a 29-day treatment course. But it would be for the 5 days, and then for four additional days.

The way we get four additional days is that if you take that terminal half-life and you think about 5 half-lives of that, that's about 90 hours, so you would add 4 days to that. So we're not asking people to stay on contraception for more than 4 days after the completion of their treatment course.

DR. BADEN: Thank you.

MS. GILLESPIE: Thank you.

DR. BADEN: Dr. Poirier, you have a question?

(No response.)

DR. BADEN: We cannot hear you if you are talking.

Dr. POIRIER: Okay. Can you hear me now?

DR. BADEN: Yes, we can hear you now. Thank you.

DR. POIRIER: Okay. I have a question, actually, for Dr. Seaton, if he's still available, or possibly for the provider.

When you talk about comparing, say, the rat dosage and the human dosage -- and I noticed this several times in Dr. Seaton's talk -- how do you do that calculation? What do you apply in order to get those numbers, and are they always the same?

I noticed in the Merck handout that we received, it was mentioned that thus and such was 10 times or 20 times the human dose, but how was that determined in your documents?

DR. SEATON: This is Mark Seaton. Thanks for the question. When we calculate exposure margins or exposure multiples, it's a fairly simple calculation where we take the mean exposure from

whatever animal species compared to the mean exposure from the clinical trial.

DR. POIRIER: Okay. You don't apply any sort of scaling factor to calculate a human equivalent dose, for example?

DR. SEATON: No. In this calculation for exposure multiples, it's simply mean compared to mean.

DR. POIRIER: Okay. Part of what I was thinking of was there's FDA-approved scaling factors, and from rat to human it's 6.2. So a rat dose of 500 milligrams per kilogram is really the equivalent of a human dose of 80 milligrams per kilogram.

The molnupiravir dose being given for 5 days would be about 23 to 27 milligrams per kilogram for a woman weighing 60 to 70 kilograms, and that's only about 4 times different from the highest dose that was used in the rat study that was 500 milligrams per kilogram rat dose. But if you calculate the human equivalent, that would have been 80. So I was wondering if you had any comment

on that.

DR. SEATON: Right. Early on in development of drug, when we do not yet have systemic exposures, or AUCs, we will use those scaling factors to make an estimate of safety margins going into first-in-human trials. But once we actually have exposures, then we can do, as I said, a comparison of mean exposure to mean exposure and calculate an exposure margin that way.

DR. POIRIER: Okay. Thank you.

DR. BADEN: Thank you.

Dr. Hunsberger, you have a question?

DR. HUNSBERGER: Yes. This is Sally. I just wanted to go back to trying to understand the differences for what could really be viewed as two independent studies.

The event rate, as we've all noted, in the placebo arm is just so dramatically different between the interim analysis group and after the interim analysis. In fact, if you do a test, it's significantly different, whereas the MOV arm is still pretty much the same. So the one thing I

could think of would be that the endpoint of hospitalization might have changed some, and it seemed that the only criteria you had for hospitalization was that you had to be in the hospital for more than 24 hours.

Were there any other definitions of hospitalization, or was there any adjudication, or have you looked at the group of people who were hospitalized in the first part compared to the people in the second part to see if there's some difference in who gets hospitalized?

DR. KARTSONIS: Thank you for that question. Our definition for hospitalization was a standard definition that did not change over the course of the study. It's defined as 24 hours of acute care in a hospital or a similar acute care facility, and that would include emergency rooms or facilities that were created to address hospitalization needs during the COVID-19 pandemic. This obviously excluded any hospitalizations for quarantine or public health reasons.

It is true it was based on the

investigator's judgment, based on the patients' unique comorbidities and clinical conditions. We didn't define specific criteria for hospital admission, and we didn't think we really could, recognizing healthcare resources may be variable during the different times of the pandemic that might occur; and that obviously dealing with an evolving pandemic like we're seeing here with a broad spectrum of pulmonary clinical manifestations, it would be hard to do it.

Now, one thing you could do to kind of mediate this, there are two things. One is we could look at the data at a country level, which is what we did earlier today, and we saw the consistency of the results. The other thing you can do is you can look at all visits, not just the ones that were in the hospital, including any acute care visit, and we did do that as well.

In this study, there were 10 acute care visits on top of hospitalizations; seven of those were on placebo, three were on molnupiravir. And if you put the slide up, please, you can see that

the efficacy was the same.

Slide up, please. I don't know if that's possible. You can see the difference that we see is generally similar to what we reported for hospitalizations or deaths. So all acute care visits on the left-hand side of molnupiravir versus placebo, we add three to the molnupiravir arm; we added seven to the placebo arm. We also looked for specifically COVID related per the investigator, and you can see the data are consistent in that sensitivity analysis.

DR. HUNSBERGER: Thank you.

DR. BADEN: Thank you.

As time is very short, I'm going to ask Dr. Perez for the last clarifying question, and apologize to Dr. Siberry and Murphy, but we need to have time for the committee's discussions.

Dr. Perez, your question, your clarifying question?

DR. PEREZ: Thank you. My question is about the eligibility criteria. It does not include patients with CKD and GFR less than 30 or

hemodialysis, but some of the conclusions of the PK analysis is that the drug can begin without dose adjustment for renal impairment.

Can you please clarify? Thank you.

DR. KARTSONIS: That is true. We've looked at the -- as part of our PoP PK analysis, we've obviously looked at a number of intrinsic and extrinsic factors, and none of them have moved the exposures from molnupiravir; everything from race to age, to gender, as well as the presence of COVID-19 infection and other extrinsic factors.

Now, in terms of drug-drug interactions, the way this drug is metabolized, as we mentioned, is it basically goes back down to uridine and cytidine, and then it just follows the normal process. We've looked at a host of in vitro studies that allow us to see if there are any potential drug-drug interactions through mechanisms like CYP3A4, P-gp, and/or other transporters. We've tested them all, and there's really no effect.

So we feel very confident that this

drug -- and that's one of the nice features about this drug, is that you don't have any impact of drug-drug interactions, particularly for this type population, which has underlying risk factors. Many of them do have cardiac conditions, many of them do have other medical conditions that they would be on, as you're alluding to, Dr. Perez, concomitant meds, and I think that's a special feature in that regard.

DR. BADEN: Thank you.

This will conclude the clarifying questions to the applicant and the agency. I would like to thank all of the FDA and Merck colleagues for providing so much data and so much clarification to all the different questions; very, very much appreciated.

We will now proceed with the charge to the committee from Dr. Birnkrant.

Dr. Birnkrant?

Charge to the Committee – Debra Birnkrant

DR. BIRNKRANT: Thank you very much.

Good afternoon. My name is Debbie

Birnkrant, and I'm the director of the Division of Antivirals. We heard from both the sponsor, Merck, and the FDA about the data submitted to support the Emergency Use Authorization of molnupiravir for the treatment of mild to moderate COVID-19 in adults who are at high risk of progression to severe COVID-19, including hospitalization or death.

We convene this advisory committee to seek your opinion on the available clinical and nonclinical data regarding the known and potential benefits and risks of molnupiravir to support the population in whom the drug should be indicated, if authorized, and any risk mitigation strategies such as limiting use in certain populations; a 5-day treatment course being dispensed in its original container with recommendations to complete the course, as we heard this morning; as well as the use of contraception.

There's a lot to consider in the charge to the committee. In preparation for the discussion points in the voting question, I would like for you to consider the following issues as you begin your

deliberations on the EUA for molnupiravir for the treatment of mild to moderate COVID-19 in patients at high risk of severe disease, if authorized, and any risk mitigation strategies.

We have had presentations on the clinical data to support the authorized use. Originally, most of the data came from the interim analysis of clinical trial 002 part 2/phase 3, where molnupiravir decreased all-cause hospitalization or death by about 48 percent in high-risk outpatients.

Molnupiravir appeared to be well tolerated, but the safety database at that time was limited. However, approximately a week ago, we received updated high-level data -- referred to as the full population or the all randomized group -- from the sponsor and from the FDA today, encompassing over 700 patients who received molnupiravir at 800 milligrams twice a day for 5 days from trial 002, with a relative risk reduction in all-cause hospitalization or death of about 30 percent.

As you are aware, we review nonclinical data

before clinical trials can be initiated. In the nonclinical database, it is known that molnupiravir and its metabolite NHC are mutagens in vitro. Follow-up in vivo studies, however, did not appear to support that molnupiravir was an in vivo mutagen; and if authorized as part of a risk mitigation strategy, based on the in vitro data and the clinical trial data, along with recommendations from the committee today, dosing of molnupiravir will be limited to a 5-day treatment course.

Nonclinical tox studies showed that molnupiravir impacted bone growth in developing animals and impacted developing fetuses in embryo-fetal tox studies. We will be asking your opinion on the use of molnupiravir in pregnancy. Specifically, we will ask you whether there are scenarios where molnupiravir should be authorized for use during pregnancy; that is, are there any scenarios where the known and potential benefits outweigh the known and potential risks for pregnant individuals? In addition, we will ask you about

use in individuals of childbearing potential and adequacy of mitigation strategies for exposure.

As there are no juvenile tox data available for review at this time, and given the results of the embryo-fetal studies, both FDA and Merck agree that, if authorized, molnupiravir will not be used in children.

Another area that was reviewed in depth with many questions was related to the virology data. High-level virology findings indicated that there is a theoretical concern for enhanced viral evolution. However, there is no evidence that the emergence of spike protein amino acid changes affected virologic or clinical outcomes in outpatients with COVID-19.

For discussion point number 1, we will ask you to discuss the use of molnupiravir during pregnancy. In your discussion, please comment if you think molnupiravir should be accessible for use in pregnancy in certain scenarios, and describe those scenarios. Please also note whether your concerns regarding the use of molnupiravir during

pregnancy extend to the use of the product in individuals of childbearing potential. And for this discussion, please comment on what, if any, risk mitigation strategies should be considered.

Discussion point number 2 asks about the observed increase rate of viral mutations involving the spike protein among participants receiving molnupiravir. In your discussion, please comment on what, if any, additional risk mitigation strategies or limitations on the authorized population could be considered. In addition, what monitoring strategies should be considered to better understand and mitigate these concerns?

