FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

(AMDAC)

Virtual Meeting

Thursday, March 16, 2023

9:00 a.m. to 3:56 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Joyce Frimpong, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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(Voting)

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(Chairperson)

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Division of Infectious Diseases

Brigham and Women's Hospital

Director, Infectious Disease Service

Dana-Farber Cancer Institute

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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're not speaking. For media and press, the FDA contact is Chanapa Tantibanchachai. Her email is displayed.

My name is Lindsey Baden, and I'll be chairing this meeting. I will now call the March 16, 2023 Antimicrobial Drugs Advisory Committee meeting to order. Dr. Joyce Frimpong is the designated federal officer for this meeting and will begin with the introductions.

Introduction of Committee

DR. FRIMPONG: Good morning. My name is Joyce Frimpong, and I'm 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: I'm Dr. Lindsey Baden. I'm an

infectious diseases specialist at Brigham and Women's Hospital, Dana-Farber Cancer Institute, and Harvard Medical School in Boston. Thank you.

DR. FRIMPONG: Dr. Green?

DR. GREEN: Good morning. My name is Michael Green. I'm a pediatric infectious disease specialist with interest in compromised hosts and transplant infections, and I work at the UPMC Children's Hospital Pittsburgh, and I'm affiliated with the University of Pittsburgh School of Medicine. Thank you.

DR. FRIMPONG: Dr. Hardy?

(No response.)

DR. FRIMPONG: Dr. Hardy?

DR. HARDY: Sorry. Hi. I'm David Hardy. I'm an adult infectious disease trained physician. I work at Los Angeles County USC Medical Center, and I'm affiliated with the Keck School of Medicine of USC.

DR. FRIMPONG: Dr. Hunsberger?

DR. HUNSBERGER: I'm Sally Hunsberger. I'm a biostatistician at NIAID, and I work in the

biostatistics research branch. Thank you.

DR. FRIMPONG: Dr. Murphy?

DR. MURPHY: Hi. Richard Murphy, infectious disease specialist at the White River Junction VA, and with Geisel School of Medicine at Dartmouth.

DR. FRIMPONG: Dr. Patel?

Good morning. My name is Nimish Patel, and I am a PharmD PhD based out of San Diego at the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California San Diego.

DR. FRIMPONG: Dr. Perez?

DR. PEREZ: Good morning. I am Federico Perez, an infectious diseases specialist at the Cleveland VA Medical Center and Case Western Reserve University.

DR. FRIMPONG: Dr. Siberry?

DR. SIBERRY: Good morning. I'm George Siberry, pediatric infectious disease physician and medical officer at the United States Agency for International Development, USAID, in Washington DC.

DR. FRIMPONG: Dr. Swaminathan?

DR. SWAMINATHAN: Hi. I'm Sankar

Swaminathan. I'm the chief of the infectious diseases division at University of Utah Health and University of Utah School of Medicine in Salt Lake City.

DR. FRIMPONG: Dr. Walker?

DR. WALKER: Good morning. I'm Dr. Roblena Walker, CEO and research scientist with EMAGAHA, Inc. in Atlanta Georgia. Thank you.

DR. FRIMPONG: Dr. Chandra?

DR. CHANDRA: Good morning. I'm Richa Chandra. I am working as the clinical development head for communicable diseases at Novartis, and at today's ADCOM, I'm representing from industry. Thank you.

DR. FRIMPONG: Dr. Adimora?

DR. ADIMORA: Good morning. I'm Ada Adimora. I'm an adult infectious diseases physician and professor of medicine and epidemiology at the University of North Carolina at Chapel Hill. Thank you.

DR. FRIMPONG: Dr. Carvalho?

DR. CARVALHO: Good morning. I'm Paula

Carvalho. I do pulmonary critical care and sleep medicine. I' m with the University of Washington and at the Boise VA Medical Center. Thank you.

DR. FRIMPONG: Dr. Clark?

DR. CLARK: Hi. Good morning. I'm Nina Clark. I'm at Loyola University Medical Center and Loyola Stritch School of Medicine in Maywood, Illinois.

DR. FRIMPONG: Ms. Terry Gillespie?

(No response.)

DR. FRIMPONG: Ms. Terry Gillespie?

MS. GILLESPIE: Sorry. I thought I was unmuted. I'm Terry Gillespie. I'm a patient advocate from Chicago, Illinois.

DR. FRIMPONG: Thank you.

Dr. Scarsi?

DR. SCARSI: Good morning. I'm Kim Scarsi. I'm a professor at the University of Nebraska Medical Center. I'm a clinical pharmacist, clinical pharmacologist, with an emphasis in HIV pharmacology.

DR. FRIMPONG: Dr. Shankaran?

DR. SHANKARAN: Good morning. I'm Shivanjali Shankaran. I'm an adult infectious diseases physician at Rush University Medical Center in Chicago.

DR. FRIMPONG: Dr. Waterman?

DR. WATERMAN: Good morning. I'm Dr. Waterman. I'm an adult infectious disease specialist at the Uniformed Services University with clinical affiliations at Walter Reed National Military Medical Center in Fort Belvoir.

DR. FRIMPONG: And now for our FDA participants, Dr. John Farley?

DR. FARLEY: Good morning. I'm John Farley, Office of Infectious Diseases, CDER, FDA.

DR. FRIMPONG: Dr. Debra Birnkrant?

DR. BIRNKRANT: Good morning. I'm Dr. Debra Birnkrant, director of the Division of Antivirals, Office of Infectious Diseases, CDER, FDA.

DR. FRIMPONG: Dr. Glen Huang?

DR. HUANG: Hi. Good morning. Glen Huang. I'm a clinical reviewer in DAV at the FDA.

DR. FRIMPONG: Dr. Stephanie Troy?

DR. TROY: Good morning. I'm Dr. Stephanie Troy. I'm a clinical reviewer in the Division of Antivirals at FDA.

DR. FRIMPONG: Dr. Jonathan Rawson?

DR. RAWSON: Good morning. I'm Jonathan Rawson. I'm a clinical virology reviewer in the Division of Antivirals, CDER, FDA.

DR. FRIMPONG: And Dr. Patrick Harrington?

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

DR. FRIMPONG: Thank you.

DR. BADEN: Does that complete the introductions?

DR. FRIMPONG: That is the conclusion of the introductions, 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 committees 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.

Dr. Frimpong will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. FRIMPONG: Thank you.

The Food and Drug Administration is convening today's meeting of the Antimicrobial Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of this committee are special government employees 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 conflicts of interest 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 discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for the 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 new drug application 217188, for Paxlovid, nirmatrelvir and ritonavir co-packaged tablets, for

oral use, submitted by Pfizer, Incorporated. The proposed indication is the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. This is a particular matters meeting during which specific matters related to Pfizer's new drug application will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Adaora Adimora and Lindsey Baden.

Dr. Adimora's waiver includes consulting for the National Institute of Health and Research Triangle Institute for which she received between $0 to $5,000 per year. Dr. Baden's waiver covers his employer's research contract for a study currently under development with funding from the National Heart, Lung, and Blood Institute and Duke Clinical Research Institute. Dr. Baden is not

aware of the funding amount being provided to his employer for this study.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasoning for issuing the waivers are described in the waiver document, which are posted on FDA's website. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267. 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 the FDA's invited industry representative, we would like to disclose that Dr. Richa 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?

DR. BADEN: We will now proceed with FDA introductory remarks from Dr. John Farley.

Dr. Farley?

FDA Opening Remarks - John Farley

DR. FARLEY: Good morning. I'm Dr. John Farley, and it is my privilege to lead the Office of Infectious Diseases in the Office of New Drugs at CDER FDA. Today we are seeking advice from the committee regarding new drug application 217188 for

Paxlovid. Specifically, we seek advice concerning whether the available data support an overall favorable benefit-risk assessment for the use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death.

FDA defines mild and moderate COVID-19 consistent with NIH COVID-19 treatment guidelines. Mild illness is defined as individuals who have any or various signs and symptoms of COVID-19 but do not have shortness of breath, dyspnea, or abnormal chest imaging. Moderate illness is defined as individuals who show evidence of lower respiratory disease during clinical assessment or imaging, and who have an oxygen saturation measured by pulse oximetry greater than or equal to 94 percent on room air at sea level.

Paxlovid consists of oral nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease, which is required for

viral replication. Ritonavir is an HIV-1 protease inhibitor and potent CYP3A inhibitor that is used to increase the plasma concentrations of nirmatrelvir. Ritonavir itself is not active against SARS-CoV-2 main protease.

The proposed indication is treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death. The proposed dosage is nirmatrelvir 300 milligrams plus ritonavir 100 milligrams orally twice daily for 5 days. For patients with moderate renal impairment, defined as an estimated glomerular filtration rate greater than or equal to 30 and less than 60 milliliters per minute, the proposed dosage is nirmatrelvir 150 milligrams plus ritonavir 100 milligrams orally twice daily for 5 days.

As you're aware, FDA authorized the emergency use of Paxlovid on December 22, 2021. Note that the authorization is the treatment of certain adults and pediatric patients 12 years of age and older and weighing at least 40 kilograms.

Our discussion today will not focus on pediatric use, as pediatric drug development is ongoing. Should this new drug application be approved, FDA anticipates that the EUA for Paxlovid will remain in effect to continue authorizing treatment of adolescents with mild-to-moderate COVID-19 and further address other access needs. Paxlovid is not recommended in patients with severe renal impairment, defined as a GFR less than 30 milliliters per minute. Drug development for this population is ongoing.

FDA will focus on three clinical trials in our presentation today. EPIC-HR is a trial that evaluated 5 days of Paxlovid versus placebo in the treatment of mild-to-moderate COVID-19 in adults who were unvaccinated for COVID-19 and at high risk for progression to severe disease. The trial was successful on its primary efficacy endpoint and demonstrated a reduction compared to placebo of COVID-19-related hospitalization or death from any cause. This trial anchors the NDA.

EPIC-SR is a trial that evaluated 5 days of

Paxlovid versus placebo for the treatment of mild-to-moderate COVID-19 in adults who were either vaccinated against COVID-19 and at high risk for progression to severe disease or unvaccinated with no risk factors for progression to severe disease. This trial failed to demonstrate any meaningful difference for the primary efficacy endpoint of time to sustained symptom alleviation through day 28.

EPIC-PEP is a trial that evaluated 5 or 10 days of Paxlovid versus placebo for the post-exposure prophylaxis of symptomatic SARS-CoV-2 infection in adults. This trial failed to demonstrate any meaningful difference for the primary efficacy endpoint of prevention of symptomatic SARS-CoV-2 infection through day 14.

As you are aware, the landscape of the COVID-19 pandemic has changed considerably since the trial EPIC-HR was conducted. FDA will focus on a number of key review issues in our presentation today. These include the efficacy of Paxlovid in high-risk adults who are vaccinated against

COVID-19 or had a prior SARS-CoV-2 infection; the efficacy of Paxlovid in the setting of the SARS-CoV-2 Omicron variant; the impact of Paxlovid on COVID-19 rebound; the optimal duration of Paxlovid treatment in immunocompromised patients; and serious adverse reactions due to drug-drug interactions.

There are limitations with the data we will discuss today. To inform the discussion of key review issues, FDA will present subgroup analyses from EPIC-HR and EPIC-PEP. These trials failed on their primary endpoints. These analyses should be considered exploratory.

FDA will present analyses of quantitative nasopharyngeal SARS-CoV-2 viral RNA shedding. FDA does not currently recommend SARS-CoV-2 virologic endpoints as primary endpoints in phase 3 trials because there is currently no established predictive relationship between the magnitude and timing of viral shedding reductions and the extent of clinical benefit of how a patient feels, functions, or survives.

Published real-world evidence studies will likely be discussed. FDA has reviewed many of these reports and found that the reports generally do not include sufficient information to allow for complete review to determine their quality and assess for potential bias.

Following presentations and discussions, we will be asking the committee to vote on the question, is the overall benefit-risk assessment favorable for Paxlovid when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death? We will also ask the committee to discuss the questions projected, and are particularly interested in your suggestions regarding what future studies might be helpful to address data gaps.

This is an overview of our agenda today. We'll begin with applicant presentations, followed by FDA presentations; a lunch break; clarifying questions; an open public hearing; charge to the committee; and then questions to the committee and

committee discussion. Thanks very much.

DR. BADEN: Thank you, Dr. Farley.

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 applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, 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 the issue of financial relationships at the beginning of your presentation, it will not preclude you from

speaking.

We will now proceed with the applicant's, Pfizer's, presentation.

Applicant Presentation - James Rusnak

DR. RUSNAK: Good morning, Dr. Baden, members of the committee, Dr. Farley, and representatives from the FDA. My name is Jim Rusnak, and I am the chief development officer for internal medicine, anti-infectives, and hospital advisor. I will begin with a brief introduction and overview of our program.

Dr. Hammond will share with the committee the efficacy from our randomized clinical trials. Dr. McLaughlin will speak on the effectiveness of Paxlovid in real-world studies. Then Dr. Hammond will return, provide our efficacy conclusions and safety data from our randomized-controlled trials. Additional safety data from postmarketing surveillance will be presented by Dr. Merchant. I will then return to discuss COVID rebound, the continued development of Paxlovid, and summarize our conclusions.

Today we will discuss the combination of a novel coronavirus specific inhibitor of the main protease, nirmatrelvir, which is co-administered with a low dose of ritonavir. The ritonavir component is not pharmacologically active against SARS-CoV-2 but rather is utilized as a pharmacokinetic enhancer for nirmatrelvir. Together they are co-packaged in blister cards as Paxlovid.

Paxlovid is currently in use for the treatment of mild-to-moderate COVID-19 in adults and children over the age of 12 and weighing greater than or equal to 40 kilograms, who are at high risk for the progression of severe COVID-19, including hospitalization or death.

Our overall program to investigate the use of Paxlovid for COVID-19 was called EPIC for the evaluation of protease inhibition in COVID-19. Based upon the results of our EPIC HR study in patients at high risk for progression to severe disease, emergency use authorization was granted by FDA on December 22, 2021. Since this time,

Paxlovid has received authorization for full approval in over 75 countries, and approximately 10 million patients in the United States and 14 million patients globally have been treated with Paxlovid to date.

Let's have a look at the mechanism of action for nirmatrelvir. The main protease, or Mpro, is essential for the SARS-CoV-2 replication cycle. SARS-CoV-2 binds and enters the cell, shown here on the top-left of the figure, enabling the viral RNA to be translated into an inactive polypeptide. Mpro cleaves this polypeptide in 11 distinct locations and generates functional enzymes and proteins. Nirmatrelvir inhibits this essential step by blocking Mpro activity. Importantly, the Mpro recognition sequence is unique and has no human homolog.

Finally, while nirmatrelvir was specifically developed to inhibit SARS-CoV-2 Mpro, this enzyme is highly conserved across the coronavirus family; therefore, it potentially has broad therapeutic activity beyond SARS-CoV-2.

Here we see the chemical structure of nirmatrelvir on the top left with a co-crystal structure of nirmatrelvir and the main protease on the right. Nirmatrelvir fits tightly into the active site of the main protease and forms a reversible covalent adduct with the catalytic cysteine residue with high affinity. This results in inhibition of the enzyme and inhibition of viral replication.

Using cultured human airway epithelial cells, nirmatrelvir prevents viral replication with both potency and selectivity. Through clinical toxicology studies, nirmatrelvir has demonstrated a favorable safety profile with no adverse findings in a 1-month preclinical study in 2 species and has no genetic toxicity.

Nirmatrelvir has been evaluated in vitro across all major variants of interest or concern. The number on the far right has been benchmarked to the original wild-type strain. As shown here, nirmatrelvir provides a consistent degree of potency across all variants tested to date, giving

confidence for the demonstration of clinical efficacy across these different variants over time.

Of particular interest, as shown in the highlighted portion of the table, the Omicron variant and currently circulating sublineages demonstrate no diminution of antiviral activity, including XBB.1.5, the current dominating circulating variant.

Next, we'll have a look at PK. Here we see the high and consistent PK of nirmatrelvir when dosed with ritonavir. The figure shows a mean plasma concentration of nirmatrelvir from a clinical pharmacology study in healthy volunteers. The dotted blue line represents the in vitro EC90 and the dotted red line indicates the no observed adverse effect level from a 1-month preclinical toxicology study.

Due to the predominant role of the liver enzyme CYP3A4 in the metabolic clearance of nirmatrelvir, low doses of ritonavir, a potent CYP3A4 inhibitor, was co-administered in clinical studies to increase the plasma concentrations of

nirmatrelvir. Population PK model was developed from phase 1 data and was used for dose selection in phase 2/3 studies.

We modeled several dose levels of nirmatrelvir and selected a dose that provides a PK/PD target for trough concentrations above EC90 after the first dose in more than 90 percent of patients. This dosing regimen also affords having trough concentrations several multiples above EC90 for the majority of patients throughout the 5-day treatment period. That dose was 300 milligrams of nirmatrelvir combined with 100 milligrams of ritonavir.

Five-day treatment duration was chosen in part based upon the durations of treatment for other acute viral illnesses and in part based upon a quantitative system pharmacology model that was supportive of this treatment duration. Importantly, we sought this type of PK profile because experience from other antiviral therapeutics suggests that higher clinical exposures of drug increases the confidence in

achieving clinical efficacy for the acute illness, as well as reduces the risk of resistance mutations emerging over time. Therefore, we looked to safely maximize exposures to nirmatrelvir during development.

Our core development program, which consists of three phase 2/3 studies named EPIC, was evaluation of protease inhibition in COVID-19 in either high risk, HR; standard risk, SR patients; or in asymptomatic participants in a post-exposure, prophylaxis study, or PEP study. Our first-in-human and single ascending dose study and multiple ascending dose studies were conducted in normal healthy volunteers. Additional studies to further investigate the clinical pharmacology of Paxlovid in our pediatric study, EPIC-PEDS, remain ongoing.

In all, the three core EPIC studies -- HR, SR, and PEP -- randomized more than 6,000 patients across 21 countries with approximately half from the United States. In EPIC-HR and SR, the primary analysis was determined on day 28, and those time

lines are represented here as solid bars. However, patients in EPIC-HR and SR were also followed through 6 months, and those time lines are shown in the hash bars. When these trials were enrolled, as shown in the solid areas of the study bars, patients in EPIC-HR were almost exclusively 99 percent infected with the Delta strain. Enrollment was extended in EPIC-SR and includes a cohort of patients with the Omicron strain, as does the EPIC-PEP study.

Beyond these studies, the emergency use authorization has led to a unique, likely unprecedented opportunity to have 10 million patients in the United States alone who could have received Paxlovid and, importantly, to understand the effectiveness of Paxlovid through real-world studies. Collectively, this provides a robust data set that allows for the determination of benefit-risk, as the virus has continued to evolve over time, and we have moved from an era of unvaccinated patients to a population that is highly vaccinated or who's developed natural

immunity.

Severe illness from COVID-19 remains a serious public health threat, and COVID-19 continues to cause significant burden in the United States. Each week, approximately 200,000 cases are reported in the United States. However, the true number of cases is likely much higher, perhaps by a factor of 11, equating to over 2 million cases each week. Each day, COVID causes between 3,000 and 4,000 hospital admissions and 300 to 400 deaths in the United States, and more than 176 million U.S. adults are at increased risk for severe COVID-19.

Despite representing only 16 percent of the U.S. population, older adults, age 65 years and older, account for almost 9 out of every 10 COVID-19 deaths. In addition to the acute disease, COVID-19 can cause long-term sequelae, also known as long COVID. Patients who experience severe COVID-19 illness, especially hospitalization or intensive care, are at increased risk of developing long COVID.

Finally, SARS-CoV-2 is unpredictable.

Anti-SARS-CoV-2 monoclonal antibodies have shown erosion of protection against continual mutations of the spike protein of the virus. Emerging sublineages of Omicron have become resistant to currently available monoclonals, and at present, there is no monoclonal antibody recommended in the United States for the treatment or pre-exposure prophylaxis against COVID-19. Thus, there is a critical need for treatment options that help address the significant burden and uncertainty of COVID-19, and the danger it possesses to those at high risk.

Our objectives today are to demonstrate to the committee the favorable benefit-risk of Paxlovid and establish that the available data support the full approval and full marketing authorization of Paxlovid for the treatment of COVID-19 in vaccinated or unvaccinated adult patients who have risk factors for severe COVID-19 illness.

I would now like to introduce Dr. Jennifer Hammond, who will present the efficacy and safety

data from the Paxlovid clinical development program.

Applicant Presentation - Jennifer Hammond

DR. HAMMOND: Thank you, Dr. Rusnak.

My name is Jennifer Hammond, and I am head of antiviral development at Pfizer. Today I will review data that demonstrate the efficacy and safety of Paxlovid. Starting with efficacy, I will focus on results of the pivotal trial C4671005 or EPIC-HR. In addition to these data, I'll review select data from two other Paxlovid studies, EPIC-SR and EPIC-PEP, that provide supportive information on the use of Paxlovid in high-risk vaccinated patients, as well as in patients infected with recent variants such as Omicron.

Let's start by looking at the EPIC-HR study design. This was a phase 2/3, double-blind, randomized, placebo-controlled trial that enrolled participants 18 years of age and older with a confirmed SARS-CoV-2 infection. Patients were required to be randomized within 5 days of symptom onset and have at least one characteristic or

underlying medical condition associated with increased risk of developing severe COVID-19 per the CDC. Examples of such characteristics or medical conditions included, but were not limited to, factors such as age; body weight; hypertension; diabetes; et cetera.

Patients were excluded from the trial if they had a previously confirmed SARS-CoV-2 infection or if they had received either convalescent COVID-19 serum or a SARS-CoV-2 vaccine. Patients were randomized 1 to 1 to receive nirmatrelvir 300 milligrams in combination with ritonavir 100 milligrams or matching placebo twice daily for 5 days. Patients recorded the presence and severity of COVID-19 signs and symptoms daily from baseline through day 28. Viral load was measured through collection of nasopharyngeal swabs at baseline and at days 3, 5, 10, and 14.

Patients were followed for safety through day 34, and long-term follow-up visits were conducted at weeks 12 and 24. Patient demographics

and baseline characteristics were distributed equally across treatment groups. Male and female patients were equally represented; 71 percent of patients were white, 15 percent were Asian, and 4 percent were black. The mean age of participants was 45 with 21 percent of patients being greater than or equal to 60 years old.

The mean BMI for trial participants was 29 with 36 percent of patients having a BMI of 30 or higher. The most common risk factors outside of age and BMI were cigarette use, hypertension, and diabetes mellitus. Looking at baseline characteristics, approximately 50 percent of patients were seropositive for SARS-CoV-2 at baseline; 62 percent had a high viral load defined as greater than or equal to 4 $\log_{10}$ copies per mL, with 27 percent having a very high viral load defined as greater than or equal to 7 $\log_{10}$ copies per mL.

The majority, or 67 percent of patients, were enrolled into the trial within 3 days of symptom onset. A total of 2,113 participants

entered into the trial and greater than or equal to 92 percent completed treatment. The most common cause of treatment discontinuation was withdrawal by the subject, which occurred at a similar frequency between treatment groups, followed by adverse events, which occurred more frequently among patients in the placebo arm.

Now let's look at the efficacy profile of Paxlovid in EPIC-HR. Paxlovid administered twice daily for 5 days resulted in a clinically and statistically significant reduction in the proportion of participants with COVID-19-related hospitalization or all-cause death through day 28, the primary endpoint for the trial. Specifically, the relative reduction in hospitalization or death was 89 percent among patients treated within 3 days of symptom onset and 86 percent when treatment was initiated within 5 days of symptom onset. These results were consistent across prespecified subgroups based on participant demographics and baseline characteristics.

There were no deaths among patients treated

with Paxlovid compared to 15 total deaths in the trial among participants in the placebo arm; 13 of the 15 deaths among placebo-treated patients occurred prior to day 34, with an additional two occurring between days 34 and week 24.

These secondary endpoints for the trial included time to sustained alleviation and resolution of all targeted COVID-19 signs and symptoms, with trial results demonstrating a statistically significant 2-day reduction in median time to symptom alleviation and a 3-day reduction in median time to symptom resolution.

Additional secondary endpoints included COVID-19-related medical visits and change from baseline in nasopharyngeal viral RNA concentrations at day 5. With respect to these additional endpoints, a 73 percent reduction in COVID-19-related medical visits was observed, along with an additional reduction in viral load of 0.78 $\log_{10}$ copies per mL relative to placebo at day 5.

So let's take a closer look at each of the

findings described here. As summarized, the primary objective of the trial was met with a clinically and statistically significant reduction in COVID-19-related hospitalization or all-cause death through day 28.

The mITT analysis population for the primary endpoint included those patients randomized within 3 days of symptom onset. Among this group of patients, 0.8 percent of patients treated with Paxlovid experienced a primary endpoint event compared to 7 percent of patients who received placebo, equating to a 6 percent absolute reduction and an 89 percent relative reduction.

The first key alpha-protected secondary analysis was among patients treated within 5 days of symptom onset, defined as the mITT1 analysis population, which showed results similar to the primary analysis. In this Kaplan-Meier figure, the time to events of COVID-19-related hospitalizations, or all-cause deaths, through day 28 in participants treated with Paxlovid or placebo is shown. Between group differences in

event rates were evident, beginning at day 3. Of the 9 hospitalization or death events in the Paxlovid-treated arm, 5, or just over 50 percent, occurred prior to day 4.

A non-exhaustive list of the subgroup analyses of the primary endpoint are captured here. Subgroup categories are described on the far left of the plot, and the relative risk reduction for each subgroup is captured on the far right of the plot. Across all subgroups, treatment differences favor Paxlovid with relative risk reductions ranging from 48 to 96 percent.

The subgroups of patients most at risk for progression to severe disease demonstrated the greatest absolute and relative risk reduction. For example, the three subgroups in which the rate of COVID-19-related hospitalization or death through day 28 among placebo-treated patients was greater than 10 percent included those greater than 60 years of age, those who were seronegative at baseline, and those with a baseline viral load greater than or equal to 7 $\log_{10}$ copies per mL.

In each of these particularly high-risk subgroups, Paxlovid demonstrated a 96, 85, and 93 percent relative risk reduction, respectively. Similarly, patients with severe or moderate symptoms at baseline were at the highest risk of hospitalization or death in the placebo arm. In contrast, Paxlovid demonstrated high and consistent efficacy regardless of baseline symptom severity, with relative risk reductions of 89, 84, and 100 percent in the subgroups of patients with severe, moderate, or mild symptoms at baseline.

In the next set of slides, we'll examine the impact of Paxlovid on outcomes of patients admitted to the hospital, as well as on the overall impact on healthcare utilization among Paxlovid-treated patients. A total of 72 patients were hospitalized for the treatment of COVID-19 during the course of the trial, 63 in the placebo arm and 9 in the Paxlovid arm, equating to an 86 percent relative risk reduction in COVID-19-related hospitalizations.

Among those patients hospitalized, there

were 9 patients in total admitted to the ICU, all of which occurred in the placebo arm. Four patients required mechanical ventilation, again, all of which occurred in the placebo arm. Lastly, all patients in the Paxlovid arm with unknown discharge status were discharged to home self-care. In contrast, 54.7 percent of patients in the placebo arm were discharged to home self-care, with the remaining having expired while in hospital or were discharged to home under the care of others or to a skilled nursing facility.

As shown in the far left of this figure, patients in the Paxlovid arm reported a 73 percent reduction in any COVID-19-related medical visit compared to placebo through day 28. These observations were consistent across all predefined types of medical visits, including visits to the emergency department, practitioner's office, urgent care, and others.

I'll now shift focus to the impact of Paxlovid on signs and symptoms of COVID-19. Time to sustained alleviation was a key secondary,

alpha-protected endpoint in the EPIC-HR trial and was defined as the first of four consecutive days when all targeted symptoms scored as moderate or severe at trial entry were scored as mild or absent and all symptoms scored as mild or absent at trial entry were scored as absent.

Patients logged the presence and severity of targeted symptoms on 3- or 4-point scales daily from day 1 through day 28. Targeted symptoms are detailed on the X-axis on the figure shown here. I'd like to first draw your attention to the far left of the figure, which shows the overall time to symptom alleviation in the trial and where a statistically significant 2-day reduction in median time to sustained symptom alleviation was achieved, with patients treated with Paxlovid and placebo achieving alleviation at a median of 13 and 15 days, respectively. In addition, the time to alleviation of individual symptoms are shown to the right of the hash line and demonstrate that Paxlovid treatment resulted in a 1-to-2 day faster alleviation of all individual symptoms versus

placebo, with the exception of GI-related symptoms such as diarrhea and vomiting.

In addition to the data from EPIC-HR, two additional Paxlovid studies, EPIC-SR and EPIC-PEP, provide supportive information on the use of Paxlovid in high-risk vaccinated patients, as well as in patients infected with the recent Omicron variant, which I will now review. Let's start with the study design of EPIC-SR.

The design of EPIC-SR closely mirrored that of EPIC-HR with two important differences. First was the eligible patient population. Whereas EPIC-HR exclusively enrolled unvaccinated high-risk patients, two different groups of patients were eligible for EPIC-SR. First were vaccinated, high-risk patients and second were unvaccinated patients without risk factors for progression to severe COVID-19.

The second important difference in the trial was the order of endpoints. Whereas COVID-19-related hospitalization or death from any cause was the primary endpoint in EPIC-HR, in

EPIC-SR, this endpoint was the first key secondary alpha-protected endpoint. Conversely, while time to sustained alleviation of targeted symptoms was the key secondary endpoint in EPIC-HR, it was the primary endpoint for EPIC-SR.

Overall, patient demographics and baseline characteristics were similar to those previously reviewed for EPIC-HR. Sixty-one percent of patients in the trial were vaccinated with risk factors for severe disease, and as expected, rates of seropositivity were higher in this trial compared to EPIC-HR. Despite the high rate of vaccination and or seropositivity, 32 percent of patients had a very high viral load, defined as greater than or equal to 7 $\log_{10}$ copies per mL at baseline. As a reminder, 27 percent of patients in EPIC-HR had a similarly high viral load at baseline despite their unvaccinated status.

In EPIC-SR, greater than 95 percent of patients completed treatment, and there were fewer discontinuations overall due to adverse events in the trial compared to EPIC-HR, likely reflecting

the lower rate of progression to severe COVID-19 among the study participants.

As previously described, the primary endpoint for this trial was time to sustained alleviation of all targeted COVID-19-related symptoms. In this trial, a 1-day improvement in time to sustained alleviation was observed among Paxlovid-treated participants both in the overall study population as well as in the subgroup of vaccinated high-risk participants; however, these differences were not statistically significant.

For the secondary endpoint of COVID-19-related hospitalization or death from any cause, a 58 percent reduction was observed among the high-risk vaccinated subgroup and a 36 percent reduction among the unvaccinated subgroup without risk factors. There was one death in the trial, which occurred in the placebo group. Trends for a reduction in healthcare resource utilization in the high-risk vaccinated subgroup were also observed with a 59 percent relative risk reduction compared to placebo. Reductions in SARS-CoV-2 viral RNA

were observed that were consistent with those observed in EPIC-HR.

We will now look at further details on the reduction in COVID-19-related hospitalization or death in the EPIC-SR trial. Looking more closely at the impact of Paxlovid treatment on COVID-19-related hospitalization or death in this standard risk population, a 1 percent absolute reduction in risk of COVID-19-related hospitalization or death was observed, equating to a 51 percent relative risk reduction in COVID-19-related hospitalization or death overall.

Among high-risk vaccinated patients, Paxlovid treatment resulted in a 1.3 percent absolute and a 58 percent relative risk reduction. Among unvaccinated patients without risk factors, Paxlovid treatment resulted in a 0.5 percent absolute and 36 percent relative risk reduction.