Voting question number 1 asks whether the known and potential benefits of molnupiravir outweigh the known and potential risks of molnupiravir when used for treatment of mild to moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death.

If yes, please describe the appropriate

authorized population, including risk factors for disease progression and scenarios for use in pregnant individuals. Please comment regarding the proposed risk mitigation strategies such as contraceptive use, 5-day treatment course, et cetera, and if additional risk mitigation strategies are needed. If no, please describe your reasons for concluding that the overall risk-benefit for molnupiravir is not favorable for any population based on the data available at this time.

Before I conclude, I wanted to reiterate the following emergency use authorization considerations.

FDA's authorization of a medical product under EUA is not the same as the agency's approval or licensure of a product. The "may be effective" standard for EUAs provides for a lower level of evidence than the effectiveness standard that FDA uses for product approvals. Further, a product may be considered for an EUA if it is determined that the known and potential benefits outweigh the known

and potential risks based on the totality of scientific evidence.

For an EUA, the agency authorizes a healthcare provider fact sheet and a patient fact sheet, which are similar to prescribing information and patient labeling for approved products, and as its authorization, FDA will establish, to the extent practicable, conditions in the EUA that it finds necessary to protect the public health. Periodically, FDA will review the circumstances and appropriateness of the Emergency Use Authorization.

We look forward to your deliberation, and I'd like to turn it back to Dr. Baden. Thank you very much.

Questions to the Committee and Discussion

DR. BADEN: Thank you, Dr. Birnkrant.

We will now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

After I read each question, we'll pause for any questions or comments concerning its wording; then we will open the question to discussion.

Question 1. Discussion. Please discuss the potential use of molnupiravir during pregnancy, both in terms of risk and benefit.

A, comment if you think molnupiravir should be accessible for use in pregnancy in certain scenarios, and if so, please describe what those scenarios might be.

B, do the concerns regarding the use of molnupiravir during pregnancy extend to the use of molnupiravir in individuals of childbearing potential? If so, are there mitigation strategies that should be considered?

One question for the agency. In discussion of this question, obviously, the committee members should not indicate how they will vote on question 3, or the voting question, but we should have a discussion as to what the issues at hand are and how to weigh them.

Is that correct?

DR. BIRNKRANT: Yes, that's correct.

DR. BADEN: Thank you.

Are there questions from the panel members about this question, clarifying questions, before we start our discussion?

I'm looking for hands. I see Dr. Green has a clarifying question about the question.

DR. GREEN: Yes, I do. Thank you, Dr. Baden. This is Mike Green.

I just want to know if a certain scenario might include the emergence and dominance of a variant for which the monoclonal antibodies, which might be an alternative therapy, are no longer active?

DR. BIRNKRANT: This is Debbie Birnkrant. Yes, that could be a scenario that you could put forth.

DR. BADEN: A clarifying question again to the agency. Under the EUA regulation, if it is not specified that this population can be treated, then it cannot be used off label.

Is that correct? What are the boundaries

around an EUA authorization versus a full approval?

DR. FARLEY: This is John Farley for the agency. There will be an authorized use statement which will define the population and the appropriate clinical circumstances for the use. Use outside of that authorization statement would be out of bounds for the EUA, and there could be situations where liability protection could no longer exist for the provider, et cetera.

I'll stop there.

DR. BADEN: Thank you.

Dr. Murphy, you have a clarifying question for the agency?

DR. MURPHY: Thank you. Richard Murphy, White River Junction VA.

My question is, would it be possible -- or shall I say, given the totality of the evidence today, we think that monoclonal antibody therapy is likely to be a more efficacious treatment, understanding that no head-to-head comparison's been done. But particularly in this patient population, I think I as a clinician would more

readily recommend a monoclonal antibody therapy.

Is there any way an EUA could reflect a preference for one therapy over another, acknowledging that there may be some areas where a monoclonal therapy is not accessible? Thank you.

DR. FARLEY: This is Dr. Farley again for the agency. We're more than happy to hear those recommendations from you during the discussion.

DR. BADEN: Thank you.

Dr. Murphy, that would be very good for us to be discussing, that kind of point, as to how we would prioritize. Thank you.

I see no other clarifying questions. If there are no questions or comments concerning the wording of the question, we'll now open the question to discussion. We shall use the same procedure that we've used throughout the day in terms of raising your hand and adding a green check mark to pile on to a particular line of discussion.

Dr. Schoeny, please start off our discussion.

DR. SCHOENY: I'm happy to do so.

I would be interested in the rest of the committee's opinions on what kind of trial [indiscernible] might result in an indication of using the molnupiravir [indiscernible - audio distorted] in pregnant individuals. Regarding [indiscernible], if in fact that person has been infected with a particular clade for which there is not monoclonal antibody treatment available.

DR. BADEN: Well, this gets tricky to have an open discussion. Anyone who wishes to respond, use the green check mark, to Dr. Schoeny's point.

Dr. Green?

DR. GREEN: Yes. Thank you. Since I sort of raised the potential example of that, in my thinking, if we had a scenario where an individual at very high risk -- and since we're talking about question 1, we might be talking about a pregnant woman who also had additional comorbidities that might really raise great concerns for progression to severe disease, hospitalization, and possible death.

Circumstances being that, to your question that there was a clade circulating or a variant of concern which is no longer covered by available monoclonals, it seems to me that would be the scenario where we might consider option 2 because we know that pregnancy is a risk factor for adverse outcome. But that would acknowledge the fact that we don't have any data in how MOV works in that population. And if there's anything about being pregnant that could interfere with its working, we haven't seen any data to answer that question.

DR. BADEN: Dr. Green, to just follow on, if, for example, a 35-year-old woman who's overweight, hypertension, COPD, perhaps has some background heart disease, and now is 2 days into a COVID infection with a variant of concern that likely escapes the mABs, is that the kind of scenario; then this could be an unpregnant woman or perhaps a 36-week pregnant woman, that one might consider this agent?

Am I hearing you correctly?

DR. GREEN: I think, Dr. Baden, that you are

hearing me correctly. And obviously decisions to use this medication in this situation would require, I believe, shared decision making between the clinician who might prescribe the medication and the pregnant woman, and perhaps with supportive input from her family members, and perhaps the father of the unborn child, if it's a pregnant woman.

I think it's a little easier if she is not pregnant and has all those risk factors because the concern for mutagenesis on a fetus is taken off the table, as long as mitigation strategies to avoid pregnancy for a period of time are available.

DR. BADEN: I think Dr. Siberry has a follow-on comment to this line.

DR. SIBERRY: Yes. Thanks, Dr. Baden.

I'm thinking that we've got data that demonstrate efficacy, and generally we extrapolate efficacy from non-pregnant trials to efficacy in pregnancy, so I think that is a known benefit.

Where the concern is, of course, is this potential risk, the safety signal, and as we think

about that, I think the scenario outline begins. But I would just broaden it to say, if an alternative treatment is not available, accessible, or acceptable, because I think that we want to make sure we're not depriving women the option -- with hearing it -- of a product with proven efficacy if there's no alternative, not just based on the circulating clade. I think there are other barriers sometimes to access. So I just would broaden it a little bit beyond the strict biologic there. Thanks.

DR. BADEN: Thank you for that clarification.

Dr. Dublin?

DR. DUBLIN: I think my comment will echo what was just said about accessibility. I'm just wondering if anyone on the committee can speak to the real-world accessibility to monoclonal antibodies right now and if there are any estimates of the proportion of potentially eligible people who live in regions, for instance, where they just don't have access.

If anyone has that data, that would be helpful to me.

DR. BADEN: Well, Dr. Dublin, to push that a little bit, what if there are some places where it's not accessible, as opposed to widespread lack of accessibility? Does that make a difference in terms of the availability of accessible alternatives, as Dr. Siberry suggested?

DR. DUBLIN: I mean, if that's not a hypothetical question, I would say, to me, yes. If there are pockets of the U.S. where it's going to be impossible for a pregnant woman to access the monoclonal antibody, and the woman is extremely high risk.

Let's say it's an older mom who's in her 40's and has pre-existing diabetes, we're looking at, really, pretty high rates of ICU stay, which is pretty terrible for the fetus as well. So I think we need to not downplay the danger to the fetus of the mom being critically ill either.

DR. BADEN: Thank you.

Dr. Weina, you have an additional comment?

DR. WEINA: Yes. Pete Weina. I just wanted to challenge Dr. Siberry's comment about extrapolation to pregnancy of the other data that's out there, because when we look at high-risk scenarios, at least from the data that we have in front of us, diabetes doesn't extrapolate to some of the other high-risk populations that were looked at.

So I'm kind of sitting on the fence as to whether you could actually extrapolate to that population without any kind of data at all.

DR. BADEN: I'm going to ask Dr. Cragan, who I know is an expert in this area, to help with this discussion, if I may.

DR. CRAGAN: Sure. This is Jan Cragan from CDC. I can give you my take on it, which is my opinion. I'm not speaking for CDC officially or anyone else, in general.

There are definite concerns about the potential effects of this drug on the embryo and the fetus based on the studies that have been done and the mechanism of action, so I don't think you

can ethically say it's ok to give this drug in pregnancy, obviously. But at the same time, I'm not sure you can ethically tell a pregnant woman who has COVID-19 that she can't have the drug if she's decided that's what she needs.

Pregnancy itself can be considered a risk factor for progression to severe COVID illness. We know that respiratory illnesses increase in severity, and they can become life threatening as pregnancy progresses, and that's certainly true of COVID. Monoclonal antibodies are available now, but pregnant women are still dying from this disease.

My personal opinion is that I think the best course of action has to be to provide as much information as we can, as soon as it becomes available, and keep that updated. Perhaps in addition to that, provide some discussion points for consideration for patients and providers. But I think, ultimately, simply because the risks are so high, and there are risks and benefits on both sides whether you take the drug or whether you

don't, I think the final decision has to come down to the individual woman and her care provider.

One of my colleagues keeps telling us that the best way to have a healthy baby is to have a healthy mother, and I think the concerns about the effects of the illness in pregnancy, I agree those need to be weighed equally.

So I totally agree with the efforts to be sure that someone is not pregnant before you give them the therapy and to make sure there's knowledge of whether monoclonal antibodies are available in the area and what benefit that they provide. But the bottom line is that it's just not always going to be practical. We're seeing that every day.

I think regardless of how the drug is authorized, there are going to be exposed pregnancies, either because it's used inadvertently when someone didn't realize they were pregnant. Maybe the pregnancy testing didn't get done. Maybe the assessment was accurate. We've seen that happen with other drugs that are known to be harmful in pregnancy. But I don't think we can

make this decision for every scenario that's out there. Every clinical situation is different. There will be women --

DR. BADEN: Dr. Cragan?

DR. CRAGAN: -- yes?

DR. BADEN: Do you make a difference in the first trimester versus the third trimester? Are there differences that you think about in terms of this risk?

DR. CRAGAN: I think that that's likely. Clearly, we don't have any information about that with this drug, but it makes sense. And certainly it's true with other types of drugs; effects in the first trimester primarily when there's organogenesis, and cells are rapidly proliferating and forming organs, and signaling, and all of that kind of thing. The effects you see there are different than perhaps used in the second or third trimester when it's mostly fetal growth that's happening.

That's not entirely true. There is differentiation happening in the third trimester,

certainly with the central nervous system particularly. But I think from what we know of development and what we're seeing with other types of drugs, there's certainly the possibility that the effects may differ. And I think that is probably something that any obstetrician would take into account when assessing the risks or benefit of use of a drug during pregnancy.

We don't have data --

DR. BADEN: Great.

DR. CRAGAN: -- on that; I wish we did. But it's definitely a consideration.

DR. BADEN: Thank you.

DR. CRAGAN: Can I make --

DR. BADEN: Please.

DR. CRAGAN: -- one more point?

I think that we should provide the best information we can, but I also think that we need to pull out all the stops to identify pregnant exposures that happen and monitor them. I think what the company's proposing is great, but I know there are people at FDA who have experience with

the issues around pregnancy registries, who've used larger data sets to link maternal exposures and infant outcomes to look at these issues.

The Organization of Teratology Information Services [sic - Specialists] also does these kinds of follow-up studies very well, and they have a lot of years of experience and define practices in how to do that. So I think we need to do everything we can to build some information about the use in pregnancy as soon as we can because we have none now. Thanks.

DR. BADEN: Great. Thank you.

Dr. Reddy, you have a follow-on in this discussion?

DR. REDDY: Yes. Thank you. As a practicing OB/GYN maternal-fetal medicine specialist, we are well aware and used to counseling pregnant individuals about a whole host of medications, where there's animal data and a dearth of human data for various conditions. So I think we should follow the same approach of shared decision making.

My opinion would be that if someone's vaccinated, we don't need to approach them. Unvaccinated pregnant individuals, or individuals who have a suboptimal immune response to the vaccine, are the ones who could potentially benefit from the medication, and as been said before, if there's a lack of other efficacious alternative therapy.

Right now, monoclonal antibodies are being offered to pregnant women. Talking to my colleagues, they're being offered in major institutions and places, but there could be a lack of access. So if there's a lack of access or it's no longer efficacious, that would be another population to hone in on.

Then, it becomes a process of shared decision making, where in the first trimester, we talk about the potential risks outweigh the benefits, and we go into the data with pregnant individuals. And we do this all the time, where we say the animal data shows this, and there's a lack of human data in this case.

Then beyond the first trimester, or second and third trimester, we don't have the concern about organogenesis, but there could be an effect on growth, and through this decision-making process, pregnant individuals do make a decision which is in their best interest.

I also have to say a couple of things about the benefit. It's really concerning. We're not sure if it works for the Delta variant. With the post-analysis data, there wasn't a difference in the primary outcome, so I think we need more information just overall.

Then the last thing I wanted to talk about was having more mandatory reporting of exposure to molnupiravir in pregnant individuals. To expect the provider to call, to fill out a form, to fill out a database, it puts a lot on providers or for patients to report it, and you're not going to get optimal data that way. So I like the idea of using electronic databases or some other means to get exposure to the medication.

DR. BADEN: Dr. Reddy, thank you very much.

Just to push you a little bit, some of the data we saw suggested that the efficacy may be diminished in those who are antibody positive --

DR. REDDY: Correct.

DR. BADEN: -- nucleocapsid antibody positive, which is separate from vaccination. So prior infection, or testing for antibody positivity, would that be a consideration as part of the shared decision making acquiring such data, or is that impractical?

DR. REDDY: It sounds like it's impractical to get their antibody status. If we could, if there was a way to rapidly get it, then definitely. But given the data that we've been presented, it seems like if you've already had COVID, I think if you're vaccinated, it doesn't seem like it would be a benefit. You may not accrue the benefit because these were unvaccinated subjects in the trials.

So personally, I think if you're vaccinated. But again, I think the key is we give pregnant individuals that information and say in the trials that unvaccinated individuals were studied, and

this is what they found. You are vaccinated.

DR. BADEN: Thank you.

Dr. Hardy?

(No response.)

DR. BADEN: We cannot hear you if you're talking. We can hear you now.

DR. HARDY: Good. David Hardy from Los Angeles.

Well, I certainly agree with what our last three advisors have said about shared decision making in pregnant women. I think we all should kind of stop and acknowledge the fact that the whole reason we're having this discussion is because the efficacy of this product is not overwhelmingly good, and it does, in fact, decrease as more patients were added after the interim analysis did in fact show a prespecified significant p-value.

I think that makes all of us feel a bit uncomfortable about the fact of whether this is truly an advance therapeutically because it's an oral medication as opposed to an intravenous

medication or an intravenous monoclonal and is still on the borderline of advancement.

The fact that the Ames test is positive and that there have been some questions about how clear mutagenicity has really been ruled out, or not, would make us focus on pregnancy, of course, first. But I think the thing we have to be careful about is that, number one, we're presuming that this will work in variants of the virus that continue to evolve.

If we just take a look at the latest Omicron variant and see the number of mutations that that virus has, I think in many ways we don't really understand which direction the virus might even be going in terms of changing. So to assume that this drug, with slightly different mechanisms of action as an RdRp inhibitor, for COVID is going to work when the monoclonals don't, it's a big jump. It's a big jump. We have no assurance of that.

So I think we need to be really careful about how we're going to allow people to use this because when the efficacy rate drops from

48 percent down to 30 percent as more patients are being added to the study, and we don't really have a good explanation for why -- other than the fact that more of them tended to be antibody positive by previous exposure but yet they still had COVID, and were symptomatic, and were high risk -- that's a population that is really a high-risk and concerning population, is that their virus is different than the ones that came before, and they're still high risk. And is this the drug that's going to be able to treat them, and going to be safe to treat them?

I question some of the basis of this, and it makes the question about pregnant women really tough. If a woman can't access monoclonal antibodies or the IV route is not acceptable, an oral drug certainly looks very good. But with no data saying that it works with new variants, I think we really have to be careful about saying that this is the way to go.

DR. BADEN: Thank you.

Dr. Swaminathan?

DR. SWAMINATHAN: Yes. Hi. I wanted to ask the maternal-fetal medicine experts and Dr. Cragan, in a best-case scenario, looking at their data, it looks like you have to treat 30 pregnant women to prevent one hospitalization.

Does that affect how you would think about this or how you would counsel the patient?

DR. REDDY: This is Uma Reddy. Should answer?

DR. BADEN: Please. Please, Dr. Reddy.

DR. REDDY: You know, in thinking about this, I think we jump to pregnant individuals, but we still need to talk about -- we are skirting the issue about is there a benefit for adults. Because usually we start with what is the benefit of the medication in adults, what has the data shown, and then we focus in on pregnancy and the issues with pregnancy.

I think we haven't addressed it. I mentioned vaccinated individuals would be a population that I personally don't think we should offer this medication to because they were not

studied as part of these trials, then the fact that the Delta variant, there wasn't a difference, and that's the predominant variant.

So I think we have to answer that question first because that's the information, then we have to talk about, I think, the context of pregnancy.

DR. BADEN: So your point is very well taken, Dr. Reddy, which is if overall efficacy is not deemed to be there, all else is moot. If overall efficacy is deemed to be there, then the question is how and in what circumstances could this be extended to this vulnerable population.

DR. REDDY: Thank you, Dr. Baden. You said it perfectly for me.

Dr. Hunsberger?

DR. HUNSBERGER: I think you have all made excellent points in these last few statements, and the only thing I want to add is that if you look at the confidence intervals, the upper confidence interval just goes to minus 0.1 percent, so that even puts us closer to do we have a benefit. So then to talk about the risk-benefit, it's just

really difficult without just discussing the, overall, is there a benefit.

DR. BADEN: Thank you.

Dr. Weina?

DR. WEINA: It's Pete Weina. Actually, it just made my point, and that is that the number needed to treat for this is around 34 and the number needed to treat for monoclonal antibodies is probably -- or the best estimates are around 15. So questions become we're having this discussion about pregnancy, but the efficacy of this, in general, seems to make the discussion very theoretical because we really don't know how to counsel them because of the huge number needed to treat. Over.

DR. BADEN: Thank you.

Dr. Hildreth?

DR. HILDRETH: Thank you, Dr. Baden.

My colleagues have made the point that I wanted to make. I'll just make it in a different way. And what this comes down to for me is do we want to reduce the risk for the mother by

30 percent of harm while exposing the embryo and the fetus to a much higher risk of harm by this drug? And my answer is no, and there's no circumstance in which I would advise a pregnant woman to take this drug. Thank you.

DR. BADEN: I see Dr. Le, and then Dr. Cragan.

(No response.)

DR. BADEN: Dr. Le, we cannot hear you.

(No response.)

DR. BADEN: We still cannot hear you, Dr. Le.

DR. LE: Hi. Can hear me now this? This is Jennifer Le.

DR. BADEN: Yes, now we can.

DR. LE: Okay. Thank you.

I echo the concerns, what has been said, in terms of while I completely agree with this shared decision, there's a lot of information here, and there are a lot of safety concerns that we need to, I think, have more data for to really have a stronger recommendation for pregnancy, let alone

non-pregnant childbearing individuals. That's all.

DR. BADEN: Understood. The absence of data is very unsettling, however, we're all struggling with the clinical reality of this infection today in many of the patients and our vulnerable patients, such as those who are pregnant; so difficult decision making and discussion, which is why I think the agency asked us to struggle with this.