In the next slide, we will compare these data to those observed in EPIC-HR. Drawing your attention to the placebo column, you'll note that the frequency of COVID-19-related hospitalizations

or death was much lower in the placebo arm of EPIC-SR compared to EPIC-HR. While 6.6 percent of patients in the placebo arm had a primary endpoint event in EPIC-HR, 1.9 percent of patients in the placebo arm of EPIC-SR experienced a primary endpoint event overall, with the high-risk vaccinated subgroup having an event rate of 2.2 percent. In contrast, the rate of COVID-19-related hospitalization or death from any cause through day 28 was approximately 0.9 percent among patients treated with Paxlovid for both studies.

The protection against severe COVID-19 afforded by vaccines is a likely contributor to the lower event rates noted in the placebo group of EPIC-SR, but as new variants emerge and/or existing immunity wanes, rates of severe COVID-19 among untreated patients may change. In this scenario, the additional protection afforded by Paxlovid treatment would continue to reduce the likelihood of progression to severe disease.

The next set of slides will examine the

impact of Paxlovid on outcomes of patients in the EPIC-SR trial who are admitted to the hospital, as well as the overall impact on healthcare utilization among Paxlovid-treated patients. In the high-risk vaccinated subgroup of participants from the EPIC-SR trial, a total of 10 patients were hospitalized for the treatment of COVID-19; 7 in the placebo arm and 3 in the Paxlovid arm, equating to a 58 percent relative risk reduction in COVID-19-related hospitalizations. Among those patients hospitalized, there were 2 patients in total admitted to the ICU, all of which occurred in the placebo arm. One patient required mechanical ventilation, which occurred in the placebo arm.

As shown on the far left of this figure, patients in the Paxlovid arm reported a 59 percent reduction in any COVID-19-related medical visit compared to placebo through day 28. While there were fewer COVID-19-related, non-hospital medical visits in the EPIC-SR trial, the results shown here are consistent with those observed in the EPIC-HR trial and further demonstrate the value of

treatment on reducing burden to the healthcare system associated with COVID-19, regardless of vaccination status.

While the primary variant in the EPIC-HR trial was Delta, both EPIC-SR and EPIC-PEP also included Omicron, and the impact of Paxlovid treatment on reducing nasopharyngeal viral RNA concentrations across the studies and variant types are shown here. I would like to point out one note regarding EPIC-PEP.

This was a trial to investigate the efficacy in Paxlovid in the setting of post-exposure prophylaxis, and patients were required to be rapid antigen test negative and asymptomatic at trial entry. However, approximately 10 percent of patients enrolled were subsequently found to be positive via the more sensitive RT-PCR assay, and the change from baseline data shown here for EPIC-PEP was among that subgroup of patients.

Among participants infected with the Delta variant in the EPIC-HR and EPIC-SR trials, Paxlovid-treated patients achieved a respective

additional 0.85 and 0.91 log reduction in viral RNA relative to placebo. Among participants infected with the Omicron variant in the EPIC-SR and PEP trials, Paxlovid-treated patients achieved an additional 1.0 and 1.8 log reduction relative to placebo, respectively. These data support the in vitro data, demonstrating broad-spectrum anti-coronavirus activity of nirmatrelvir, and together the in vitro and in vivo data suggests that Paxlovid will retain clinical utility against current and future variants of concern.

I'll now turn the presentation over to my colleague, Dr. John McLaughlin, to review effectiveness data from real-world studies.

Applicant Presentation - John McLaughlin

DR. McLAUGHLIN: Thank you, Dr. Hammond.

Good morning. My name is John McLaughlin. I'm an epidemiologist and vice president and global medical lead for COVID and influenza at Pfizer. Following the EUA in December of 2021, Paxlovid has been used by more than 10 million patients in the United States.

On this slide, we summarize five key U.S. studies that are published in peer-reviewed journals. You can see in the title row that these studies are published in high-impact journals, including CID, Annals of Internal Medicine, and Lancet ID, or as a CDC MMWR. Further, except for Ganatra, et al., which reported no funding, all were funded by NIH, CDC, or both.

Moving down the table, in the first row describing study endpoints, you can see that all studies reported real-world effectiveness of Paxlovid against either hospitalization or hospitalization or death, consistent with endpoints from the clinical trial setting.

Next, in the second row describing the study period, note that all studies were conducted during the Omicron era, providing contemporary information about Paxlovid effectiveness against Omicron sublineages, including BA.1, BA.2, and BA.4/5. The studies move from left to right in chronological order, with the most recent data on the far right.

In the third and fourth rows, you will see

information about data source and study population. We'll note two things. First, combined, nearly 1 million patients have been studied, and data come from large and diverse populations, including large health insurance databases like TriNetX, or EPIC Cosmos, or from large health systems like Mass General, the University of Colorado Health system, or Kaiser Permanente.

Second, the study populations reflect current CDC criteria for Paxlovid use, including 12 or 18 and older with high-risk factors that could include age alone, or the one study by Dryden-Peterson, et al., which restricted the analysis to those age 50 or older.

Perhaps most importantly, in the fifth row, you'll see that all studies were conducted in highly vaccinated, highly boosted populations. Thus, findings are representative of the world we live in today, and all studies report Paxlovid effectiveness restricted to subgroups of vaccinated individuals. More on that in a moment.

The sixth row highlights study methodology;

in particular how each analysis attempted to control for potential differences between persons who sought Paxlovid treatment and those who did not. All studies used well-accepted approaches for covariate adjustment, including propensity score or stratified matching; inverse probability treatment weights; regression analyses, which included logistic regression or Cox proportional hazards modeling; or a combination of these methods to control for potential confounding by differences in age group, underlying comorbid conditions, vaccination status, and other variables potentially related to prior healthcare utilization or healthcare-seeking behavior.

And finally, let's look at the results. In the second-to-last row, you can see that the relative effectiveness against hospitalization is statistically significant and very consistent across all five studies at roughly 50 to 60 percent when estimated without information about the timing of symptom onset.

In contrast, as you can see in the last row,

only one study, the Kaiser Permanente report, included information about the timing of treatment initiation relative to the timing of symptom onset. In this report, in the bottom-right, among patients who received Paxlovid within 5 days of symptom onset, effectiveness was 80 percent or higher, similar to that seen in the EPIC-HR trial, underscoring that prompt treatment with Paxlovid likely improves clinical benefit. Finally, you can see that all studies showed effectiveness among vaccinated patients, with most studies showing little difference in relative effectiveness between vaccinated and unvaccinated groups.

In summary, real-world studies conducted in the United States to date have shown high effectiveness of Paxlovid in that it provides an additional layer of protection beyond that conferred by vaccination alone. Notably, these findings are contemporary, and these results have been observed, one, in the Omicron era; two, in populations defined as high risk by current CDC guidelines; and three, regardless of vaccination

status.

I'll now turn the presentation back over to Dr. Hammond.

Applicant Presentation - Jennifer Hammond

DR. HAMMOND: Thank you, Dr. McLaughlin.

To conclude the efficacy presentation, Paxlovid is an effective treatment option for high-risk adults irrespective of prior vaccination status. High-risk unvaccinated and vaccinated adults treated with Paxlovid within 5 days of symptom onset achieved an 86 percent and 58 percent relative risk reduction in COVID-19-related hospitalization or death through day 28, respectively. There were a total of 16 deaths, 15 observed in EPIC-HR and 1 observed in the EPIC-SR trial, all of which occurred in the placebo arm of the trial.

In addition, Paxlovid-treated patients achieved reductions in COVID-19-related medical visits and a reduction in time to sustained alleviation of symptoms. Significant reductions in nasopharyngeal viral RNA were observed across all

studies, patient types, and variants, suggesting that Paxlovid will be an important tool in the fight against COVID-19, even as new variants continue to emerge. Lastly, real-world data collected across multiple U.S. studies confirm findings in Omicron era among vaccinated patients and among CDC-defined high-risk groups.

I'll now transition to a review of the safety profile of Paxlovid, including a review of adverse events, serious adverse events, and clinical laboratory and vital sign evaluations from the clinical development program. The safety profile of Paxlovid is based on data from approximately 6300 participants across four phase 2/3 and nine phase 1 studies, of which more than 3600 participants received Paxlovid. An integrated safety pool comprised of patients from the EPIC-SR and EPIC-HR trials demonstrates that Paxlovid was well tolerated, with 96 percent of adverse events being mild to moderate in severity.

The incidence of serious adverse events or adverse events leading to treatment discontinuation

was less than 2 percent. As noted previously, a total of 16 deaths have occurred across the EPIC-SR and HR trials, all of which occurred in the placebo arms of the studies.

Lastly, no clinically meaningful changes in laboratory values, vital signs, or ECG results have been identified. In total, the safety profile characterized to date support a positive benefit-risk assessment for the treatment of COVID-19 in patients with risk factors for progression to severe COVID-19. The next few slides provide additional details on the safety profile of Paxlovid.

Across the EPIC-SR and HR studies, the frequency of patients reporting adverse events was similar between treatment groups. In contrast, the frequency of patients reporting serious adverse events was higher among patients in the placebo arms of the trials, an observation driven by the higher rate of progression to severe COVID-19 among untreated patients and the serious adverse events associated with that progression.

The proportion of patients with a grade 3 or 4 adverse event also mirrored that of serious adverse events, with patients in the placebo arm being more likely to experience a grade 3 or 4 adverse event. Lastly, the proportion of patients discontinuing treatment due to adverse events was very low and similar between treatment arms.

It was frequently reported all causality adverse events across the EPIC-SR and HR trials were dysgeusia and diarrhea, which occurred more frequently in Paxlovid-treated participants than placebo. These events were non-serious, mild or moderate in severity, and led to just 7 discontinuations from treatment in total. Conversely, more patients in the placebo arms experienced adverse events associated with progression of COVID-19 such as pneumonia compared to those treated with Paxlovid.

Adverse events with a frequency less than 1 percent but with a greater than or equal to 5-participant difference between Paxlovid and placebo groups included myalgia, chills, and

product after taste. Each of these AES occurred in less than 0.5 percent of Paxlovid-treated patients.

As described previously, fewer patients treated with Paxlovid experienced a serious adverse event compared to placebo, with 1.6 percent of patients in the Paxlovid arm and 5.2 percent of patients in the placebo arm reporting a serious adverse event. The serious adverse events reported across studies in one or more participants are detailed here, and you'll note that the majority of events were related to COVID-19.

With respect to hematology and clinical chemistry laboratory test results, there were no clinically meaningful differences between treatment groups and no potential Hy's law cases identified in any patient through day 34 follow up. Similarly, no clinically meaningful differences in vital sign measurements or ECG results were observed, and results of a concentration QTc analysis indicated that Paxlovid is not associated with clinically relevant QTc prolongation. An analysis of safety across participant

subpopulations, including age, gender, race, BMI, vaccination status, or the presence and number of COVID-19 risk factors, suggests that no special precautions are required for Paxlovid use.

In summary, the safety profile of Paxlovid characterized to date supports a positive benefit-risk assessment for the treatment of COVID-19 in patients with risk factors from progression to severe COVID-19. The assessment of safety for Paxlovid is based on data from more than 3100 participants in the integrated safety pool of EPIC-SR and HR, which shows that most adverse events are mild or moderate in severity with a low incidence of either serious adverse events or adverse events leading to discontinuation from treatment. There have been no deaths in the Paxlovid arm of any trial compared with a total of 16 deaths across placebo arms from the EPIC-SR and HR trials. Lastly, no clinically meaningful changes in clinical labs, vital signs, or ECGs were observed.

The robust safety database from the Paxlovid

phase 2/3 trials is further supplemented by post-EUA clinical use experience, where more than 10 million patients have received Paxlovid since EUA approval in December of 2021 in the U.S. and more than 14 million patients have been treated globally.

I'll now turn the presentation over to Dr. Lubna Merchant to review postmarketing safety.

Applicant Presentation - Lubna Merchant

DR. MERCHANT: Thank you, Dr. Hammond.

Good morning. My name is Lubna Merchant, and I'm in Pfizer's Risk Management Center of Excellence, and I will be providing an overview of postmarketing safety.

Proactive surveillance of adverse event reports based on an estimated global patient exposure of 14 million, which includes 10 million in U.S. to date, has shown that the safety profile in the postmarketing setting is generally consistent with the known safety profile of Paxlovid characterized in the clinical program. Ninety-three percent of the cases reported have

been non-serious, with the majority of adverse events reported either being consistent with the adverse drug reactions already described in the label or associated with underlying disease progression.

Frequent signal evaluation of safety events has led to some updates to the EUA fact sheet over the last year. These updates include the addition of hypersensitivity to the warnings and precautions section of the label, additions to the drug interaction table and list of contraindicated drugs to support the appropriate use of Paxlovid, and the addition of anaphylaxis to the list of potential adverse drug reactions.

To support our ongoing characterization, we have active pharmacovigilance and pharmacoepidemiology programs in place. Our pharmacovigilance program is robust and designed to detect unexpected safety signals rapidly, using spontaneous adverse event reporting with active follow-up and frequent signal detection and evaluation. Supplementing our routine

pharmacovigilance, we plan to have two pharmakoepidemiology studies in pregnancy, which will include follow up on their incidence.

We have implemented a proactive risk mitigation strategy that ensures adequate labeling and includes prescriber supporting materials such as eligibility checklists, education materials, Pfizer sponsored and academic sponsored drug interaction checkers. And finally, we are proposing an updated packaging presentation to improve ease of use for patients and their caregivers.

Moving on to drug interactions, drug interactions with Paxlovid are primarily due to ritonavir mediated inhibition of CYP3A4 enzymes, and to a lesser extent, CYP2D6 enzyme and p-glycoprotein drug transporter. There are two major reasons for contraindications for use with Paxlovid. First, several drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions, these drugs are

contraindicated. Second, potent CYP3A inducers are also contraindicated, as they may reduce nirmatrelvir concentration.

Most of the potentially important drug-drug interactions can be managed by either dose reduction, increased monitoring of adverse events, monitoring of drug levels when feasible, or temporary interruption of the concomitant medication. This is coupled with a short 5-day duration of therapy, which is an inherent risk mitigation factor. The clinical management of DDIs are detailed in the fact sheet and is a very important consideration when prescribing and dispensing Paxlovid.

Pfizer has implemented a comprehensive and enhanced risk mitigation plan that employs several risk mitigation tools and communications to amplify the awareness among healthcare providers to address the risk of DDIs. Understanding that the majority of the prescribers are primary care practitioners, we have prioritized engagement with primary care providers regarding education on DDIs. We are

closely monitoring the uptake of the risk management tools and have seen their increased utilization.

As seen on the slide, Pfizer has utilized multiple modalities that intend to inform a wide range of stakeholders across the spectrum of medication use process, spanning from prescribing to administration. The EUA fact sheet and the proposed USPI extensively and adequately describes the risk of interaction with detailed instructions on how to successfully manage patients on these drugs during the short duration of therapy with Paxlovid.

The most common medications with DDIs could potentially be managed by either holding the drug, adjusting the dose of the drug, close medication level monitoring, and/or monitoring for adverse events. Pfizer ensures that the existing risk mitigation activities that have been implemented will continue to remain in place post-NDA and be supplemented with additional activities such as inclusion of an alert that is proposed for the

product packaging and an FDA-approved patient labeling.

In addition, Pfizer is developing continuing education programs that will increase healthcare provider knowledge uptake on management of DDIs when prescribing Paxlovid. In addition to the proposed risk mitigation plan, Pfizer also commits to providing periodic metrics using process and outcome indicators to support the assessment of effectiveness of these activities.

Our robust risk mitigation strategies have supported appropriate DDI management in the postmarketing setting. We have an ongoing and active pharmacovigilance that has been in place for over a year. In order to better understand how the varied range of prescribers are managing DDIs, we reviewed all valid U.S. postmarketing Paxlovid cases that have been retrieved using an approach that identifies all cases that reported a preferred term suggestive of drug interaction with contraindicated drugs or drugs that can be used with caution, as submitted to the Pfizer safety

database.

I want to draw your attention to the chart on this slide. The dark blue bar graph represents the patient exposure per month and the light blue line represents the number of drug-drug interaction cases per monthly exposure. During the period from January to December, we have identified a total of 427 DDI cases. This is amongst a U.S. patient exposure of 8.6 million during that period, which represents a low reporting rate of 0.005 percent.