Dr. Cragan?

DR. CRAGAN: Yes. I will echo that I totally agree, and we don't have enough information to make these decisions, and I don't really think to make good recommendations. I agree that the decision around whether this drug is of sufficient benefit to be authorized for anyone is one question. I feel that if it is, then probably the assessment of its risk and benefit in pregnancy, given that we don't have much information, has to be left up to the shared decision making of the woman and the care provider.

But I also wanted to follow up on something

Dr. Reddy said, her call for more active follow-up of pregnancies that are exposed. What was done, what's been done, and is in progress with the COVID vaccines is that at the time you got the vaccine, there was an -- at least I got an information sheet that said if you go online and sign up for this, they'll follow up on whether you have any reactions or anything. And it was a very simple thing on your phone to do. It took 2 minutes each time they contacted you.

But one of the questions early on was were you pregnant at the time of the vaccine. If you were, then you went into another follow-up set of questions and a more lengthy follow-up to get information about the outcome. But it was done at the time you received the vaccine, and that's how pregnant women for follow-up were identified.

I'm not clear what the analogous situation would be with a medication that you get from the pharmacy, but perhaps -- I don't know if there's a way to have pharmacies identify prescriptions that are given to pregnant women or some other kind of

follow-up, but I wonder if there's a little bit of a model in what happened with the vaccines that could be done with the medication because I'm way more concerned about the effects of the medication used in pregnancy than I am about the vaccine. Thanks.

DR. BADEN: Thank you.

Dr. Poirier?

DR. POIRIER: Yes. I'm here.

I'm not a clinician, so perhaps my opinion is not as valuable as most of the people who've spoken already, but one thing that jumped out at me when I was reading this data is the value for people 60 and over. It seems like there's something like an 83 percent reduction in people hospitalized or dying if they're over 60 years old.

So my thought was limit it to this age group, and then you don't have to worry about the mutagenesis and the problems with pregnancy. On the other hand, I realize the problem is larger, but personally I would never recommend it for a member of my family who's pregnant. Thank you.

DR. BADEN: Thank you.

Dr. Dublin?

DR. DUBLIN: Thank you. As I listened to the discussion about shared decision making, one thing that really struck me is in an ideal world, I think it would be great if my patients could do shared decision making with their OB, but in practice we should consider who's most likely to be seeing these women.

This is a medication that, if approved, sounds like would be approved only for use in the first 5 days after symptoms. And my suspicion is that certainly in many healthcare systems, these diagnoses are going to be made in drive-thru testing or the high-risk people are not going to be presenting super ill already. These are mild to moderate cases, so we're talking about maybe ER physicians or primary care physicians needing to be able to do the shared decision making.

I just wanted to comment a little more on how are we going to follow up on pregnancy exposures. There's just been a ton of -- I do

pharmacoepi, and some of the work I do is to try to study birth defects in pregnant women after exposure to medications using real-world data, and it's just tremendously challenging whatever method you use. But there are huge difficulties with registries, as Dr. Reddy pointed out the burden on providers and patients. And even for the voluntary registries, when you try to do a recruitment of women to do mobile phone reporting of things, you might get 3 to 5 percent of women participating, and it can be a very self-selected group of women.

So I really want to think about all the creative ways we can study these, including, again, the Sentinel database that FDA has funded and created that has hundreds of millions of people under passive observation. So their electronic medical record data is going to be a really important component of following pregnant women, in addition to every effort to get women to voluntarily respond to surveys.

DR. BADEN: Thank you.

Dr. Coffin?

(No response.)

DR. BADEN: We cannot hear you, Dr. Coffin.

(No response.)

DR. BADEN: We still cannot hear you.

Dr. Reddy?

DR. COFFIN: Can you hear me now?

DR. BADEN: Yes, now we can hear you, Dr. Coffin.

DR. COFFIN: Alright. It seems a little slow to turn on the microphone.

Yes. I've been thinking about this, and I had come to the same kind of conclusion that Dr. Poirier had. I'm also not a clinician, so maybe that has something to do with it.

We're batting around the pregnancy issue, where everybody has a concern for what we just don't know could be happening to a fetus. Even under conditions of a very early pregnancy, these are highest risk areas for all we know, and that's really uncontrollable in this, I think.

Also, there's the practical aspect of all these mitigation theories. If they take time, then

that's time off the clock from which will certainly start to cut into the efficacy of the treatment. So I don't see a good solution to this, except perhaps to go to an over-60 limitation eventually.

DR. BADEN: Thank you.

So I will conclude our discussion on question 1, and I think I am supposed to summarize the discussion. So I'll take the chair's liberty to say that I think it fell on two sides of almost the same view.

First, what it's all predicated on is, is their efficacy or not, that will be dealt with separately. But the issue of is the risk too high or is the benefit needed to protect mom in order to protect the baby, and that's a very difficult decision.

The question of accessibility, perhaps safe alternatives like mABs should be seriously considered. If there are no other available or acceptable options, and assuming that efficacy is better understood in this population for which there are no data at this time, then it's almost a

black box warning; and then the question of how to make sure there is proper information for the clinicians across the country to do shared decision making with the best information, realizing the incredible temporal scenario that is involved here, particularly given how testing is done.

So I think there is substantial discomfort among the committee members, but there is the weighing of protecting mom versus the unknowns about the degree of efficacy in a given pregnant population versus the degree of risk, which is largely unknown.

Let me conclude the discussion with question 1. I see no objections from my panel members, and it's 3:54. Let's take a 7-minute break and resume at, I guess, 4:02, and then we will deal with question 2 and the voting question. So a quick break, and we'll resume at 4:02. Thank you.

(Whereupon, at 3:54 p.m., a recess was taken.)

DR. BADEN: It's now 4:02, and we shall

resume.

We will now move on to question 2. Please discuss the concern regarding the observed increased rate of viral mutations involving the spike protein among participants receiving molnupiravir. In your discussion, please comment on what, if any, additional risk mitigation strategies or limitations on the authorized population could be considered. What monitoring strategies should be considered to better understand and mitigate these concerns?

Are there clarifying questions for the agency about this question?

(No response.)

DR. BADEN: Seeing none, we can now open this question up for discussion, and I think I saw Dr. Coffin ready to lead us off.

So, Dr. Coffin, please start our discussion.

(No response.)

DR. BADEN: We cannot hear you.

(No response.)

DR. BADEN: We still cannot hear you.

DR. COFFIN: Are you able to hear me now?

DR. BADEN: Now we can. Now we hear you.

DR. COFFIN: Okay. I know what happened. It got turned on automatically at the same time I turned it off again, I think.

Anyway, this is an issue that has gotten a lot of press, as we all know. For starters, I'm not very happy with the way they've done the sequencing. This 5 percent frequency, they're not seeing the mutation rate; they're seeing the result of selection or a very small sampling, which is unclear. It's never clear how many sequences they looked at, actually.

So it's really unclear what's going on there as far as this goes. But in my opinion, actually, it's a fairly small risk. The rate that they saw relative to placebo is still only a 2-fold difference; not a big enough difference, in my opinion, to make a large difference.

The main factor in generating mutations like this is not actually the mutation rate. It's, in fact, selective coefficient of the mutation and the

number of replication cycles under selection that are concerned. And they're probably seeing as much those in their studies as they are the actual mutation rate, which has some effect, but it's not the major effect in terms of generating those mutations, in terms of a population which then gets spread and passed out.

So in my opinion, it's an issue, but it's not, I think, an important issue in the sense that there's not a major issue. Let's put it that way; it could potentially be important. The occurrence of these variants, obviously, each one is very, very rare. Out of millions of infected individuals, the Omicron popped up once, and it's spreading.

Also, keeping treated individuals under lock and key is probably the best way to prevent these possible mutations from spreading anyway if they're infected this way, if they go to the symptomatic condition. The spread of these mutations, the few examples we have seems to be initiated by a rare individual in whom the virus can persist for a very

long time to allow a much greater extent of mutation, and selection, and replication [inaudible – audio feedback]. So I'll just make that general comment.

DR. BADEN: Dr. Coffin, just to push you a little bit for clarity, it's a 2-fold increase compared to placebo. So that level of mutation compared to global replication, does that seem like a small selection pressure, so to speak, compared to what's going on globally with replication?

DR. COFFIN: Yes. Selection pressure is probably not different. There's no reason to believe that the drug affects selection pressure. It would be hard to imagine why. It's what you would get if the virus were replicating for a few days more.

But when you model out the effects -- that's what I did years ago with HIV -- of the patient selection and then replication, it's actually that differences in mutation rate make the smallest difference in what you see in terms of the outcome as far as mutants arising our concern. Selective

effects and numbers of replication cycles are really the big ones.

DR. BADEN: So along those lines, then, the use of this agent in someone with a profoundly weakened immune system, which then allows more cycles of replication, how do you think about that problem?

DR. COFFIN: That probably combined with immunotherapy could create more of an issue. Again, I don't think it would be a huge difference as compared to just a virus without this treatment.

DR. BADEN: Yes.

DR. COFFIN: And if you knock the replication down with a virus, then you would actually, in a sense, compensate for it.

DR. BADEN: Thank you.

Dr. Siberry, you have a follow-on?

DR. SIBERRY: I do. You mentioned immunocompromised patients, and I think one of the follow-ons could be a dedicated study in immunocompromised patients with intensive sampling for the mutations to pressure the system to see, in

the absence of the immune response contribution to viral clearance, whether this is more of a problem.

Otherwise, I think based on the mechanism of action and the data we've seen, I don't think this is a big concern overall, but I think a dedicated study of immunocompromised patients could be really beneficial.

DR. COFFIN: And I'm not very -- I was going to say I'm not very happy with the way they did the assay. I think that could have been done better.

DR. BADEN: And that's what I was going to suggest with your comments, Dr. Coffin, about high resolution sequencing, looking for very minor variants, not just dominant variants.

DR. COFFIN: Exactly. They're the ones doing this.

DR. BADEN: Yes.

Dr. Hildreth, you have a follow-on?

DR. HILDRETH: Yes. Thank you, Dr. Baden.