While we recognize that a reporting rate has its own limitations and is not analogous to an incidence rate, it does give us a measure of the observed trend of DDIs. This trend has remained consistent despite the increased utilization of Paxlovid. The cases are primarily non-serious with reported adverse events consistent with the known safety profile of Paxlovid. Of the serious cases, 44 resulted in hospitalization. These outcomes were not necessarily due to the drug-drug interaction but due to multiple confounding factors, including underlying comorbidities,

concomitant medications, COVID-19 infection, or undetermined due to insufficient information. This includes the two fatal cases in which both patients had multiple comorbidities and neither completed the 5-day course of Paxlovid.

The rate of DDIs remain low, and Pfizer remains committed to ensure a strong infrastructure continues to be in place to support healthcare providers and patients in the management of this potential risk. We are aligned with the agency that labeling is adequate to mitigate the potential risk of DDIs.

Now, I would like to turn it to Dr. Rusnak who will provide a review of special topics and benefit-risk conclusion.

Applicant Presentation - James Rusnak

DR. RUSNAK: Thank you, Dr. Merchant.

Rebound of COVID, symptomatic or asymptomatic, detected with PCR, or more commonly rapid antigen test, has garnered much attention in the scientific community, press, and social media. The term "Paxlovid rebound" was coined in the press

and social media, rather than the appropriate term, "COVID rebound," as multiple data sources indicate the COVID rebound occurs in similar frequency in untreated patients, as well as patients receiving other antiviral therapies. Overall, with a variety of different definitions for COVID rebound, the incidence is similar between Paxlovid-treated patients and placebo-treated patients.

COVID rebound is not associated with severe disease, including hospitalization or death. It is not associated with low nirmatrelvir exposure. It is not associated with the emergence of resistant viral mutations. However, it has been suggested that the concern over COVID rebound is leading to the underutilization of Paxlovid in high-risk patients vulnerable to hospitalization and death.

To interrogate our EPIC-HR data for COVID rebound, we evaluated both symptomatic and asymptomatic viral load rebound. We aligned our definitions with those definitions used by NIH as published from the placebo group of the ACTIV-2 trial. As you can see on the bar graph on the far

left, the vast majority of patients exhibit no rebound with respect to either symptoms or asymptomatic viral load rebound as detected by PCR in the EPIC-HR study.

Moving to the right, a modest number of patients experienced a rebound of symptoms defined as any improvement in COVID-19 signs or symptoms that worsened with a total symptom score that increased by four or more points. These clinically symptomatic rebounds in EPIC-HR were numerically greater in the placebo group. A smaller group of patients experienced viral load rebound only, and the intersection of patients exhibiting both viral load rebound was quite uncommon.

Several literature reports evaluating viral or symptomatic rebounds have been published. The methodology and frequency of data collection varies across studies and may differ from that which was used in our EPIC program. Nonetheless, within each study, similar to our EPIC data, these reports show the COVID-19 rebound occurs in placebo-treated patients and also occurs amongst patients treated

with other antiviral agents. In the ACTIV-2 study, for example, investigators at the NIH, NIAID, and DAIDS study group reported a 6.5 percent incidence of COVID-19 viral load rebound using a threshold of greater than or equal to 5 $\log_{10}$ copies per mL of viral RNA. In the same cohort, the symptomatic COVID-19 rebound rate was 26 percent.

A real-world evidence study from the TriNetX database showed comparable rates of COVID-19 viral load rebound and COVID-19 symptom relapse between Paxlovid and molnupiravir. Finally, a study from Mayo Clinic shows low rates less than 1 percent of symptomatic COVID-19 rebound following treatment with Paxlovid.

In May 2022, a CDC health advisory was issued regarding COVID-19 rebound after Paxlovid treatment. In part, this CDC health advisory states, "A brief return of symptoms may be part of the natural history of SARS-CoV-2 infection in some persons independent of treatment with Paxlovid and regardless of vaccination status. Limited information currently available from case reports

suggest that persons treated with Paxlovid who experience COVID-19 rebound have had mild illness and that there are no reports of severe disease. Collectively, these data indicate that COVID rebound is a facet of the disease and occurs irrespective of treatment."

We have an ongoing program to monitor for clinical resistance. We currently have no evidence that clinical resistance to Paxlovid has been observed. During the study conduct of the EPIC trials through today, we've conducted viral genomic surveillance of the EPIC participants and public databases for Mpro mutations and shared the results in monthly reports with the FDA under our current EUA commitments. During this time, circulating dominant variants of concern evolved from a predominantly Delta to Omicron variant. Importantly, there were no hospitalizations or deaths for patients in EPIC-HR, SR, and PEP associated with Mpro mutations.

One single mutation, the E166V mutation, that was also identified in in vitro resistance

selection studies with nirmatrelvir emerged in 3 participants out of all the participants with sequenced virus that have received treatment in the EPIC trials to date, and those 3 participants did not experience hospitalization or death and effectively controlled the mutant virus. In the public database, GSED, through the end of 2022, E166V is present in only 16 out of over 13 million samples sequenced. These data suggest that there is no evidence of emerging clinical resistance to Paxlovid.

I would like to now finish by focusing on continued development and conclusions. We are very committed to the continued development of Paxlovid. We have initiated a Pfizer-sponsored study in immunocompromised patients, the EPIC-IC study, to address this patient segment with the highest remaining unmet need. EPIC-IC will study the use of Paxlovid in immunocompromised outpatients. All treatment groups will receive active Paxlovid, differing only by treatment duration, 5, 10 or 15 days. This phase 2 study has virologic and

clinical endpoints and may serve the basis for a future registrational phase 3 study.

We are also pleased to be collaborating with NIH, NHLBI, and NIAID on the RECOVER program in which Paxlovid will be tested for both treatment of highly symptomatic patients with long COVID and also tested for the prevention of long COVID. In our retreatment trial, patients that have symptomatic COVID-19 rebound and a positive rapid antigen test, we will study retreatment for 5 days of Paxlovid versus placebo. Finally, we have several ongoing PK studies in special populations, namely in pediatric patients, severe renal impairment patients, and pregnant or lactating women.

Based upon efficacy and safety of over 6,000 participants from EPIC-HR and supportive studies EPIC-SR and EPIC-PEP, we believe that the treatment of patients who are at increased risk for severe COVID-19 illness have a substantially reduced risk of being hospitalized due to COVID-19 or dying with the use of Paxlovid, irrespective of

vaccination status. The overall relative risk reduction in EPIC-HR was 86 percent for important clinical endpoints of hospitalization and death, and for death alone, there were 16 deaths reported in the EPIC program, all of them in the placebo group. This relative risk reduction was consistently observed across patient demographics and disease characteristics at baseline.

To date, we have no evidence of loss of antiviral efficacy across all variants or emergence of viral mutations that impair clinical efficacy. Paxlovid was safe and well tolerated when administered for 5 days in EPIC-HR, SR, and PEP, and also for 10 days in over 900 participants in EPIC-PEP. There were no critical adverse events, concerns, or clinically meaningful effects on clinical laboratory and vital signs or ECG parameters. The efficacy and safety is further supported by a growing body of real-world evidence, 14 million patients globally and 10 million within the United States. These data confirm the effectiveness against Omicron strains regardless of

vaccination status.

The completion of planned and ongoing studies and the robust pharmacovigilance and surveillance for viral resistance will further enable the safe use of the product. Approval of the new drug application for the use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults is warranted. This ends Pfizer's presentation. Thank you.

DR. BADEN: Thank you, Drs. Rusnak, Hammond. McLaughlin, and Merchant for covering a tremendous amount of data so clearly. The committee appreciates it.

We're a little ahead of schedule. Let's make it a 14 minute break, till 10:40, if that is ok with my FDA colleagues. So we'll break till 10:40 and start five minutes early. Panel members, please remember there should be no chatting or discussion of the meeting topic with other panel members during the break. We'll resume at 10:40. Thank you.

(Whereupon, at 10:26 a.m., a recess was

taken.)

DR. BADEN: It is now 10:40 [am], and we shall proceed with the FDA presentation, starting with Dr. Huang.

Dr. Huang, the floor is yours.

FDA Presentation - Glen Huang

DR. HUANG: Thank you, Dr. Baden.

Good morning. My name is Glen Huang, 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 presentations on data in support of Pfizer's new drug application for Paxlovid. I will now present an overview of the clinical development program.

As mentioned by Dr. Farley earlier, the purpose of today's advisory committee is shown on this slide, and also mentioned previously, here is shown the proposed indication and dose of Paxlovid. I would like to highlight that in moderate renal impairment, the dose of Paxlovid is nirmatrelvir 150 milligrams and ritonavir 100 milligrams orally

twice daily for 5 days.

The FDA issued an emergency use authorization for Paxlovid on December 22, 2021, for the treatment of mild-to-moderate COVID-19 for adult and pediatric patients 12 years of age and older weighing at least 40 kilograms, who are at high risk for progression to severe COVID-19. The EUA issuance was supported by adult interim data from EPIC-HR in which Paxlovid demonstrated reduced risk of COVID-19-related hospitalization or death from any cause through day 28 when compared to placebo.

In the U.S., other available COVID-19 therapeutics for mild-to-moderate COVID-19 in the high-risk outpatient population included remdesivir, which is an FDA-approved therapy administered intravenously in non-hospitalized adults, and molnupiravir, which is an oral therapy available under EUA for the treatment of adults who are at high risk for progressing to severe disease and for whom alternative antiviral therapies are not accessible or clinically appropriate.

This is an overview of EPIC-HR, which was the pivotal trial used to support this NDA. As the applicant presented previously, EPIC-HR was a double-blind, placebo-controlled phase 2/3 trial, studying the population of unvaccinated adult outpatients with mild-to-moderate COVID at high risk for progression to severe disease. This trial met the primary endpoint of proportion of participants with COVID-19 hospitalization or death from any cause through day 28. Additionally, this trial enrolled subjects from July 2021 to November 2021, when the predominant variant of concern was Delta.

This table is an overview of the supportive trials EPIC-SR and EPIC-PEP, both of which did not meet their primary endpoints; however, as we will discuss later, these trials were used for assessment of key review issues. I would like to highlight here the variants of concern during these trials on the right side of the table.

In EPIC-SR, the variant of concern was Delta during the enrollment period of August 2021 to

November 2021. The trial then reopened and enrolled from March 2022 to June 2022 for patients who were unvaccinated and not at high risk for progression to severe disease. The variant of concern during this time was Omicron. EPIC-PEP enrolled from September of 2021 to March 2022, and the variant of concern during that time were both Delta and Omicron.

This slide describes EPIC-HR in further detail as demonstrated by the figure at the top. Subjects were treated with Paxlovid from days 1 to 6, and followed until week 24. Key exclusion criteria for this trial included previous SARS-CoV-2 infection or hospitalization for COVID-19 and prior receipt of convalescent COVID-19 plasma or COVID-19 vaccination. Any medication or substance with clinically significant drug interactions with Paxlovid were prohibited during study treatment

This slide displays select baseline demographics and characteristics of subjects in EPIC-HR. Overall, 2,113 unvaccinated subjects were randomized. The most common risk factors were BMI

greater than or equal to 25 in approximately 80 percent of subjects; cigarette smoking in approximately 40 percent; hypertension in approximately 30 percent; and age greater than or equal to 60 years in approximately 20 percent. Notably, 13 subjects, or less than 1 percent, had the comorbidity of immunosuppression in this trial. Approximately 50 percent of enrolled subjects had a positive SARS-CoV-2 serology at baseline. This was likely from prior non-confirmed or asymptomatic SARS-CoV-2 infection or early seroconversion from the current SARS-CoV-2 infection.

As presented earlier by the applicant, EPIC-HR met the primary endpoint of COVID-19-related hospitalization or death from any cause through day 28 using the modified intent-to-treat-1 population, which was defined as subjects dosed within 5 days of symptom onset who did not receive nor were expected to receive therapeutic monoclonal antibody treatment. This endpoint was met in 0.9 percent of subjects in the Paxlovid arm and 6.5 percent of subjects in the

placebo arm, and as stated before, both EPIC-SR and EPIC-PEP did not meet their primary endpoints but were used in assessment of key review issues.

Here's an overview of the Paxlovid clinical safety database. In summary, across the three aforementioned phase 2/3 trials, 3,401 subjects received Paxlovid, including 2,490 subjects who were exposed to 5 days of Paxlovid. Post-authorization reports of adverse events after Paxlovid use were also reviewed to detect safety signals outside of the clinical trial setting.

This is an overview of adverse events in three clinical trials. Paxlovid demonstrated an overall safe, favorable safety profile in these clinical trials. As demonstrated in the table below, both serious adverse events and adverse events leading to discontinuation of study drug were infrequent in the Paxlovid arm of all three trials. Finally, most adverse events that occurred were either mild or moderate in severity.

This slide summarizes the most common adverse events across the three clinical trials.

Notably, dysgeusia and diarrhea occurred at higher frequency in the Paxlovid group when compared to placebo, as demonstrated in the table below. Additionally, the majority of these events were mild in severity. I would like to mention here that prior COVID-19 vaccination and baseline SARS-CoV-2 serostatus had no discernible impact on the safety of Paxlovid.

The following adverse reactions have been identified by the Office of Surveillance and Epidemiology or the applicant during use of Paxlovid during the EUA: anaphylaxis or other hypersensitivity reactions; headache; hypertension; abdominal pain; nausea and vomiting; and malaise.

In conclusion, Paxlovid demonstrated an overall favorable safety profile in the EPIC-HR, EPIC-SR, and EPIC-PEP clinical trials. Note that any medication or substances with clinically significant drug interactions with Paxlovid were prohibited during study treatment; therefore, drug interaction risk cannot be assessed through the phase 3 clinical trial data. This issue will be

discussed by Dr. Stephanie Troy later in the presentation.

Next, we will go into key review issues in this NDA. I will now pass it over to Dr. Troy, presenting on the efficacy of Paxlovid in high-risk adults who were vaccinated against COVID-19 or had a prior SARS-CoV-2 infection. Thank you.

FDA Presentation - Stephanie Troy

DR. TROY: Thank you, Dr. Huang.

Good morning. My name is Stephanie Troy, and I'm a senior medical officer in the Division of Antivirals at FDA, and as Dr. Huang mentioned, I'll be talking about the efficacy of Paxlovid in high-risk adults who were previously vaccinated against COVID-19 or who had a prior SARS-CoV-2 infection.

The COVID-19 pandemic has continuously evolved, both in terms of the baseline immunity of the population and in terms of the circulating SARS-CoV-2 variants. I'm showing here in red the EPIC-HR enrollment period in relation to the cumulative vaccine doses administered over time in

the United States on the left and in relation to the cumulative COVID-19 cases over time in the United States on the right. As you can see, the number of people in the United States who have received a COVID-19 vaccine or who have had a prior SARS-CoV-2 infection is not the same now as it was during EPIC-HR.

As the applicant and Dr. Huang discussed, EPIC-HR demonstrated a relative risk reduction of 86 percent and an absolute risk reduction of 5.6 percent in Paxlovid versus placebo recipients for the primary endpoint of COVID-19-related hospitalization or death from any cause through day 28; however, EPIC-HR enrolled unvaccinated adults with no prior confirmed SARS-CoV-2 infections.

Currently, in 2023, the vast majority of the U.S. population has some baseline SARS-CoV-2 immunity either from prior vaccination, prior SARS-CoV-2 infection, or both. And from here forward, when I talk about baseline SARS-CoV-2 immunity, I'm referring either to receipt of

COVID-19 vaccination or SARS-CoV-2 seropositivity, meaning detectable antibodies against SARS-CoV-2 in the blood. I'm not talking about any specific amount of protection from SARS-CoV-2 infection or protection from COVID-19 complications, as that could be highly variable.

According to the CDC, by February 2023, 79 percent of all adults and 94 percent of all adults 65 years and older in the United States have completed a COVID-19 primary vaccination series. In addition, there is abundant evidence that even unvaccinated adults have some SARS-CoV-2 immunity by now from prior infection.

For example, in EPIC-PEP, which enrolled asymptomatic household contacts who tested negative for SARS-CoV-2 at trial entry, 12 percent of subjects had received any COVID-19 vaccine dose, but 91 percent were seropositive at baseline, which if not from vaccination would likely be from prior infection.

Consequently, we looked at three subgroups in EPIC-SR and EPIC-HR to look for the benefit in

high-risk adults who have some baseline SARS-CoV-2 immunity. The first subgroup we looked at was the vaccinated high-risk subgroup, in EPIC-SR, and I want to point out here that EPIC-SR was not powered for the hospitalization and death endpoint, and enrollment of this group ended after Paxlovid was available through EUA because it was no longer considered acceptable to enroll high-risk adults into a placebo-controlled trial.

The second subgroup is a SARS-CoV-2 seropositive subgroup in EPIC-HR, which, as Dr. Huang mentioned, in this case seropositivity may represent pre-existing immunity from a non-confirmed prior infection or an early immune response to the current infection. And the third subgroup was a SARS-CoV-2 seronegative subgroup in EPIC-HR, which we used for comparison.

This slide shows the proportion of subjects in these three subgroups who met the endpoint of COVID-19-related hospitalization or death from any cause through day 28. The orange bars represent the placebo recipients and the blue bars represent

the Paxlovid recipients. On the left, we have the EPIC-SR vaccinated high-risk subgroup, in the middle, the EPIC-HR seropositive subgroup, and at right, the EPIC-HR seronegative subgroup.

As you can see, the relative risk reduction was similar in these three subgroups. It was 85 percent in the EPIC-HR seronegative subgroup and 88 percent in the EPIC-HR seropositive subgroup. It was somewhat lower in the EPIC-SR vaccinated high-risk subgroup at 58 percent, but it was still over 50 percent, and the overall pattern is similar to what you see in the EPIC-HR seropositive subgroup. As mentioned before, EPIC-SR was not powered for the subgroup, and this risk reduction did not meet statistical significance in the EPIC-SR vaccinated high-risk subgroup.

While the relative risk reductions were similar, the absolute risk reduction was much higher in the EPIC-HR seronegative subgroup, and this is because baseline immunity reduces the risk of progression to severe disease. So in the EPIC-HR seronegative subgroup, 11 percent of

placebo recipients met the endpoint of COVID-19-related hospitalization or death from any cause through day 28. In contrast, in the two subgroups with some baseline SARS-CoV-2 immunity, only 2 percent of placebo recipients met this endpoint.

As the applicant discussed, there have been a number of observational cohort studies or real-world evidence looking at the effectiveness of Paxlovid in the current era where most of the population is vaccinated. These studies have a number of limitations and can be subject to bias, but overall, the findings in those studies were similar to what I'm presenting here from the clinical trials.

We see similar findings with looking at SARS-CoV-2 RNA levels over time. On the left again, here, is the EPIC-SR high-risk vaccinated subgroup, in the middle is the EPIC-HR baseline seropositive subgroup, and at right is the EPIC-HR baseline seronegative subgroup. The blue lines represent the mean SARS-CoV-2 RNA levels over time

among Paxlovid recipients and the red lines represent the mean SARS-CoV-2 RNA levels over time among placebo recipients.

Paxlovid led to significantly greater reductions in nasopharyngeal SARS-CoV-2 RNA levels versus placebo from baseline to day 5 in all three subgroups; however, the baseline SARS-CoV-2 RNA levels were highest in the EPIC-HR baseline seronegative subgroup on the right.

So in conclusion, EPIC-HR and EPIC-SR clinical trial results support the efficacy of Paxlovid for the treatment of mild-to-moderate COVID-19 in high-risk adults regardless of COVID-19 vaccination status or evidence of prior SARS-CoV-2 infection. Pre-existing SARS-CoV-2 immunity is among the many factors that impact the risk of progression to severe COVID-19, and so should be considered when making a benefit-risk assessment for an individual patient on the use of Paxlovid.

At this point, I will pass it off to my colleague, Dr. Jonathan Rawson, for the next efficacy issue. Thank you.

FDA Presentation - Jonathan Rawson

DR. RAWSON: Alright. Thank you, Dr. Troy.

My name is Jonathan Rawson. I'm a clinical virology reviewer in the Division of Antivirals at the FDA. Today I'll be presenting on the efficacy of Paxlovid in the setting of the SARS-CoV-2 Omicron variant.

In the pivotal clinical trial, EPIC-HR, in which subjects were enrolled from July to November 2021, 99 percent of subjects with available sequencing data were infected with the SARS-CoV-2 Delta variant. However, soon after the completion of EPIC-HR, the Omicron variant emerged and quickly replaced the Delta variant, and nearly all infections in the United States today are caused by the Omicron variant, mainly by the Omicron subvariants BQ.1.1 and XBB.1.5.

In the first half of the EPIC-SR trial in which subjects were also enrolled in 2021, 98 percent of subjects were infected with the SARS-CoV-2 Delta variant similar to EPIC-HR, whereas in the second half of EPIC-SR in which

subjects were enrolled in 2022, 100 percent of subjects were infected with the SARS-CoV-2 Omicron variant, mostly BA.2 and BA.2.12.1. However, vaccinated subjects at high risk for severe disease could not be enrolled during the second half of EPIC-SR due to the availability of Paxlovid under EUA, and no subjects during this part of the trial experienced COVID-19-related hospitalization or death from any cause through day 28. Thus, the data from this trial were insufficient to directly determine the clinical efficacy of Paxlovid in patients infected with the Omicron variant who were also at high risk for severe disease.

To determine whether Paxlovid is likely to retain efficacy in the setting of the SARS-CoV-2 Omicron variant, we evaluated nonclinical virology, genomic surveillance, and clinical virology data, as well as real-world evidence studies conducted during the Omicron time period.

In terms of nonclinical virology data, the activity of nirmatrelvir, the SARS-CoV-2 Mpro inhibitor within Paxlovid, was investigated in

biochemical assays against recombinant Mpro proteases with amino acid polymorphisms from different SARS-CoV-2 variants. This table includes data for the 10 most frequent Mpro polymorphisms and the publicly available GISAID EpiCoV sequence database. The left column indicates the specific polymorphism that was tested, the middle column indicates its cumulative frequency as of November 30, 2022, and the right column indicates the K_i, or inhibition constant, fold change relative to a wild-type enzyme.

The K_i fold change of 1 indicates no change in nirmatrelvir activity, whereas a fold change greater than 1 indicates reduced activity and a fold change less than 1 indicates enhanced activity. Just for awareness, note that two polymorphisms mentioned in the briefing document, L30I and T45N, were not included in this table because they had cumulative frequencies below 0.1 percent.

As you can see from the table, nirmatrelvir retained activity with K_i fold changes below 3

against Mpro proteases with these polymorphisms. Most importantly, as shown at the very top of the table, nirmatrelvir retained activity against Mpro with a P132H polymorphism. This is the only consensus polymorphism in the Omicron variant and all major Omicron subvariants to date.

In addition, as described in the first bullet point on this slide, nirmatrelvir also retained activity in cell culture with EC_{50} value fold changes below 3 against different SARS-CoV-2 variants, including Alpha, Gamma, Delta, Lambda, Mu, and Omicron subvariants BA.1 and BA.2, BA.2.12.1, BA.4, and BA.5.

As shown in the table, in one set of experiments, four Omicron subvariants were compared to a reference, USA-WA1/2020. These subvariants had only a single amino acid polymorphism in Mpro, the P132H polymorphism. The table shows the EC_{50} values, EC_{90} values, and fold change in EC_{50} or EC_{90} values relative to the reference virus. As before, a fold change of 1 indicates no change in activity, whereas a fold change greater than 1 indicates

reduced activity and a fold change less than 1 indicates enhanced activity.

Nirmatrelvir had EC_{50} and EC_{90} value fold changes slightly below 1 against the four Omicron subvariants, indicating comparable activity to the reference virus. In addition, the applicant very recently provided data demonstrating that nirmatrelvir retains activity against XBB.1.5 in cell culture, which is currently the major Omicron subvariant in the United States.

Independent groups have also reported that nirmatrelvir retains activity against different SARS-CoV-2 variants in cell culture, including major Omicron subvariants up through BQ.1.1 and XBB. These results are consistent with the fact that major Omicron subvariants typically don't have any polymorphisms in Mpro besides this P132H polymorphism.

In addition to nonclinical studies, bioinformatic analyses of the SARS-CoV-2 Mpro protease and its 11 cleavage sites were provided based on the publicly available GISAID EpiCoV

sequence database. After filtering, this database included 12.7 million sequences as of the cutoff date, November 30, 2022. This analysis found that only 10 Mpro protease polymorphisms had a cumulative frequency of at least 0.1 percent. They ranged in frequency from 0.1 to 1.4 percent, excluding the P132H.

As shown on the previous slides, nirmatrelvir retained activity against Mpro enzymes with these polymorphisms in biochemical assays. The frequency of Mpro polymorphisms known to be associated with resistance to nirmatrelvir in cell culture was low, and we have not observed evidence that such polymorphisms have increased in frequency over time, whether due to Paxlovid use or otherwise.

In terms of the 11 cleavage sites, only 5 Mpro cleavage site polymorphisms had a cumulative frequency of at least 0.1 percent, and they ranged in frequency from 0.1 to 0.5 percent. The effects of these polymorphisms on nirmatrelvir activity have not yet been determined; however, Mpro

cleavage site substitutions have not been associated with nirmatrelvir resistance in cell culture, except for two near the Mpro protease C-terminus which overlaps one of the cleavage sites. Thus, these polymorphisms are considered unlikely to affect nirmatrelvir activity.

Overall, these analyses demonstrate that the SARS-CoV-2 Mpro protease and its cleavage sites are highly conserved and that nirmatrelvir is likely to retain activity against Omicron variants. More recent analyses of sequences in the database through January 31, 2023 are consistent with these findings.

Lastly, we examined SARS-CoV-2 RNA shedding data from the EPIC-SR trial. As stated earlier, in the first part of EPIC-SR in 2021, 98 percent of subjects with available sequencing data were infected with the Delta variant, whereas in the second part, in 2022, all subjects were infected with the Omicron variant. In this study, SARS-CoV-2 RNA levels where determined in nasopharyngeal swab samples collected at baseline,

day 3, day 5 or end of treatment, day 10, and day 14 using qRT-PCR.

As shown in the graph, average viral RNA levels decreased over time in both the placebo and Paxlovid arms in both time periods. However, Paxlovid led to significantly greater reductions in SARS-CoV-2 RNA shedding in both time periods, within approximately 0.9 log greater decline versus placebo on day 5 in the pre-Omicron period, which is shown on the left, and an approximately 0.7 log greater decline versus placebo on day 5 in the Omicron period, which is shown on the right.

In addition, as shown in the table, the proportion of samples with RNA levels below the lower limit of quantification, or LLOQ, was higher in the Paxlovid arm than the placebo arm on day 5 in both time periods. These data indicate that Paxlovid retains clinical activity against the SARS-CoV-2 Omicron variant in terms of reducing viral RNA shedding.

To summarize, based on nonclinical virology, genomic surveillance, and clinical virology data,

Paxlovid is expected to retain activity against currently circulating Omicron subvariants. We also note that real-world evidence reports in the literature have concluded that Paxlovid retains effectiveness in terms of preventing hospitalization and death against the SARS-CoV-2 Omicron variant; however, these reports do not include sufficient information to allow for a complete review.

With that, I'll turn it over to Dr. Patrick Harrington to discuss COVID-19 rebound.

FDA Presentation - Patrick Harrington

DR. HARRINGTON: Thank you, and good morning. My name is Patrick Harrington, and I am also a clinical virology reviewer on this application, and I am going to discuss the key review issue regarding the impact of Paxlovid on COVID-19 rebound.

I think everyone is quite familiar with COVID-19 rebound by now, so I'm just going to start by stating that FDA is in alignment with the applicant on the impact of Paxlovid on COVID-19

rebound. Specifically, analyses of virologic and symptom reporting data from the EPIC-HR and EPIC-SR trials showed a subset of Paxlovid- and placebo-treated subjects experienced virologic and/or symptomatic rebound after the end of treatment on day 5, and there was no clear or consistent association between virologic or symptomatic rebound and Paxlovid use.

Now, for the next several slides, I will summarize FDA's independent analyses focusing on viral RNA rebound, symptom rebound, and combined viral RNA plus symptom rebound. I'll first start with analyses of viral RNA rebound in nasopharyngeal samples as measured by quantitative RT-PCR.

One observation that we made very early in these analyses is that the rate of post-treatment viral RNA rebound depends greatly on the analysis parameters and on the frequency of sample collection for viral RNA assessments. Post-treatment visits for NP sample collection in the EPIC-HR and EPIC-SR trials were conducted on

day 10 and day 14, reflecting 5 and 9 days post-treatment, respectively. We defined the day 10 rebound, based on a day 5 viral RNA level less than the lower limit of quantification or less than LLOQ and day 10 viral RNA at or above the LLOQ; or if day 5 viral RNA was above LLOQ, we would call a viral RNA rebound if the day 10 viral RNA was at least a half-log greater than the day 5 result.

Day 14 rebound is essentially the same, except now we are comparing day 5 and day 14 viral RNA results, and day 10 or day 14 rebound identifies any occurrence of viral RNA rebound from day 5 to either day 10 or day 14, based on the same criteria. These analysis parameters were intended to be sensitive in detecting any occurrences of post-treatment increases in viral RNA levels regardless of magnitude, and note that the clinical relevance of any specific level of viral RNA rebound has not been established.

First focusing on EPIC-HR, the rebound rates at day 10 and day 14 are summarized here. I will

present several charts like these, which show the viral RNA levels in NP swab samples from individual subjects, with blue lines indicating Paxlovid-treated subjects and red lines indicating placebo-treated subjects. Those identified with viral RNA rebound are shown in the foreground and the rest of the study subjects are illustrated in the background for comparison. The dashed line at 2 logs indicates the assay lower limit of quantification.

As you can see, the overall rates of rebound at day 10 or day 14 are similar between Paxlovid and placebo recipients, though slightly greater in the Paxlovid group, but the differences are not statistically significant. Also, note more subjects had viral RNA rebound at day 10 than at day 14. You can see there is extensive variability in the viral RNA levels, and when you look at the viral RNA patterns across individual subjects, there are no obvious differences in the patterns or magnitude of rebound between Paxlovid and placebo recipients.

Then when we consider rebound at day 10 or day 14, the rates again are similar between Paxlovid and placebo recipients, but in this case, the rate in the Paxlovid recipients was significantly higher with a nominal p-value of 0.04, although, again, with no clear differences in the patterns or magnitude of rebound between Paxlovid and placebo recipients.

Now, it is important to note in these analyses that you have to take into consideration the impact the active treatment has on early viral RNA responses, which ultimately can bias the calculated rates of post-treatment rebound. This is because a rebound implies first a decrease followed by an increase in viral RNA level, and not surprisingly, nearly all subjects with post-treatment viral RNA rebound had a clearly measurable virologic response through day 5, based on either achieving viral RNA less than LLOQ or having at least a 1-log decline in viral RNA from baseline to day 5.

It is well established that subjects treated

with Paxlovid have a greater viral RNA response through day 5 compared to placebo-treated subjects, and therefore the calculated rate of viral RNA rebound could be biased by the greater impact of Paxlovid on the early viral RNA decline.

To account for this potential bias, viral RNA rebound rates were assessed for those with comparable virologic responses through day 5 or end of treatment. In other words, we were asking if you have Paxlovid- and placebo-treated patients with similar viral RNA declines through day 5, what happens when the antiviral pressure of Paxlovid is taken away? Does it result in more patients having a rebound in viral RNA compared to those who received no antiviral treatment?

When we analyze the data this way, focusing only on those who have a virologic response through day 5, we actually see a narrowing of the rates of post-treatment viral RNA rebound between Paxlovid and placebo recipients; again, a slightly higher rate in the Paxlovid group, but the difference is no longer statistically significant, and there's

not an obvious signal of viral RNA rebound driven by the removal of that Paxlovid antiviral pressure because we see this occurring in a similar proportion of placebo-treated subjects as well.