While the risk in any one individual might be low for these kinds of events to occur, if this drug is given to millions of people, in multiple

settings around the world, including those with a lower immune response, or compromised immune response, the emergence of an escape mutant is a real danger, and it cannot be dismissed. And I still say that some study needs to be done to determine the frequency by which those events occur until we're comfortable using this on a widespread basis. Thank you.

DR. BADEN: Thank you.

Dr. Swaminathan, you have a follow-on?

DR. SWAMINATHAN: Yes. In a way, it's a funny situation, right? If you had a drug that helps people get over an infection, you consider it effective, and you don't necessarily -- maybe we should, but we don't usually take the calculus of public health into our decisions about whether a new antibiotic should be approved.

The widespread use of a lot of antibiotics leads to resistant bacteria that are causing all kinds of problems. If it's effective, though, it seems that the overall risk to public health is probably minimal in people where virus replication

is really quashed in 5 days.

I think the issue of immunocompromised patients does need not only follow-up, but some consideration as to what type of quarantine and other measures might need to be taken to prevent escape of these potential resistant variants. People on CD20 inhibitors, CLL, these types of patients we know will continue to shed for a long time, and in addition to doing high-def sequencing of those people serially, there might need to be some guidance as to their isolation.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Yes. Thank you. This is a follow-on, but I was actually going to raise this question myself.

It seems to me that when we asked earlier in the day if there was any data on contacts of those treated in terms of what the likelihood of person-to-person spread was on individuals who were treated, and if any effort was done to look at the outcome in those individuals, and also to look at

the virus that they might have had, I agree that this is something that ideally would be excellent to study.

But I also think that as we think about mitigation strategies, we already should be asking household contacts, ideally, to use some mitigation strategies in their household when somebody is positive, particularly if there is anybody else in the household who is also at increased risk for worse outcome due to the presence of comorbidities.

So the recommendations that might be put forward if this drug did get an authorization might be very much encouragement that individuals on therapy, to the extent possible, should try to stay in their own room; use their own bathroom. Those providing care for them should do so wearing a mask, asking the patient to wear a mask if tolerated, and then generating a time period for which we would do this.

I would presume that this treatment, which seems to drop viral load and/or replicate the virus relatively quickly -- but so does placebo, it

seems -- that you still use that 10-day in the absence of a factor that would make them be contagious, say, for 20 days, or need to have 2 negative tests to come out of isolation.

So these public health mitigation strategies that we've been using all along should be re-emphasized because they could protect against the untoward outcome should a strain emerge in a treated individual that was what we're worrying about; that is a bad strain. Thank you.

[Pause.]

DR. YU: Hello, everyone. This is Joyce Yu, the DFO. We're going to get Dr. Baden reconnected.

You're reconnected, and we'll resume.

DR. BADEN: Hello? Can you hear me?

DR. YU: Yes, we can hear you now.

DR. BADEN: Okay. I apologize. For some reason, my phone, the hospital phones, decided to cut me off. I apologize. But I was able to hear Dr. Green's comments.

I think we have additional comments from Dr. Le.

DR. LE: Yes. This is Jennifer Le. I definitely agree with Dr. Green's comment in terms of mitigation strategies. I'm just wondering how that can be done at home in the real-world setting. That's going to be quite a bit of obstacle to have close contact and everyone do the masking and everything.

But along those lines, I do agree that there needs to be mentions of that, if this gets approved with EUA, but also perhaps -- and, again, I don't know how the logistic can be with this -- for anyone who's on therapy, who subsequently gets hospitalized, obviously death, lack of response to therapy, immunocompromised, and household contact -- to get some samples and to be able to test that in a central lab, if that is even feasible.

I'm trying to correlate this to more of can there be a point of contact where patients can provide samples. Similar to what we're getting with COVID testing, as well as the COVID vaccine, could this be facilitated through pharmacies as

well as to perhaps maybe -- because I know I got weekly testing, or texting, of a reminder to do this, a reminder to report any symptoms. And I don't know how feasible that is, but that would greatly help better understand the risk of this.

DR. BADEN: Thank you.

Dr. Swaminathan?

(No response.)

DR. BADEN: Do you have a follow on? Dr. Swaminathan, we cannot hear you.

DR. SWAMINATHAN: Sorry. I forgot to lower my hand, I think.

DR. BADEN: Okay.

Then we have Dr. Hildreth. Do you have a follow-on?

DR. HILDRETH: No, Dr. Baden. I'm sorry. I forgot to lower my hand.

DR. BADEN: And, Dr. Green, please lower your hand.

Dr. Weina?

DR. WEINA: Pete Weina.

My follow-on, as I thought about this

question, the same line as Dr. Green, point one, was this is an outpatient therapy, so these individuals are going to be out there. They're going to have exposure; so all the public health issues.

But the other aspect that I thought about regarding additional risk mitigation strategies is that one of the lessons learned, I think, from HIV and from TB is the idea that we didn't have a whole lot of respect for these bugs and the public health risk of these bugs, and one of the ways that we kind of got a handle on it, at least a little bit, had to do with not using single drugs. Maybe having a single drug out there is just going to potentially drive more mutations, especially in an outpatient setting, which we don't necessarily have the kind of control that we have for individuals that are inpatient.

Those were some of the thoughts that I had regarding this question. Over.

DR. BADEN: Thank you.

Dr. Burgess?

CAPT BURGESS: Thanks, Dr. Baden.

Tim Burgess from Bethesda, and I was just going to add my voice to Dr. Siberry's and Dr. Green's comments about the need for investigation in immunocompromised patients who might be expected to have prolonged viral replication, as well as household contacts.

But I guess I would ask the question of colleagues; additional study, but pending that additional study, should that be a specific consideration for a delimiting parameter if there is an authorization? In other words, should the authorization exclude individuals who might be thought to be at risk of prolonged replication, and if so, how would you articulate that?

DR. BADEN: Thank you.

Dr. Murphy?

DR. MURPHY: Richard Murphy. I just wanted to make a point that compared to clinical trials, adherence in real-world settings is always going to be a little bit lower. We know that even from short-course therapy for malaria. If we think that

low adherence is going to be a risk factor for immune escape variants, eventually, I think we should just recognize the reality that we'll see all sorts of levels of adherence in different patients if this is rolled out more widely.

I'm not sure what the mitigation strategy would be for that, but I think we should recognize that that will be a factor.

DR. BADEN: Thank you.

Dr. Siberry?

DR. SIBERRY: Yes. I just want to comment on the question about whether we should recommend limiting the use under an EUA for immunocompromised patients. I would suggest that we not limit it, but that we advocate that those studies be undertaken immediately. These should be relatively straightforward to set up and get going, but that we not limit it for this population who could potentially benefit. Thanks.

DR. BADEN: Thank you.

Dr. Coffin?

(No response.)

DR. BADEN: We do not hear you, Dr. Coffin.

(No response.)

DR. BADEN: We still do not hear you.

DR. COFFIN: Alright. Now I think you can hear me.

DR. BADEN: Now we hear you.

DR. COFFIN: Okay.

Yes, I would agree with that. I think as pointed out, the same thing should be done in all individuals who are immunocompromised and at risk for prolonged infection for that reason, and not just ones that have been treated with the drug. That's almost certainly where a lot of these variants have come from. At least the two examples that we have would certainly suggest that.

How much the risk increases by having a somewhat higher mutation rate is unclear to me, but I don't think the increase is great, as I said before, and it is probably mitigated, to a great extent, by the fact that the virus is being knocked out by the treatment.

The immunocompromised population is probably

one that, if this is working well, stands to gain the most from this, actually, and it's probably a lot better than treating those individuals with immune therapy, with monoclonals, or whatever, because those actually will serve to provide a good selective environment to bring these mutations to full extent.

DR. BADEN: Thank you. These are random as opposed to selective pressure with the mABs.

DR. COFFIN: Right.

DR. BADEN: Dr. Green?

DR. GREEN: Yes. In response to the comments we just heard -- and I know we're past the point of speaking to the agency or the sponsor, but one question we never asked was, was there any evidence of rebound load in any of the patients that were treated?

We saw some data at day 5 and then day 10, but if we're worried that in the immune compromised we're going to see prolongation -- we do see the potential effect of the drug is to drive load or replicating virus way down initially; the question

is, what happens when we stop? And I don't know if it's appropriate for us to see if there are any data available to address that question.

DR. BADEN: I think we're beyond that discussion, Dr. Green, but I think we can summarize for the agency this discussion, which will, I'm sure, lead to such discussions amongst the community, and I'm sure the sponsor and the agency. But I see that we have exhausted people's comments for question 2, and I do want to save the half hour for the voting question since that is ultimately the most important question.

So to summarize this discussion, there is substantial concern about the mutagenicity potential of this agent. The previous question, it was on host genome; here, it is on viral genome, and there's substantial concern in that. However, in the face of efficacy, the real risk is in the prolonged replication, as commented by several of our committee members, rather than short-term replication, particularly in the context of host clearance.

There is a substantial amount of mutations emerging from natural infection, which dwarfs what is done by this agent. But as pointed out by one of the committee members, it depends how much of this is used, how widely, and with what level of compliance. So that speaks to making sure this is used in the most targeted way for benefit.

As noted by some of the committee members, the issue of this is a concern with any antimicrobial in terms of the selective pressure it puts on organisms that then can become resistant. So it is a bit of a generic concern, although it is special in this setting, given how quickly this pathogen replicates, spreads, and the mechanism of action of this agent.

The populations of greatest concern are those who may have prolonged infection such as those with weakened immune systems and having an aggressive sampling frame, some would argue in general. Others, it's very important for those being treated to better define the mutation risk, and therefore better quantify what this concern is,

and that requires optimal sampling and sequencing to look at minor variants, not just major variants.

Then the question of secondary transmission in these higher risk settings is worth some consideration as one thinks about mitigation strategies; so significant concerns, but strategies that can mitigate these concerns, given the mechanism and the overall burden of replication, globally, that this would fit into.

Any other comments from panel members of any of the concepts that I did not capture correctly?

(No response.)

DR. BADEN: If not, then we can move to question 3.

DR. YU: Thank you, Dr. Baden. This is Joy Yu, the DFO. I will now provide the instructions for the voting question for number 3.