Viral RNA rebound in EPIC-HR was not associated with the primary endpoint of hospitalization or death. There were only 4 subjects with post-treatment viral RNA rebound at day 10 or day 14 who were hospitalized at any point, with no deaths. Three of the four subjects received placebo, and there was only one case where the rebound and hospitalization events were temporarily associated, and, again, this was in a placebo recipient.

For the sake of time, I will just very briefly summarize some additional analyses from EPIC-HR. Post-treatment viral RNA rebound was not associated with immunosuppression risk, although as already noted, there were only 13 such subjects in EPIC-HR, so this is obviously a very small sample size, and only one subject had a post-treatment viral RNA rebound, and this was, again, in a

placebo recipient.

Post-treatment RNA rebound was generally not associated with resistance. I use the word generally because there were 2 subjects representing about 3 percent of Paxlovid recipients with post-treatment viral RNA rebound who had a treatment-emergent substitution detected at an Mpro amino acid position potentially associated with nirmatrelvir resistance, and this included E166V or T304I.

In both cases, the substitutions were detected at day 10 and were not predominant in the viral population, so it is unclear if these played a role in the viral RNA rebound, and by day 14, viral RNA levels in both subjects had declined to less than LLOQ.

Finally, based on some more recent analyses conducted by the applicant, post-treatment viral RNA rebound was associated with detection of cell culture infectious virus in a subset of subjects. The applicant assessed for cell culture infectious virus using Vero TMPRSS2 cells by two different

assays, including a viral recovery assay and a more quantitative viral titration or $TCID_{50}$ assay. Among subjects with post-treatment viral RNA rebound, the results varied somewhat by assay but, in general, there was a similar rate of samples from Paxlovid- and placebo-treated subjects testing positive by SARS-CoV-2 cell culture.

Now, the relationship between viral cell culture infectivity and transmissibility is not fully established, but these results imply that in some subjects, including those treated with Paxlovid or placebo, there may have been transmissible virus present at the time of rebound on day 10 or day 14.

Similar analyses of viral RNA rebound were conducted for the EPIC-SR trial, and here I've summarized the post-treatment day 10 or day 14 rebound rates in EPIC-SR with the data split by the enrollment time period to show the rebound rates in subjects who enrolled in the pre-Omicron period, primarily reflecting infections with the Delta variant in comparison with those who enrolled in

the 2022 Omicron period.

As you can see, the rates of post-treatment viral RNA rebound were quite similar across these subgroups and, again, similar between Paxlovid and placebo recipients, with only that one EPIC-HR analysis that I mentioned earlier showing a significantly higher rate of rebound in Paxlovid recipients. In the Omicron period of EPIC-SR, the overall numbers of subjects are smaller, and you see a slightly higher number of rebounds in the Paxlovid recipients, but this reflects a difference of only 3 subjects, and this is not a statistically significant difference.

Now, regardless of any possible significant or non-significant differences in post-treatment viral RNA rebound rates, in EPIC-HR and in both the pre-Omicron and Omicron periods of EPIC-SR, there was a consistently lower percentage of Paxlovid recipients compared to placebo recipients who had quantifiable levels of viral RNA at all on-treatment and all post-treatment study visits. Based on these results, there is no evidence that

Paxlovid treatment is more likely to result in prolonged viral RNA shedding through day 14.

I want to come back to the variability in viral RNA results to make one more important point. Viral RNA [rebound] not only can be observed in the post-treatment period, but you can also observe the equivalent of viral RNA rebound in the treatment period. Here we used essentially the same analysis parameters that we used for post-treatment rebound analyses, and we identified a substantial number of subjects with on-treatment increases in viral RNA levels between day 3 and day 5, again, with a similar rate in Paxlovid and placebo recipients. In fact, this is actually a higher rate than we observed for post-treatment rebound, indicating a lot of these fluctuations in viral RNA may simply reflect natural variability or perhaps technical variability in sampling using NP swabs.

This observation of a higher rate of, quote/unquote, "rebound" during treatment makes it really challenging to attribute a post-treatment viral rebound to some sort of recrudescence or

relapse in viral replication after stopping treatment.

Now, switching to analyses of symptom rebound, as with viral RNA rebound, the calculated rates of symptom rebound can vary widely depending on the analysis parameters and the available data. Symptom data in EPIC-HR and EPIC-SR were recorded daily by study volunteers using electronic diaries through day 28. Our primary statistical reviewer, Dr. Jie Cong, conducted these analyses, focusing on subjects who first achieved at least a short-term symptom recovery, which was defined as the first day of at least two consecutive diary entries, where all targeted symptoms were absent and the subject could not have been hospitalized prior to symptom recovery.

Symptom rebound was identified in subjects after they had achieved short symptom recovery, and this was defined as having at least two consecutive diary entries after day 5 with any targeted symptom regardless of severity, or this could also include hospitalization, and rebound was assessed through

day 28. Moderate symptom rebound was defined as those with symptom rebound who had at least one reported moderate or severe rebound symptom or at least 2 symptoms at any time of rebound, or hospitalization, or death, again, all occurring after short symptom recovery.

Dr. Cong also assessed combined symptomatic and viral RNA rebound by first identifying subjects with combined recovery, which was defined as virologic responders through day 5 and with short symptom recovery by day 14. Among these subjects with combined recovery, symptomatic viral RNA rebound was defined as viral RNA rebound through day 14 and symptom rebound at any time after symptom recovery.

Now, there are some important limitations to these analyses that must be considered when viewing the data on the subsequent slides. First, not surprisingly, there were extensive fluctuations in self-reported symptoms, and there is no standard established definition for what constitutes symptom recovery and symptom rebound. There were also some

data quality issues, including a high frequency of missing symptom data, and then probably the biggest limitation of these analyses is the relationship between viral RNA rebound and symptom rebound could not be fully investigated due to the nature of the available data.

Symptom data were collected daily while viral RNA data were collected more sparsely, so daily changes in symptom patterns often could not be linked directly with viral RNA shedding data collected at the same time. Furthermore, the majority of symptom rebounds identified based on these parameters occurred after day 14, while viral RNA data were only available through day 14.

I'll first present the symptom rebound analyses through day 28. Again, the rates shown here reflect symptom rebounds after a period of symptom recovery, and this is all regardless of any virologic results. Across EPIC-HR and the pre-Omicron and Omicron periods of EPIC-SR, 10 to 16 percent of Paxlovid and placebo recipients experienced symptomatic rebound of any severity

through day 28. As you can see, most of these analyses actually showed a numerically lower rate of symptom rebound among Paxlovid recipients, but this was not consistent across all analyses, and our interpretation of these results is that Paxlovid and placebo recipients generally had similar rates of symptom rebound and moderate symptom rebound. There was no signal that Paxlovid treatment led to a higher rate of symptom rebound through day 28.

As for the combined symptom plus viral RNA rebound analysis, again, keeping in mind the limitations of the available data, only a very small number of subjects who met the combined recovery definition were identified as having combined symptomatic viral RNA rebound, again, with no consistent differences between Paxlovid and placebo recipients across EPIC-HR and the pre-Omicron and Omicron periods of EPIC-SR.

Based on these analyses of virology and clinical outcome data from the double-blind, placebo-controlled EPIC-HR and EPIC-SR trials, we

have concluded that rebound in SARS-CoV-2 RNA or virus shedding or COVID-19 symptoms occurs in a subset of infections, is not clearly associated with Paxlovid treatment, is not associated with severe disease outcomes, and likely reflects natural COVID-19 disease progression and/or technical variability in virology assessments.

Thank you for your attention, and I will now pass the presentation back to Dr. Troy, who will next address the review issue related to the optimal duration of Paxlovid treatment in immunocompromised patients. Thank you.

FDA Presentation - Stephanie Troy

DR. TROY: Thank you, Dr. Harrington.

As discussed, I will now be talking about the optimal duration of Paxlovid treatment in immunocompromised patients.

COVID-19 can have unique clinical manifestations in the immunocompromised population. While most people with mild-to-moderate COVID-19 clear the infection within 10 days of symptom onset, people who are moderately to severely

immunocompromised can remain infectious beyond 20 days. A small fraction of highly immunocompromised patients, about 14 percent in one study of patients with hematologic malignancy, can have persistent SARS-CoV-2 infection for 30 days or longer. Persistent SARS-CoV-2 infection in this highly immunocompromised population can lead to not only morbidity and mortality from COVID-19, but also to interruption to clinical care for other conditions such as interruption in chemotherapy or delay in organ or stem cell transplant.

So, one question that came up during the review was whether a longer treatment course for Paxlovid could be beneficial in this population. To look into this, we looked at all the available clinical data on Paxlovid use in immunocompromised patients. As has been discussed, enrollment in EPIC-HR was open to immunocompromised patients, but only 13 subjects in EPIC-HR were classified as having immunosuppression. None of these 13 subjects met the primary endpoint of COVID-19-related hospitalization or death, and none

of the six randomized to Paxlovid had evidence of increased SARS-CoV-2 RNA levels after treatment was stopped on day 5.

We've also approved a number of emergency INDs for prolonged use of Paxlovid, from 10 to 28 days, in severely immunosuppressed patients with persistent SARS-CoV-2 infection that ranged from about 1 month to up to 6 months of persistent SARS-CoV-2 positivity in nasopharyngeal swabs or in BAL samples. We now have outcome data from 15 of these patients. Two of the patients died, but one was in the intensive care unit at baseline and died on day 2 of Paxlovid treatment and the other had a number of other complications like cavitary pulmonary aspergillosis and had decreasing SARS-CoV-2 RNA levels at the time of death. The other 13 reported improvement either in terms of symptoms, or viral clearance, or in many cases both, with some patients reporting full recovery. While these results are encouraging, the small numbers, along with the heterogeneity of dosing durations, the use of other antivirals, the varied

clinical presentations, and the lack of a control group limit the interpretation of these results.

My pharmacokinetics colleagues also analyzed data from a quantitative systems pharmacology, or QSP model, that was developed by the applicant to select the Paxlovid treatment duration in EPIC-HR, and then later to select a Paxlovid treatment duration being studied in EPIC-IC, the ongoing clinical trial of Paxlovid for the treatment of mild-to-moderate COVID-19 in immunocompromised patients.

The QSP model incorporates the current mechanistic understanding of the interplay between viral replication and immune responses in the absence or presence of antiviral products and includes over 200 parameters. Virtual patients were calibrated and validated using longitudinal data from multiple observational studies that looked at biomarkers in SARS-CoV-2 infected patients over time and with aggregate virology data from three randomized-controlled trials looking at other antiviral products.

The resulting QSP model can describe aggregate viral RNA data in patient populations reasonably well, although there are still uncertainties and limitations such as predicting viral RNA patterns with the newer variants. The review team considered the model appropriate for use in selecting treatment durations to study in clinical trials.

As mentioned, this model was first applied to select the duration of Paxlovid for EPIC-HR in the general high-risk population and concluded that 5 days versus 10 days of Paxlovid treatment would have similar viral suppression. Once epic HR viral RNA data were available, the QSP model was further calibrated by these data.

For immunocompromised patients that manifest prolonged viral shedding, virtual patients were generated using two approaches. The induced approach refers to inducing a prolonged viral shedding profile by manually reducing the effect of two immune mediators that are partially responsible for killing of the infected cells, specifically

type 1 interferon and CD8 positive T cells. The resembling approach refers to selecting a subset from the general high-risk virtual population that resembles the long viral shedding phenotype, and specifically they looked at the 85th percentile and above for viral shedding duration.

This slide shows results from the QSP model looking at the effect of different treatment durations on viral shedding. The two figures illustrate the viral dynamics with 5, 10, and 15 days of Paxlovid treatment versus placebo in these two virtual immunocompromised populations. We have the induced virtual immunocompromised population on the left and the resembling virtual immunocompromised population on the right.

In both of these figures, the black lines show the viral dynamic profile of the virtual general high-risk population, referred to as the nominal population, and the red or the blue lines show the viral dynamics of the two virtual immunocompromised populations. The solid lines are placebo recipients and the dashed lines are

Paxlovid recipients with different treatment durations.

Key points in the QSP model results include the following. Both virtual immunocompromised populations show prolonged viral shedding with a slightly different profile around the peak viral load. By day 5 of treatment, in either of the virtual immunocompromised populations, represented here by the blue dot, the average predicted viral load is substantially higher than that in the nominal population, suggesting that ending treatment after 5 days may not be optimal for immunocompromised populations.

From a viral reduction perspective for immunocompromised patients using this model, 5 days of Paxlovid treatment is better than no treatment; 10 days of Paxlovid treatment is better than 5 days; and 15 days is about the same as 10 days. However, I want to note that this is modeling and not clinical data, and that the model is predicting effect on viral shedding and not on a clinically significant outcome like hospitalization and death.

These QSP modeling results support studying these treatment durations in clinical trials like EPIC-IC that can evaluate efficacy and safety in actual immunocompromised populations; however, these modeling results are not a replacement for, nor do they eliminate the need for, clinical trial data.

In conclusion, clinical trial data are needed to determine the optimal Paxlovid treatment duration in the immunocompromised population, particularly as a longer treatment duration may impact drug-drug interaction management in this population. The clinical trial EPIC-IC is currently ongoing to help provide some of these data, and I've included the clinicaltrials.gov link here for further information.

Now I'm going to move on to the key safety issue, which is the risk of serious adverse reactions due to drug-drug interactions or DDIs. On this slide, I'm showing the 10-page list of drug interactions that is included in the Paxlovid EUA fact sheet for healthcare providers.

As previously discussed, Paxlovid consists

of co-packaged oral tablets of nirmatrelvir and ritonavir. Nirmatrelvir is the actual SARS-CoV-2 antiviral product, while ritonavir is a potent CYP3A inhibitor that is included only to increase nirmatrelvir plasma levels. The DDIs are mainly associated with ritonavir, and the list of drugs with DDIs generally aligns with those in the ritonavir and boosted HIV protease inhibitor labels. Those of us who have been the primary HIV treatment provider for people living with HIV are very familiar with ritonavir DDIs.

The list of DDIs in the Paxlovid EUA fact sheet for healthcare providers starts with a statement that the list is not comprehensive and includes 143 separate drugs with Paxlovid DDIs, of which 37 are contraindicated with Paxlovid; 21 are not contraindicated but have an avoid concomitant use recommendation; 49 have a recommendation for dose adjustment; and 6 have a recommendation for therapeutic drug concentration or pharmacodynamic laboratory marker monitoring such as monitoring INR for warfarin or closely monitoring serum tacrolimus

levels for tacrolimus.

As has been discussed, concomitant use of medications with clinically significant Paxlovid DDIs was prohibited in the three phase 3 trials supporting this NDA application, so the risk of serious adverse reactions due to Paxlovid DDIs cannot be assessed through the existing clinical trial data.

Consequently, we assessed this risk through three analyses conducted by our Office of Surveillance and Epidemiology colleagues since Paxlovid was authorized in December of 2021. We first looked at the proportion of the Paxlovid-eligible population in the United States who are taking drugs with Paxlovid DDIs at the time of COVID-19 diagnosis; then second looked at the type of Paxlovid prescribers in the United States; and then third looked at reports of serious adverse events in Paxlovid users that were assessed as possibly or probably related to DDIs that were included in labeling.

This slide shows the proportion of

Paxlovid-eligible patients on drugs with DDIs with Paxlovid, which I'll call DDI drugs from here on out, at the time of COVID-19 diagnosis, and on the right in purple, the proportion of actual Paxlovid users on DDI drugs at the time Paxlovid was prescribed. The top half is from the Medicare database and the bottom half is from an analysis using the VA database. With both databases, two different definitions of Paxlovid-eligible patients were used.

The left one is defined as patients with a diagnosis of COVID-19 and without severe renal or hepatic impairment, who are either 65 years or older or who had at least one high-risk comorbidity. The middle one has a broader age range but is otherwise identical because per the CDC, age is one of the strongest risk factors, and just being over age 50 could be considered a high-risk condition. So for this definition, being either 50 years or older or having at least one high-risk comorbidity was considered high risk.

Starting with the definition on the left,

you can see that 67 percent of Paxlovid-eligible patients using the Medicare database and 65 percent using the VA database were on DDI drugs at the time of COVID-19 diagnosis. These included 10 percent of subjects on contraindicated drugs and about 40 percent on drugs with a recommendation of avoid concomitant use. With a broader definition of high risk in the middle, I'm going to focus on the VA database since Medicare, as you know, is primarily people 65 years and older.

Using this broader definition, we see a slightly lower rate of Paxlovid-eligible patients being on DDI drugs at the time of diagnosis at 57 percent, as would be expected since we're adding 50-to-64-year-old patients with no high-risk comorbidities, but it's still over 50 percent. Then when we move to the right, to the actual Paxlovid users, we see similar numbers; 66 percent of actual Paxlovid users were on DDI drugs at the time Paxlovid was prescribed and 62 percent of Paxlovid users in the VA database were on DDI drugs at the time Paxlovid was prescribed.

There are limitations with this analysis. For the Paxlovid users, we can't tell what the prescriber did about the DDI drugs, so the prescriber might have appropriately managed the DDIs by holding a drug, or reducing a dose, or clinically monitoring, and we can't tell that from this database. In addition, the Medicare database is predominantly people 65 years and older and the VA database is disproportionately male. However, this analysis still demonstrates that being on DDI drugs is not uncommon and that over 50 percent of Paxlovid-eligible patients may be on a DDI drug at the time of diagnosis.

This slide shows the top 10 DDI drugs used by Paxlovid-eligible patients in the VA database. There are 11 drugs listed because the ninth and tenth drugs were different, using the two different definitions of Paxlovid-eligible patients, and these are the ones circled in blue at the bottom. The list is topped by atorvastatin followed by amlodipine.

The key takeaway here is that most of these

DDIs with these ten most common DDI drugs could be managed by holding the drug, dose adjustment, or increased monitoring; however, it is crucial that prescribers look for these DDIs so that they can be appropriately managed. Similar results were seen for the top ten DDI drugs that Paxlovid-eligible patients were taking in the Medicare database.

This table shows the estimated number of Paxlovid prescriptions dispensed from U.S. outpatient pharmacies, stratified by top prescriber specialties, from December 2021 through January 13, 2023, aggregated. Outpatient pharmacies included retail, long-term care, and mail-order specialty pharmacies. The key takeaway here is that 74 percent of Paxlovid prescriptions in the United States are from adult primary care practitioners, followed by 7 percent from emergency room practitioners. This is very different from the prescribing pattern of other ritonavir-containing products that are used to treat HIV, which are mainly prescribed by providers who focus on HIV treatment, and so may be more familiar with

managing ritonavir DDIs.

The third analysis was looking at the adverse events following Paxlovid use under EUA for the treatment of COVID-19 that were reported to three sources. The vast majority of the events, over 99 percent, came from the FDA Adverse Events Reporting System or FAERS. Adverse events were also analyzed that were obtained from the FACT Pharmacovigilance Project Subregistry and the medical literature, including case series and case reports.

271 cases of serious adverse events were assessed as possibly or probably related to Paxlovid DDIs, meaning that these serious adverse events were thought to be caused by the Paxlovid DDIs. These included 147 reporting hospitalization and 6 with a fatal outcome; 4 with tacrolimus; 1 with verapamil; and 1 with both nifedipine and atorvastatin.

We are grateful to the healthcare providers and patients who took the time to report these cases, as they let us know that these serious

adverse reactions due to DDIs, including deaths, are occurring. Although reporting requirements are different for a drug under EUA, I want to stress that FAERS is a passive reporting system, meaning that it is dependent on healthcare providers or consumers, such as patients and their families, choosing to fill out a MedWatch form to report an adverse event or choosing to report an adverse event to the manufacturer; so you cannot calculate the incidence of serious adverse reactions related to Paxlovid DDIs based on these reports.

For example, if you try to calculate the incidence of serious adverse events due to DDIs by taking these reported cases and dividing by the total number of Paxlovid prescriptions, you could be greatly underestimating the incidence because the correct denominator to calculate the incidence would not be the total number of Paxlovid prescriptions but rather the number of Paxlovid prescriptions for which a serious adverse event due to a DDI would have been reported to FAERS if it had occurred, and we don't know that number.

So I'm showing this slide here as a reminder of the benefit of Paxlovid in 2023 when most people in the United States have some baseline SARS-CoV-2 immunity in order to better discuss how the risk of serious adverse reactions due to DDIs fits into the benefit-risk assessment. As a reminder, the absolute risk reduction for the hospitalization and death endpoint was between 1 and 2 percent with Paxlovid versus placebo in the trials among high-risk subjects with some baseline SARS-CoV-2 immunity, and the relative risk reduction was about 50 to 90 percent.

So when we're talking about the benefit-risk assessment in the United States in 2023, you have to think about it differently on a population level versus on an individual level. On a population level, we believe that the benefit of Paxlovid use outweighs the risk. In January 2023, each week in the United States there were still 4,000 COVID-19-related deaths and 35,000 COVID-19-related hospitalizations.

So even if you use a conservative estimate

of population benefit, and you say that 75 percent of the high-risk population is not on medications with DDIs that would preclude Paxlovid treatment, a 50 to 90 percent relative risk reduction could still result in 1500 or more lives saved and 13,000 or more hospitalizations avoided each week with Paxlovid use, assuming that these deaths and hospitalizations occurred in high-risk adults who had not taken any SARS-CoV-2 antiviral product prior to hospitalization.

However, on an individual level, the benefit of Paxlovid will not outweigh the risk in all high-risk patients, particularly if the DDIs are not adequately managed. As a reminder, the absolute risk reduction for hospitalization and death in the population with some baseline SARS-CoV-2 immunity is between 1 and 2 percent, and the risk of serious adverse reactions due to DDIs could be greater than this with concomitant use of certain medications.

To illustrate this, I want to go through the benefit-risk assessment of one family who developed

mild-to-moderate COVID-19 and saw a healthcare provider for evaluation for Paxlovid. Everyone in the family was fully vaccinated and boosted, and no one had severe renal or hepatic impairment, so the main considerations were the risk for progression to severe disease and the risk due to DDIs.

Starting with the top woman on the left, the 79-year-old woman, she is high risk for progression to severe disease based on age alone, and she does not have any DDIs. The healthcare provider assessed that the benefit outweighed the risk for Paxlovid and prescribed her Paxlovid.

The next gentleman, the 80-year-old man, is also high risk based on age alone, and he also has hypertension, but he's on rosuvastatin and amlodipine, which both interact with Paxlovid; however, these drug-drug interactions are manageable, and this particular gentleman is very compliant with medical instructions. So the healthcare provider advised him to stop taking the rosuvastatin while he was on the Paxlovid, and because she was more concerned about the risk of

hypotension from overexposures of amlodipine than hypertension from underdosing amlodipine, she told him to reduce the dose of amlodipine by 50 percent while on Paxlovid, and with those dose adjustments, she thought that the benefit outweighed the risk, and she prescribed him Paxlovid.

The next gentleman, the 52-year-old man, is the lowest risk of anyone in this family. He's the youngest, and he has no significant medical history, but he's also not on any concomitant medications. And just by being over age 50, he could be considered high risk for progression to severe disease, so the healthcare provider assessed that the benefit of Paxlovid outweighed the risk in this gentleman, and she prescribed him Paxlovid.

Then we move on to the gentleman on the right. He is the highest risk of anyone in this family. He's the oldest at 81, and he also has a number of high-risk comorbidities, including atrial fibrillation, hypertension, diabetes, and chronic kidney disease, but he's on amiodarone and rivaroxaban.

Amiodarone is contraindicated with Paxlovid. The drug-drug interaction is cardiac arrhythmias, which could be fatal, and the healthcare provider knew from experience that when this gentleman stopped taking his amiodarone, he would go into symptomatic atrial fibrillation and require hospitalization for electrocardioversion, so holding the amiodarone did not seem like a safe option.

Rivaroxaban is not contraindicated with Paxlovid, but it has an avoid concomitant use recommendation due to the increased risk for bleeding. This is an 81-year-old gentleman who's somewhat unsteady on his feet and recently has had a number of falls, so putting all of this together, the healthcare provider assessed that the benefit of Paxlovid did not outweigh the risks, and she prescribed him an alternative SARS-CoV-2 antiviral product instead.

I went through this exercise because this is what every healthcare provider has to do in order to safely prescribe Paxlovid. You have to get a

complete list of medications, and you have to check for drug-drug interactions with Paxlovid. And if you identify any drug-drug interactions, you have to determine whether they can be safely managed or whether Paxlovid is not an appropriate choice, and a different treatment such as remdesivir or molnupiravir should be considered.

In conclusion, serious adverse reactions due to DDIs are the key safety concern with Paxlovid. Safety surveillance data indicate that over 50 percent of Paxlovid-eligible Medicare and VA patients are on medications with Paxlovid DDIs at the time of COVID-19 diagnosis, though many of these DDIs could be managed with dose modification, holding the drug, clinical monitoring, et cetera.

Seventy-four percent of Paxlovid prescriptions were from adult primary care practitioners who may not be experienced with managing ritonavir DDIs, and serious adverse events due to labeled Paxlovid DDIs have been reported, including deaths. So to safely prescribe Paxlovid, all providers must review all concomitant

medications to assess for Paxlovid DDIs, and if Paxlovid DDIs are identified, determine if the benefit of Paxlovid outweighs the risks, and if yes, take appropriate actions to manage the DDIs.

At this point, I will transition to the overall FDA conclusions from the presentations today. Paxlovid, which is an oral drug product, significantly reduced the risk of COVID-19-related hospitalization or all-cause death through day 28 in high-risk adults with mild-to-moderate COVID-19. Efficacy was seen in adults with baseline SARS-CoV-2 immunity, and Paxlovid is expected to retain activity against currently circulating SARS-CoV-2 Omicron subvariants.

We did not identify any clear association between Paxlovid use and COVID-19 rebound, and we believe that COVID-19 rebound may be a natural part of the COVID-19 clinical course in a small subset of patients. More data are needed on the optimal Paxlovid duration in the immunocompromised population, and the ongoing clinical trial EPIC-IC will hopefully provide some of that data. The key

safety issue is the risk of serious adverse reactions due to Paxlovid DDIs.

On behalf of the people who presented today from FDA, we would like to thank the many colleagues who contributed greatly to this work, both in the Division of Antivirals and Office of Infectious Diseases, as well as across CDER review divisions in other offices, some of which are named here. Thank you for your attention.

DR. BADEN: Thank you, Drs. Huang, Troy, Rawson, and Harrington for presenting a tremendous amount of data in a very interpretable fashion. We are very appreciative.

As many of the viewers noted, at times the camera in the Great Room at the FDA was not functioning adequately, however, the slides and the discourse came through very clearly. This has been fixed and I'm sure during break will be rectified. So after lunch, we will have uninterrupted communication with our colleague in Bethesda.

We will now break for lunch. We'll reconvene at 12:40 Eastern Time. Panel members,

please remember that there should be no chatting or discussion of the meeting topic with other panel members during the lunch break. Additionally, you should plan to reconvene around 12:30 to ensure you're connected before we resume the meeting at 12:40. Thank you, and we're now on lunch.

(Whereupon, at 11:50 a.m., a lunch recess was taken.)

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

(12:40 p.m.)

Clarifying Questions

DR. BADEN: It is now 12:40, and we shall resume. Please pull up slide 5.

We will now take clarifying questions for the applicant and the agency. To my committee members, please use the raise-hand icon to indicate that you have a question and to remember to lower your hand by clicking the raise-hand icon after you've asked your questions. 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 your follow-up question with, "This is all for my questions," so we can move on to the next panel member.

One additional element for my panel members is if you have a follow-on question to a line of discussion, please use the green checkbox so that I

can call on you so that we can interrogate a specific line of questioning with as much consistency as possible, and then once we are done with a specific line of questioning, we'll then move on to additional questions.

So let us start now with questions to my panel members, and as I get set up, I can see that, Dr. Murphy, you have a question. And please turn on your camera.

DR. MURPHY: Thanks, Dr. Baden.

My question is for the company. I'm wondering if you're going to be seeking an indication that's related to a specific time frame. The pivotal trials that showed efficacy provided the medicine within a 5-day of symptom onset time frame, so it would make sense for the indication to reflect that. And then if not, I was wanting to know why not. Thank you.

DR. RUSNAK: Yes. In our clinical trials, our primary endpoint was a 3-day endpoint, but our first alpha protected endpoint went out to 5 days. We do have some data which indicates that

throughout that treatment period, it is better to have earlier intervention than later. That's not to say that there won't be any benefits past day 5 from symptom onset with treatment. We just don't have any data to reflect that.

DR. BADEN: Dr. Rusnak, what I will do is as panel members ask questions to the applicant, I will have you decide whom among your team is best to respond, unless it's pointed to one of your team members. Thank you for that clarification.

Dr. Clark?

DR. CLARK: Yes. Thank you. This is regarding the potential argument against the need for Paxlovid, given the relatively low absolute risk of hospitalization or death in those with prior immunity, and this is for the applicant.

There's waning of immunity that can happen over time, and there's been well uptake of the bivalent booster. So I was wondering if you have any other information about the pre-existing immunity in the EPIC-SR group and any heterogeneity response according to that; so looking at subgroups

according to their time from last vaccine, or number of vaccine doses, or even antibody levels. Thank you.

DR. RUSNAK: I don't think that we have any of that information from EPIC-HR. There has been some real-world evidence that has suggested that there is certainly waning of immmunity, and as we see that, there's not a great uptake for the bivalent vaccines and that the SARS-CoV-2 is very unpredictable in its virulence, as well as transmissibility. We do think that Paxlovid, as it retains efficacy for the Omicron variant, will be useful as we continue to have this virus present in an endemic phase.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thank you, Dr. Baden. I think this is for FDA, and I believe it would be for Dr. Troy.

When you were doing your presentation, you gave us the drugs that were responsible for drug-drug interaction associated deaths. If I'm

remembering the slide correctly, I think there were also from the real-world data 147 hospitalizations thought to be driven by drug-drug interaction, and I'm wondering if you have any information on which of the drugs was primarily responsible for that.

In particular, I'm thinking that four of the deaths were associated with tacrolimus, and as someone who takes care of organ transplant patients, I'm very well aware of the really intense drug-drug interaction with even one dose of ritonavir on tacrolimus. And I'm just wondering if 147 drug-drug interactions were also substantially attributable to a calcineurin inhibitor drug, as this is a population that maybe we would just say don't use it, but then our concern for DDIs would go substantially down. Thank you.

DR. TROY: Thank you for that question. I'm actually going to call up Dr. Kate McCartan to answer this, and we have a slide ready for that question, slide 42 for the backup slides.

Kate?

DR. McCARTAN: I'm Kate McCartan from the

Division of Pharmacovigilance. Looking at the total cases -- not just hospitalization but the 271 cases reporting a serious adverse event that we assessed as to be possibly or probably related to the DDI -- the most common drug class involved in the DDIs were the immunosuppressants, which were reported in 44 percent of the cases. This was largely driven by tacrolimus cases, which accounted for 41 percent of the total cases with any DDI drug.

The next most common drug classes were calcium channel blockers with 17 percent of the cases; sedatives and hypnotics with 8 percent of the cases; and anticoagulants and HMG-CoA reductase inhibitors, each with 7 percent of the cases. As far as hospitalizations, as you can see, since tacrolimus was the greatest number of cases, similarly for hospitalizations, it was also the greatest percentage of cases reported of the hospitalizations.

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

DR. SCARSI: Thank you. I have a couple of questions for the FDA and the sponsor, so I'll start with the FDA since we're on there, and then right now.

I really appreciated your discussion around the population versus individual risk-benefit assessment related to drug interactions and safety, and you importantly note the importance of appropriate management of those drug interactions.