Question 3 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding

the wording of the question are complete, the chairperson will announce that the voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the roster and each voting

member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to. However, you should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

Dr. Dublin?

DR. DUBLIN: Are we going to have a chance or group discussion before we move to voting?

DR. YU: Do you have a question about the wording of the question?

DR. DUBLIN: No. My question is about the general process. I feel like we've kicked the can down the road a lot of times about whether there's truly a benefit and whether we believe there's a benefit. And I guess I was just assuming there would be some time for discussion of that as a group.

DR. YU: If you can incorporate that into your justification, Dr. Dublin, we'll go on to the vote. So we should only be voting on the question,

but you can incorporate your discussion into [inaudible – audio fades].

Dr. Schoeny, did you have a question about the voting process?

DR. SCHOENY: Yes. My screen blanked out for a few minutes. When you read the vote by person, frankly, I couldn't hear what you were saying at that point. Would you please go over the last part of the procedure after votes have been displayed?

DR. YU: Sure. After I read the vote results from the screen into the record, the chairperson will go down the roster, and each voting member will state their name and their vote into the record. You should also state the reason why you voted as you did if you want to, but also address any subparts of the voting question.

DR. SCHOENY: Yes.

DR. YU: Does that answer your question, Dr. Schoeny?

DR. SCHOENY: Yes, it does. Thank you.

DR. YU: Okay. I don't see any more hands

about the voting procedure, so Dr. Baden?

DR. BADEN: Question 3, the one voting question. Do the known and potential benefits of molnupiravir outweigh the known and potential risks of molnupiravir when used for the treatment of mild to moderate COVID-19 in adult patients who are within 5 days of symptom onset and are at high risk of severe COVID-19, including hospitalization or death?

A, if yes, please describe the appropriate authorized population such as risk factors for disease progression and pregnant individuals. Please comment on the proposed mitigation strategies and if additional risk mitigation strategies are needed.

B, if no, please describe your reasons for concluding that the overall benefit-risk of molnupiravir is not favorable for any population based on the data available at this time.

Are there any questions concerning the wording of the question that anyone would like clarity on?

I see, Dr. Coffin, you have a question about the question.

DR. COFFIN: Yes. My question has to do with mild. Does that include asymptomatic or do you need to have a sniffle?

DR. HODOWANEC: Hi. This is Dr. Hodowanec from FDA. No, mild and moderate would include only symptomatic patients. This would not apply to asymptomatic patients.

DR. COFFIN: It seems like the best benefit would be, actually, if it could be given to patients at high risk as soon as they test positive, even if it's in a screening, or contact tracing, or whatever.

So that's taken out of this. So there has to be some kind of a symptom --

DR. HODOWANEC: Yes, that's correct.

DR. COFFIN: -- for somebody to benefit from this.

DR. FARLEY: Dr. Baden, Dr. Farley for the agency.

Dr. Coffin, thank you for that question.

Certainly, if you believe that the product should be authorized for any population, the question is constructed so that you would vote yes. But there is an opportunity to tell us if you think the population should be broader than the way it's been phrased in your discussion. Thank you.

DR. BADEN: Thank you, Dr. Farley.

DR. COFFIN: Thank you.

DR. BADEN: Any other questions about the question?

(No response.)

DR. BADEN: If there are no further questions or comments concerning the wording of the question, we will now begin the voting --

DR. YU: Dr. Baden, I think Dr. Fuller has a question about the wording of the question.

DR. BADEN: Please, Dr. Fuller.

DR. FULLER: Yes. Can you hear me?

DR. BADEN: Yes.

DR. FULLER: I'm not sure this is included in the wording, but in A, are we asking that this is a drug -- or will this be a drug that is

absolutely prescribed and available only to the health provider, or is this something that could be available in some other way? And maybe that's not what's in this question. Maybe that's not a decision we're being asked to make.

DR. FARLEY: Dr. Baden, Dr. Farley. I can [inaudible].

DR. BADEN: Please.

DR. FARLEY: There will be a prescribing healthcare provider. This is not anticipated as an over-the-counter authorization, if that was your question. I just want to make sure I understood what you were asking.

DR. FULLER: Yes. That is my question. So the access, if it is given, an EUA for anyone would be from a absolute health provider prescribed situation. So I couldn't just do an at-home test and feel bad, and somehow get to this particular reagent.

DR. FARLEY: No. You are correct. A prescription would be required.

DR. BADEN: And, Dr. Farley, it would come

with the required information sheet that is part of the EUA statute.

DR. FARLEY: Yes. We were envisioning that the healthcare provider would need to provide the patient with the fact sheet that is written for the patients, at the patient level of understanding. And there may be other duties that the healthcare provider prescribing the drug may be required to do, including, as Dr. Hodowanec mentioned, verification of pregnancy status.

DR. FULLER: Okay. Thank you.

DR. BADEN: Dr. Walker, you have a question about the question?

DR. WALKER: Hi. This is Dr. Walker, and I think this has been addressed, but I just wanted some clarity on B, if no, not favorable for any population? I guess I just needed a little more clarity on not favorable for any population.

DR. BADEN: One of the FDA colleagues, please.

DR. FARLEY: Sure. I can comment on that. Thank you very much for the question.

We had structured the question this way because it would be most helpful to the agency if you would indicate in your vote whether you thought this product should be authorized for any population.

If you do not, that would be a no vote. If you did, it would be most valuable for us to hear your comments regarding the appropriate authorized population, in your view, as well as any risk mitigation strategy comments that you felt would be helpful to us. Thanks.

DR. BADEN: Thank you.

Dr. Reddy?

DR. REDDY: Yes. Thank you.

As part of answering the question A, if you think additional studies need to be done or performed on particular populations, is it possible to add that to the answer to A?

DR. FARLEY: Certainly, we'd be happy to -- this is Farley for the agency -- to hear those comments. If you feel that those studies are necessary prior to an authorization, then we were

imagining that would be probably a no vote. But if you thought that the studies could be done following an authorization for some population, then that would be a yes vote.

DR. REDDY: Okay. Thank you for the clarification.

DR. BADEN: Seeing no other questions about the question, then we will now begin the voting on question 3.

Dr. Yu?

DR. YU: Yes. We will now move voting members into the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. YU: The voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. BADEN: Dr. Yu, will you --

DR. YU: Yes. Thank you, Dr. Baden.

The vote results are now displayed. I will

read the vote totals into the record. The chairperson will go down the list, and each voting number will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to. However, you should also address any subparts of the voting question.

The vote is 13 yeses, 10 noes, and zero abstentions. Thank you.

DR. BADEN: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You also may provide justification of your vote, if you wish.

We will start with Dr. Eastmond.

DR. EASTMOND: Thank you. I'm assuming you can hear me.

DR. BADEN: Yes.

DR. EASTMOND: I voted yes. I feel like the potential benefits outweigh the risks in this case. I do, I guess, have comments.

I think that the FDA should not approve it

for the use in pregnant women, except under really exceptional circumstances. I do think that they should limit the use of this drug to high-risk individuals. I believe the FDA has chosen -- the risk mitigation approaches that they have proposed seem reasonable to me.

I would advise that the company engage in post-exposure monitoring for mutations in treated patients. The evidence indicates that this drug does not cause mutations in vivo, but it would be useful to verify that in patients after the fact. Thank you. I think that's it for me.

DR. BADEN: Thank you.

Dr. Cragan?

DR. CRAGAN: Hi. This is Janet Cragan. I voted yes. I do think that FDA should require pregnancy testing for individuals before treatment has begun or at least non-pregnant status being verified. If someone is pregnant, I think they must be referred or obtain counseling from a knowledgeable provider before they fill the prescription. But those are the only limitations I

have, specifically.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thank you. This is Michael Green. I voted yes. This was clearly a very difficult decision, and I think the death signal was what was most impactful in my decision making. I would also say there's potential concern for lack of availability of an alternative therapy for those at high risk, perhaps including the possibility of loss of efficacy of monoclonals with emergence of variants not attributable to use of this medication.

I would use it in high-risk, non-vaccinated individuals, and looking at the data that we have, obesity looks like a good signal; age, although outcomes less than 60 and greater than 60 were similar in the information provided to us by the sponsor.

I would consider it in those with multiple risk factors that are present. I'm uncertain about whether I would use it in transplant recipients,

but I would possibly do so because it's mechanism of action should actually perhaps decrease the likelihood of emergence of a mutant strain rather than increase it, and studies in that population would be of value.

For pregnancy, I would only use it if there's no alternative therapy available, and I don't think I would use it in the first trimester. I agree with the multiple mitigation strategies proposed by the agency, as well as those that were added in the discussion, including emphasizing the importance of household contacts trying to limit their exposure to positive patients, which I counsel families on, on a daily basis anyhow.

Finally, to one of the public comment speakers, should an alternative oral agent become available that had a better safety profile and equal to or better efficacy profile, the agency might reconsider its authorization. Thank you.

DR. BADEN: Thank you.

Dr. Reddy?

(No response.)

DR. BADEN: Cannot hear you, Dr. Reddy.

DR. REDDY: Sorry. Can you hear me now?

DR. BADEN: Can hear you now.

DR. REDDY: I voted yes and would like to stick with the high-risk criteria that was in the original trial, so focus on unvaccinated patients or patients who had a suboptimal response to the vaccine. There's a lack of an efficacious alternative therapy, so if there is an alternative therapy that's efficacious, like monoclonal antibodies currently or a future medication, that would be the priority.

In terms of pregnancy, I think the potential risks outweigh any benefit in the first trimester, so would make that clear, if that's the only alternative for pregnant individuals on discussing the potential risks and benefits beyond their first trimester. Then I strongly recommend getting more data on a U.S. population on all patients, and then the pregnancy surveillance, making it a stronger surveillance, not depending upon providers to voluntarily provide that information.

DR. BADEN: Thank you.

Dr. Swaminathan?

DR. SWAMINATHAN: Yes. This is Sankar Swaminathan. I voted no. I felt that the overall absolute effect in the total trial population was modest, at best. The risk of mutagenic effects on the patient is not firmly established or characterized, and given the large potential population affected, the risk of widespread effects on potential birth defects, especially delayed effects on the male, has not been adequately studied. Thank you.

DR. BADEN: Thank you.

Dr. Dublin?

DR. DUBLIN: This is Sascha Dublin. Can you hear me?

DR. BADEN: Yes.

DR. DUBLIN: I voted yes. I agree with others, this was a difficult decision. I think that, for me, it was important to consider the results of the clinical trial in total and not get too obsessed with why the second half of the trial

looked so different.

I think that the population, it will be really important to get it right, and I totally agree with people, as they've said that this needs to be a really high-risk population. With that in mind, I would favor sticking pretty close to the trial population and not expanding to be as broad as the current population of all high-risk individuals listed in the CDC guidelines because that gets pretty expansive. For instance, it seems to include people who are even overweight rather than just obese.

I would not recommend a limitation based on age, say limiting to people over 60 as suggestions in some of our discussion. I agree with the general approach of several others like Dr. Cragan has suggested for pregnancy, where I wouldn't recommend it, but I think it does need to be available in very extreme situations where there is no alternative and a woman's life is really in danger, and I think shared decision making will be crucial.

I favor approving it for individuals who are unvaccinated or agree with Dr. Reddy, vaccinated individuals who we predict have a very poor immune response, which could be based on factors such as age over 75 or being immunosuppressed.

I think other really important points would be to continue to do efficacy monitoring by viral clade and understand if there truly is a real finding of much less efficacy against Delta virus; that would be important to know. Ideally, I would love to see a head-to-head trial against an alternative such as monoclonal antibodies.

I think the proposal to monitoring patients after exposures is important, tying into Dr. Swaminathan's concern about the potential risk of mutations that could lead to delayed birth defects.

I agree with Dr. Cragan that we should require pregnancy testing before treatment, and I agree with the prior suggestion that if another medication becomes available under an EUA, this EUA should be revisited and have the potential to be

withdrawn.

I also like the comments that were made earlier about this may end up being a situation where a multidrug strategy is advisable, and the idea of combining this drug with another as part of a multidrug strategy should be kept in mind for the future.

DR. BADEN: Thank you.

I will just say it's 5:00 now. We're likely going to go 15 or 20 minutes over.

Dr. Burgess?

CAPT BURGESS: This is Timothy Burgess. I voted no. It was a challenging decision. I was persuaded to vote no on the basis of the very difficult to explain difference in the population in P002 evaluated after the interim analysis, as well as some apparent heterogeneity in the apparent beneficial effect; for example, with the risk factor of diabetes.

I think there are concerns with respect to the uncertainty about risk for genotoxicity. I certainly recognize the need for additional

therapeutic agents to be available, particularly with the emergence of developing clades and strains, but as the question was articulated, on the basis of the available data, I voted no. Thank you.

DR. BADEN: Thank you.

Dr. Le?

DR. LE: Jennifer Le. I voted no. Likely coming from the clinical pharmacologist inside of me, I appreciated the pharmacologic safety is generally more evident postmarketing surveillance, yet the premarketing studies that we've seen here demonstrate highly relevant signals for safety concerns; so in light of multiple safety signals appreciated and discussed today.

Also, coupled to the modest benefit for mild to moderate -- and I note not severe symptomatic COVID-19, especially against the Delta strain, in reducing hospitalization and/or death -- I voted no based on the currently available data. I think I just need more efficacy and safety data perhaps with more subjects against placebo or other

treatment strategies before I can vote a yes.

DR. BADEN: Thank you.

Dr. Weina?

DR. WEINA: This is Peter Weina. I voted no because I was not convinced that the potential benefit of a 3 percent decrease in overall hospitalizations and deaths outweighed the known and potential risks of the proposed treatment, even under the protections of an EUA.

The number needed to treat of around 34 means that a potentially large amount of virus is going to be exposed to the drug for every potential benefiting patient, and this relatively large number needed-to-treat concern plays into the questions surrounding the mutagenicity of the spike proteins and potential for creating new variants.

As an outpatient therapy, there's really no effective way to control the manner in which the patient is taking the medication and may potentially transmit to family or their close contacts while taking the medication, or soon afterwards.

Another issue that assisted in formulating my decision, including the questionable and contradictory benefit seen in the diabetic group -- and that called into question, at least in my mind, the possible benefit and other high-risk groups not included in the trial that was used to support this application. There will be real difficulty in defining the high-risk group, potentially, who benefit from the therapy without a large departure from the current criteria list for high-risk population. Thanks.

DR. BADEN: Thank you.

Dr. Hardy?

(No response.)

DR. BADEN: We cannot hear you, Dr. Hardy.

(No response.)

DR. BADEN: We still cannot hear you.

We can go to Dr. Schoeny, and when Dr. Hardy gets audio, we will have his comments.

DR. HARDY: Here I am. Sorry.

DR. BADEN: Dr. Hardy?

DR. HARDY: I pressed the wrong button

again. Dr. Hardy from Los Angeles.

I voted yes because COVID-19 is still a emergency situation. As a frontline clinician and treating patients, both inpatient and outpatient, there is a need for something like this. This is the first opportunity that an oral outpatient medication for mildly symptomatic to moderate symptomatic persons would be available.

Although I do have questions about its overall longer term efficacy, it did meet its prespecified statistical boundness of showing a 48 percent improvement in terms of hospitalization and death.

I think as far as mitigation strategies, there just needs to be a warning about using this in pregnant women but also give it up to a discussion between the woman and her physicians, as well as the fact that pregnancy should be tested for so that that discussion can occur. If the woman does not know she's pregnant, and particularly if she's in the first trimester, that could be a concern.

It should be indicated for persons who are high risk and who are outpatients, and we'll see what happens as time goes on.

DR. BADEN: Thank you.

Dr. Hildreth?

DR. SCHOENY: This is Dr. --

DR. BADEN: I'm sorry; Dr. Schoeny. I got confused.

Dr. Schoeny, please? I apologize.

DR. SCHOENY: No problem. This is Rita Schoeny. I voted yes. The sponsor presented that any likely mutagenicity is low. The data indicates that in vivo mutagenicity is not an enormous hazardous from the data thus far.

I think that the high-risk criteria that were used in the trials are appropriate. I feel that the mitigation strategies that have been proposed by the agency are also appropriate. I would suggest that the drug be offered to pregnant individuals and that decisions be made with the physician and the pregnant individual, particularly as they seem to be various alternatives available

to pregnant individuals. I would not limit the drug to people over 60, and I think that will do it. Thank you.

DR. BADEN: Thank you.

Dr. Hildreth?

DR. HILDRETH: Thank you, Dr. Baden.

I voted no. It was an easy vote for me to vote no. I think the genotoxicity data and mutagenicity data, there are more questions than answers. I also think that the potential for this drug to drive some very challenging variants into the public is a major, major concern. And for those reasons, there being more questions than answers, I cannot completely vote yes for this, so I voted no. Thank you.

DR. BADEN: Thank you.

Dr. Gillespie?

MS. GILLESPIE: I voted no. Mainly, I agree with all the no votes. My biggest reason was that I feel that there's not enough investigation on the changes that could be -- or that can cause fetal distortion. I also don't think that the benefits

are high enough for the risks. That's it.

DR. BADEN: Thank you.

Dr. Baden. I voted yes, and I agree with all that's been said by both the yes and no voters. I see this as an incredibly difficult decision, and as has already been stated, there are many, many more questions than answers. However, as I see the regulatory framework, are there circumstances where the benefit may exceed the risk?

I think the mortality data I found compelling. I think we saw at least three studies: the inpatient study where it did not work and maybe the mortality went the wrong way; the phase 3 trial where part A had tremendous efficacy and part B went the wrong way.

So I think that speaks to the right patient population and the right virus at the right time. But for me, that at least suggests that there are populations where there may be benefit. That then puts a burden on the agency, and on the applicant, and on the community to continue to vigorously study so that we can better define who's likely to

benefit.

It's in not-hospitalized individuals. It's early in illness. I think the CDC criteria for increased risk makes sense for very practical issues of how to roll this out, but I would ask the agency to consider adding a supplement to say strongly encourage the criteria associated with the study.

We need to understand the behavior with variants, and the assumption that it will work evenly across variants may be true, but that needs to be tested and understood. I think the unvaccinated population is very important, as well as those who have not had prior infection, and those are parameters that will have to be better understood since they may modulate the efficacy. But overall, I trust our practitioners that if we educate them properly, they can deploy this properly.

I think there are several mitigation strategies to be considered, as already discussed. I think there needs to be studies in vaccinated

individuals, studies in those with prior infection, and studies in the immunocompromised, particularly to understand safety and the multiple cycles of replication, and therefore the risk of variant emergent of concern, and that needs to be quantified.

I think the pregnancy issues have been discussed, and I think the question of secondary transmission also needs consideration, more to prove the negative because I think the presence of data that's reassuring will be reassuring. It's the absence of data that makes many of us uncomfortable, and that will need to be generated. But I can see scenarios where there are benefit, and therefore having this available for those scenarios makes sense to me. Thank you.

Dr. Walker?

DR. WALKER: Thank you, Dr. Baden. You took the words out of my mouth. Solely under the EUA consideration is why I voted yes. This was a very difficult decision for me. I literally toggled back and forth, as I know everyone has on this.

While data of this magnitude can show some type of emerging hope for more COVID vaccines or therapies to come, there is room for the efficacy of the overall risk within the population to be fully addressed.

I do think -- and this has been stated time and time again -- this should really be provided to high-risk individuals who have not been vaccinated. I think it was stated that in order for a patient to even receive this drug, they have to show some type of symptoms. I think that needs to be addressed and they have to receive a prescription.

I don't think this study did full justice or it really took into consideration the minority population that may not have full access to a primary care physician in order to receive a prescription in order to take the drug, aside from going to an emergency room. So I think more data is needed on this subset as well as the effect on pregnant women, especially me as a woman of childbearing age. I don't think I would want to take this drug not knowing the effects it could

have on my unborn child.

Post-exposure monitoring also needs to be done, as well as a separate evaluation of immunocompromised individuals, and more data is needed on individuals who have had transplants such as bone marrow transplants.

Additionally, when it comes to monitoring strategies, it's still fully unknown what will really be employed to ensure that 5-day regimen will be taken in its entirety once the patient receives a prescription. What check-ins are being done to ensure that on day 3 that patient is taking the drug?

It will also be vital to ensure proper language is fully disseminated so that patients fully understand the risk and the benefits. Proper training and education for clinicians is needed to ensure that they do take into careful consideration who this drug should be administered to. Thank you.

DR. BADEN: Thank you.

Dr. Poirier?

DR. POIRIER: Yes. Thank you.

I voted yes, and I believe that the appropriate authorized population should be individuals age 60 and over. I do not believe that this drug should be used in pregnancy. However, if the agency does decide to use it in pregnancy, I would recommend that they consider lactating women be given the same mitigation as women of childbearing age and pregnant women, and also consider men who are interested in becoming fathers.

I think in the case of individuals who are immunocompromised, the mitigation steps that we discussed earlier should be employed, and also that there should be virus testing at various times after the initiation of therapy so they can really learn how long that virus lasts.

Finally, I think at this point, the genotoxicity situation is still a black box, but I would hope that in the future, when there's more data available, that the agency would reconsider the situation. Thank you.

DR. BADEN: Thank you.

Dr. Murphy?

(No response.)

DR. BADEN: I think, Dr. Murphy, you're on mute or you may not be connected, in which case we'll go to Dr. Siberry, and we'll come back to Dr. Murphy when he's available.

Dr. Siberry?

DR. SIBERRY: Hi. It's George Siberry. I voted yes. While I was disappointed to see a reduction as the point estimate and reduction in hospitalization and death from the preliminary to the final data set, the final data set still represented a 30 percent reduction in hospitalization and death with a separate significant reduction in death.

Now, that motivated me towards the yes vote. This was clinically well tolerated. I think the evidence shows that there's a very low risk of clinical mutagenicity, especially for a drug taken for only 5 days.

I agree with Dr. Baden that the CDC

high-risk criteria should be used, but we do need to take into account immunization status and then what's known about current and emerging circulating variants. I would also suggest that instead of putting an age of 18, the label simply -- the EUA -- indicate this is for adults. Girls uniformly close their growth plates by age 6, and many boys do before age 18 as well, so I recommend just leaving this as adults without a specific age.

The reproductive toxicity is a obvious concern. I would say this is a safety signal that needs follow-up and represents a potential risk, not a known risk, and one that deserves a lot of further evaluation and also clear counseling when it comes to women, or people who are pregnant, or may become pregnant.

So I agree that this is not for routine use in pregnancy, but I do not think people who are pregnant should be stopped from being able to use this. If they meet the criteria for being at high risk to progression for severe disease or death, they need to be informed of the preclinical

findings that raise concern and only use this if an alternative treatment is not available, accessible, or acceptable. Thanks very much.

DR. BADEN: Thank you.

Dr. Perez?

DR. PEREZ: Federico Perez, Cleveland VA. I vote for Emergency Use Authorization of this oral agent because it can serve as an alternative to monoclonal antibodies where these may not be available. I think the eligibility criteria used in this study are valid for its use, adding the immunosuppressed category with the caveat that the dynamics of viral clearance needs to be studied in this population.

In regard to the question of women of reproductive age, a pregnancy test is indicated, and then unvaccinated pregnant women without access to monoclonal antibodies who meet the eligibility criteria would need to have shared decision making with their providers. Thank you.

DR. BADEN: Thank you.

Dr. Horton?

DR. HORTON: Daniel Horton from Rutgers. I voted no, though like Dr. Baden, I agree with members who voted either yes or no.

For me, I was struck by a modest benefit in the highly adherent trial population, and then the unclear benefit and unclear efficacy, particularly in the latter half of the trial when you had increasing circulation of the Delta variant. Also, the impressive mortality benefit seen early on was no longer apparent, and I worry about even lower levels of effectiveness in the setting of real-world use, particularly with lower levels of adherence overall.

Also, I was concerned about safety, particularly potential mutagenic effects, especially when used in large populations, as well as the possibility for increased pressures for viral evolution, again, in the setting of lower adherence in the real world. I agree with others about the importance of additional data on safety and efficacy, as well as effectiveness if this is authorized, including comparative effectiveness.

Thank you.

DR. BADEN: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I voted no. I agree with pretty much everything the no people have said. I just want to emphasize that I think it's a pretty minimal benefit and I have concerns about the change in the placebo rate from the beginning to the end. I don't really think we know what groups this is benefiting. So I think, really, another study should be done, and if it gets the EUA, then I don't think that would happen.

So that would be a big reason I would like to vote no because I still have equipoise in whether it's beneficial or not. Thank you.

DR. BADEN: Thank you.

Dr. Coffin?

DR. COFFIN: Yes. I voted yes. Like the speakers before me, I also agree with almost everything that has been said so far, and I have little to add.

I do think that the issue of pregnancy and

mutagenesis needs to be evaluated further, and I would favor limiting at least the initial authorization to high-risk groups other than pregnancy, and perhaps only to individuals over 60 or so, as one of the previous speakers suggested.

As a long time HIV researcher, I've been waiting for a long time to see a small-molecule treatment available. I'm not sure that this is really the one we've been waiting for, but it's all we've got right at the moment. So that said, I think in an appropriate high-risk population, I think this is a benefit, and the issues around the mutagenesis may not be as severe as they might be, pending further research.

Also, as I suggested in the question, I think it would be a good idea to at least consider broadening within the high risk group, in the highest risk group, the criteria for administering the drug to everybody who test positive, whether symptomatic or not, because it's very clear that the earlier the drug is administered, the greater the benefit is likely to be. So that's my stand on

this. Thanks.

DR. BADEN: Thank you.

Dr. Fuller?

DR. FULLER: Yes. This is Oveta Fuller. I voted no, the reason being that I would really love to have an effective drug that can reduce virus replication and reduce hospitalizations and disease that can be taken at home.

However, with the efficacy that we see and the many questions that were left unanswered -- such as what's the rebound effect; what's the effect on host, both males who cannot take a pregnancy test, as well as females who may be pregnant or may not know they're pregnant -- there were too many questions for me.

To be able to release a reagent that, even in the most remote possibility of helping the virus evolve -- because this is a respiratory-spread virus that has no boundaries, we can't separate, and we can't easily stop it -- I just felt that there were too many reasons and too many risks for the level of benefit that we see at a 30 to

40 percent reduction in hospitalizations when there still are other options.

This would have to be for the unvaccinated, for the not pregnant, for those who would be completely compliant, and for those who would have no rebound effects. There were just too many things that tilted me to the no, even though I would love to have something that would work in the way that this possibly could. And I want to thank Merck and others for their studies and hope that we will continue to make this better. Thank you.

DR. BADEN: Thank you.

Dr. Murphy?

DR. MURPHY: This is Richard Murphy. I voted no. It was a difficult decision. I think it came down to the fact that under the most ideal circumstances, it had a very modest efficacy, with a number needed to treat that was probably over 30, and very uncertain efficacy against Delta.

I think added to that are the logistical difficulties of getting drug to persons within the first 5 days of symptoms, which are significant. I

had concerns about risk for viral escape and mutagenicity in humans that I don't think were settled during the discussion.

I think if an EUA is given, there should be guidance that it's not a preferred therapy but an alternative when monoclonal antibodies are not available or not active against the circulating variant. I think if an alternative agent comes along with better efficacy and fewer safety concerns, that this EUA should be reconsidered. Thank you.

DR. BADEN: Thank you.

So I will recap, as succinctly as I can, what I think I heard. The vote was 13 yeses, 10 noes. There were some who think it's absolutely no, some who are very inclined to yes, and most in the middle, where the big questions are how to interpret the efficacy. On the yes side, the efficacy outweighed the risk and the unevenness in the data reported, where an efficacy signal was apparent, albeit with issues that have to be weighed.

Post-exposure monitoring is needed. This needs to be focused on high-risk individuals. The pregnancy question I think has been discussed substantially. One of the important factors is the limited availability of alternative treatments, so in that context, the uncertainties about the genotoxicity and the mutagenesis weigh less because there aren't alternatives, and there may be a mortality benefit, which is different than other settings where this might be considered, and that risk-benefit ratio would be different.

The role that this plays in high-risk patients such as transplant patients needs to be better investigated and how to look at it in the unvaccinated or those with suboptimal immune responses with different variants of concern circulating and its activity. However, overall the benefit outweighed the risk.

For the noes, there are just too many uncertainties. The efficacy signal is wobbly, and different measures of it, such as the first half and the second half of the study, came to different

conclusions. The genotoxicity, the mutagenicity, and the impact on viral replication and viral escape were all very important considerations, and the data are lacking to fully inform these risks. Therefore, these risks in the context of a marginal benefit did not seem appropriate. I think that, for the most part, captures the overall discussion.

I would like to thank the applicant for doing so many studies and presenting so much data; to the agency for further synthesizing that data and helping us interpret it; to the committee members for incredible dedication for reviewing all this material, synthesizing, and participating in such a robust discussion; and to our agency handlers for enabling this meeting to be successful in these trying times of COVID, where we're not allowed to be together. So I cannot thank everyone enough for all of the contributions.

Before we adjourn, I'd like to go back to the agency, and Dr. Birnkrant, Dr. Farley, if there's anything we can clarify or if you have any last comments for the committee.

DR. FARLEY: Thanks, Dr. Baden. This is Dr. Farley. We want to add our thanks to everyone for their contributions today. We thank the sponsor for their work on a clear presentation and their work over the last week revising that presentation so that the all randomized population data could be presented clearly today to the committee.

We want to thank the open public hearing speakers, as well as the many people who have made contributions to the open public docket for this meeting. Those contributions were very valuable. The committee had an excellent breadth of expertise, and we thank you for all the work preparing for the meeting, as well as for your highly valuable input today.

We want to thank you, Dr. Baden, for excellent facilitation in this challenging virtual setting. The agency remains deliberative concerning this proposed EUA and will consider all of the input we've received today as we continue our review. Thank you very much.

Adjournment

DR. BADEN: Thank you.

I can say that in my many years of chairing this committee, this is the first meeting that has gone over, which I think speaks to the complexity of the issues that we have had to deal with. I would like to thank everyone for joining, and we will now adjourn the meeting. Have a good evening.

(Whereupon, at 5:33 p.m., the meeting was adjourned.)