Are you able to comment on additional drug interaction studies that may be proposed or required of the sponsor to further support the management of clinically significant drug interactions? For example, in the current EUA, there are some recommendations that have specific guidance around the duration of withholding a medication and specific management advice; others are a little more broad about just contraindicated or withhold. So just curious if you can offer some additional insight there.

DR. TROY: Well, thank you for the question. In terms of other studies that will be required,

since most of the drug-drug interactions are due to ritonavir, and ritonavir has been around for decades, I don't think there are any other specific studies that are required. But in terms of the recommendations that are listed, I'm going to actually defer to Dr. Cristina Miglis, who should be coming in remotely.

DR. MIGLIS: Hi. This is Cristina Miglis from clinical pharmacology. Yes, the applicant did conduct several clinical DDI studies, so two were evaluating Paxlovid as a victim, so that was studies with itraconazole and carbamazepine. The only gap which we identified was there were no studies conducted to evaluate moderate or with weak CYP3A inducers, so we did ask the sponsor to come up with a plan for that. They submitted some PBPK modeling, and we had our PBPK group evaluate that, and it was concluded that there's not a significant risk with moderate or weak CYP3A inducers. That was the only gap in which we identified with the studies that evaluated Paxlovid as a victim.

There were also two studies conducted to

evaluate Paxlovid as a perpetrator. Those were with midazolam and dabigatran, and these clinical DDI studies are included in the current labeling. So as far as specific drugs, we continue to evaluate those on a case-by-case basis, but I think it's very difficult to include every possible DDI due to CYP3A inhibition.

DR. SCARSI: If I could just follow up to that, I completely agree that it's great we can use the information we have about ritonavir in a chronic use for patients living with HIV, but I do think there is a gap in the extent of induction that occurs over a 5- or 10-day course of Paxlovid, and I don't see any data that was provided evaluating that.

So the assumptions that appear to be made, or that the induction properties may be similar to chronic use with ritonavir, that's led to some of the recommendations in the label. So I'm curious as a perpetrator if you plan to further evaluate the extent of the potential interactions with a shorter course related to induction.

DR. MIGLIS: We did not suggest that. That's a great point. The data from the midazolam studies does not suggest induction. We don't have any specific data with the current 5-day course, but we recognize that and we appreciate that insight. I think some of these DDIs will have to be evaluated on a case-by-case basis, as Dr. Troy very nicely laid out in her presentation.

DR. SCARSI: Thanks. I'm happy to defer my question to the sponsor for later, and it may come up in other topics.

DR. BADEN: Okay, and take down your check so that you can be brought back in as you intend.

Dr. Siberry?

DR. SIBERRY: Thanks very much, Chair. This is George Siberry, and this question is for the applicant about some special population studies, and namely children and pregnant people.

I note that Study 1026 in children aims to enroll 140, and I wanted to know how many participants were already enrolled and a projected end date. Similarly, Study 1035 aims to enroll

45 participants, and I wanted to know specifically how many pregnant participants have been enrolled thus far, and finally, what the proposed language will be for pregnancy; so status on the peds in the pregnancy trials and proposed language for pregnant people. Thanks.

DR. RUSNAK: Thank you. If I could please have backup slide 294.

Our overall design for the EPIC-PEDS 1026 trial is shown here. It is a 5-cohort study, starting with the oldest age children, and then we will successfully work down through the cohorts sequentially until we get into a very young neonate population. Most of the cohort 1 previously enrolled. We did some evaluation of this, and decided to increase the overall sample size of this cohort. So that will begin to enroll again, and I do believe that we'll have that data from that cohort prior to the end of the year.

For the other study, the cohort for pregnant women, the special population, if I could have slide BU-237, and if we could show that slide,

please.

So this shows the design of the EPIC pregnancy study, Study 1035. Overall, 45 patients will be enrolled. There is a stratification into cohort 1 and 2. Depending upon the trimester, we intend to enroll 15 from each of those, as well as a non-pregnant cohort. The non-pregnant cohort was recruited very quickly and has been full for some time, and in the other cohorts 1 and 2, we have 2 subjects to date. It's been rather challenging to enroll this study.

DR. SIBERRY: Thanks very much.

Do you have proposed language for pregnant people for the indication?

DR. RUSNAK: Currently, there are no restriction for pregnancy. There is safety data that has been collected in over 39,000 pregnant women, and there has been no unusual safety anomalies noted in that cohort of 39,000 pregnant women.

DR. SIBERRY: Great. Thanks very much. That's it for me, Chair.

DR. BADEN: Thank you.

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

DR. GREEN: I do. Thank you, Dr. Baden, and this question is for the agency.

I just wanted to confirm that the extension of the EUA for the adolescent greater than 12 and greater than 40 kilograms would be in place, and will remain in place until the data from the pediatric special population study was available to analyze and to make a decision on. Certainly we have gotten used to being able to treat this age group under the EUA, and I would hope that it would stay open until you have data that tells you that the groups should either be approved or not approved. Thank you.

DR. TROY: Thank you for that question. I'm going to defer to Dr. Farley to answer that.

DR. FARLEY: Thanks, Dr. Green. Farley for the agency, and that answer is yes; that is the agency's intention. Thanks.

DR. BADEN: I will ask a question now to Dr. Troy and the agency, two questions. One is,

you note that there are 30,000 hospitalizations and 4,000 deaths. I think those were the numbers of that scale ongoing associated with COVID infections from the CDC.

How comfortable are you that COVID, SARS-CoV-2, causes the hospitalization and death versus is present in the context of other medical conditions? How confident are we that we understand the current burden of severe illness due to COVID?

DR. TROY: You know, that is an excellent question and, yes, that is one of the weaknesses I think with the data, is that it's not entirely clear whether COVID-19 caused the hospitalizations and deaths or whether the person had COVID-19 and died or was hospitalized for other reasons.

DR. BADEN: Then my second part to the question, which goes to your slide 74, is something I've been struggling a lot with and very much appreciate your presenting absolute numbers as opposed to relative risk reduction, which always worries me when it's a 10 percent to 1 percent

versus a 1 percent to 0.1 percent. The relative risk is the same and impressive, but the absolute numbers are different.

On your slide 74, that data you just presented, 2 percent to 1 percent seemed to be sort of the benefit. So even though it may still be a 50-to-90 percent benefit, it's actually a small number, and I worry that the side effects aren't proportionate in that way. With background immunity, that doesn't change the side effect profile.

How should we be thinking about the risks of side effects that may be greater than the risk of benefit in weighing this; though some of the side effects like dysgeusia, nausea, and diarrhea may be moderate, while Dr. Green raised earlier, drug interactions can cause hospitalization and death, which are more numerator observations? But how is the agency trying to weigh these uncertainties of a preserved relative risk reduction but of a much smaller number in the context of a continuous level of risk? Thank you.

DR. TROY: Thank you for that question, and you bring up a very excellent point. I think that goes to that you have to look at it on a patient-by-patient basis because we believe that the biggest risk is the risk of drug-drug interactions. So if you have a patient who doesn't have any drug-drug interactions, for example, then I would think that the benefit would likely outweigh the risk in a high-risk adult, but then you have to weigh it for each individual patient who has a drug-drug interaction and look at what the potential risks are, et cetera.

As you noted, the other safety findings with Paxlovid from the trial, the dysgeusia and the diarrhea, really aren't that serious, so I think, again, the key safety concern is the drug-drug interaction risk.

DR. BADEN: Thank you, and I will just appreciate to both you and the applicant, and for our community, relative risk is more complex. It is wonderful to see absolute numbers presented and highlighted so that we can weigh these types of

risk-benefit ratios. So thank you for presenting the data this way.

DR. TROY: Thank you.

DR. BADEN: Dr. Adimora?

DR. ADIMORA: Hi. Thank you. This is Ada Adimora, and this question I think is largely for the applicant, although the FDA may wish to weigh in; I don't know.

My question is about people with HIV. What are the plans for, and to what extent will EPIC-IC evaluate people with HIV, specifically those with low CD4 counts? I ask this because this is important for the U.S. and certainly globally, not just for the health of people with HIV, but also because to the extent that there are a lot of people who are severely immunocompromised due to infection, they may be a source of subsequent mutants that can spread globally, and also because the nature of their immunocompromise differs from those of the more traditionally immunocompromised, like transplant patients, et cetera. Thank you. That's the end of my question.

DR. RUSNAK: If I could have backup slide 235, please, and please project that slide.

This is the trial design for our EPIC-IC study. Of note from the main presentation, this is that all treatment groups received active Paxlovid, differing only by the treatment duration for 5, 10, and 15 days. In the gray chevrons, you'll see that as we continue along after the active treatment phase of the 5- and 10-day period, we will control that phase with active ritonavir so that we can maintain blinding as well as adequate modification of drug-drug interactions during that period.

Overall, we're looking for sustained viral load reduction through day 44 after the active treatment period ends. We will allow HIV-positive patients in this study. In our previous study for EPIC-HR, we did have 13 patients who are immunocompromised. Mainly that immunocompromised status resulted from the use of TNF inhibitors, as well as corticosteroids. We wanted a broader population here, so we've actually capped that population at 25 percent. In EPIC-HR, we had one

HIV-positive patient, so we are looking to enrich that population within the study, and we'll be reporting out on this trial in the third quarter of this year, and we're about two-thirds of the way enrolled.

DR. ADIMORA: Can I just ask a quick follow-up to that? So you're going to proactively recruit sufficient people with HIV and low CD4 counts to be able to say something meaningful, I assume, about them.

DR. RUSNAK: They're permitted to be in the study, but we're not proactively enriching. We are enriching for severely immunocompromised patients, HIV as well as patients receiving B-cell depleting therapies or transplant patients. This is a phase 2 study. We hope to learn the optimal treatment duration from this phase 2 study, and then that would serve the basis for a follow-on phase 3 trial.

DR. ADIMORA: Thank you.

DR. BADEN: Ms. Shankaran, you have a follow-on question?

DR. SHANKARAN: Yes, thank you. One of them had been the one that the company just answered, which was what kind of immunocompromise the patients had, but the other question was the two patients that developed the E166V. Were they immunocompromised or were they not immunocompromised?

DR. RUSNAK: They were not immunocompromised. Two of the patients were in the placebo group and one was in active and not immunocompromised.

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

DR. GREEN: Yes. With regard to the immunocompromised, so EPIC-IC, will you allow transplant patients on tacrolimus or cyclosporine -- so calcineurin inhibitor -- to be enrolled in this study; and if so, what are you doing in terms of guidance in terms of the drug? Then secondly, will you allow HIV patients who are receiving ritonavir as part of boosting with a protease inhibitor into the study as well? Thank

you.

DR. RUSNAK: We do require therapeutic monitoring for transplantation drugs -- in particular, tacrolimus -- in this trial with dose adjustments, and to the best of my recall, we are, yes, allowing ritonavir-boosted patients in this trial.

DR. GREEN: Thank you.

DR. BADEN: Dr. Patel?

DR. PATEL: My question is for the agency. If they can pull [inaudible].

DR. BADEN: Dr. Patel, you inadvertently went mute.

DR. PATEL: Sorry.

My question is for the agency. If they could pull up backup slide 42 that was presented a few moments ago, my question is in regards to drug-drug interactions.

It looked like calcium channel blockers were the second most frequent cause of serious effects or serious adverse events reported with DDIs. Just thinking about the language in the applicant's drug

interaction tool on their website, I'm assuming that the most common calcium channel blocker that was implicated was diltiazem, but when you put that into the interaction check on their website, it just says to use with caution.

Has the agency thought about strengthening this? Knowing that roughly 20 percent of these serious adverse events are caused by calcium channel blockers or related to calcium channel blockers, has the agency considered strengthening some of the language around calcium channel blockers, specifically to move from used with caution to contraindicated?

DR. TROY: I think I might defer to two different people to answer that question. I'll start with Dr. Kate McCartan, who can talk about some of the serious adverse events that were seen with the calcium channel blockers, and then I'm going to defer to Dr. Cristina Miglis to talk about the difference between contraindicated and other things in the label.

DR. McCARTAN: So for the calcium channel

blockers, the most common adverse events that we observed in the DDI cases were things like hypotension, bradycardia, and there were some cases of AKI or acute kidney injury.

Cristina, I'll let you answer next as well.

DR. MIGLIS: Thank you. Cristina Miglis from clinical pharmacology. Could we put backup slide 49 up, please?

We are working on that.

(Pause.)

DR. BADEN: While they pull up the slide, I just want to comment how impressive it is, from both the agency and the applicant, to be able to call up backup slide 49 and backup slide 237. It speaks to the amount of work that has gone into being able to present data to the community properly, so very grateful and appreciative.

Back to you, Dr. Miglis.

DR. MIGLIS: Thank you.

So regarding the question of contraindicated versus avoid concomitant use language, the agency has very specific definitions on what a

contraindication entails based on the guidance, and also cited that in the slide. Contraindication really only applies to a situation for which the risk clearly outweighs any possible benefit, and this includes only known or anticipated hazards, and not a theoretical possibility.

The avoid concomitant use scenario applies where the concomitant use should be avoided in most scenarios, but there could still be a scenario where the benefit outweighs the risk, and this would require careful risk assessment on behalf of the provider. I do recognize the nuances between these two. There are delineated criteria in our guidance, and in addition, we have aligned a lot of the Paxlovid label with the current ritonavir-boosted protease inhibitor labeling.

DR. BADEN: Thank you.

Seeing no follow-up, Dr. Swaminathan?

DR. SWAMINATHAN: Hi. I wanted to ask the agency about the analysis that they did to account for a more rapid decrease in viral load in the treated patients, appearing to lead to more

rebound. And as I understand it, you've compared the treated patients to untreated patients who had a similar early rapid decrease, but are you substituting one problem for another when you do this? Because that subset of untreated patients who had a rapid decline presumably might have had a stronger innate immune response and would be expected to have less rebound because they're just better controlling the virus from the get-go.

DR. TROY: Thank you for that question, and I'm going to defer to Dr. Pat Harrington to answer that one.

DR. HARRINGTON: Pat Harrington, FDA. Thank you for the question. The point of that analysis was really to get at the question of what happens when you take away the Paxlovid antiviral pressure.

I understand your point of those on placebo who have a more rapid decline that could be immune based, but what we found, though, was that when you take away the Paxlovid or the placebo, a similar proportion of individuals in both arms had virologic rebound. So to us, that indicates that

the rebound that we were observing in the Paxlovid group was not driven by the removal of that antiviral pressure of Paxlovid due to perhaps inadequate treatment duration or something along those lines.

I'm sorry. For the Chair, can I make one point, a point that the applicant made a few moments ago? They mentioned that there were three individuals with the E166V substitution that emerged, and two of whom received placebo, if I understood that correctly. That is not correct. To my understanding, it was three individuals who received Paxlovid who had treatment-emergent E166V and zero placebo-treated subjects who had that. So I just wanted to correct that for the record. Thanks.

DR. BADEN: Thank you.

Dr. Carvalho?

DR. CARVALHO: Thank you, Dr. Baden. This is actually a quick question on some clarification for the applicant, and this on the upcoming or I guess already ongoing study, EPIC-IC, for patients

that are non-hospitalized that are immunocompromised.

They're looking at the varying doses, varying duration of doses, with I think a maximum of 15 days of treatment, and what I'm wondering is, how long will the viral load assessments continue? Will they stop at 15 days? Will they go beyond that? Because this is so clinically relevant now in patients that we see coming in. Thank you.

DR. RUSNAK: If I can please have backup 235 shown? On the bottom portion of the slide, it is listed as a primary endpoint, so it's the proportion of participants with sustained NP swab with SARS-CoV-2 viral RNA less than the lower limit of quantitation through the end of active treatment, and then followed up for 44 days. We wanted to make sure that we had a long-term assessment for this.

DR. CARVALHO: Thank you very much.

DR. RUSNAK: Great.

DR. BADEN: I have a couple of questions, and Dr. Rusnak I want to test how deep your backup

slides are to understand the data as much as possible where available, and look forward to my panel members raising their hands.

One set of observations raised -- and again, I apologize if I missed it -- was that cultures were done in a subset. Are there data correlating the NP viral load with what is culture positive as we try to, as a community, think about transmissibility? Do you have such data where you correlated what NP viral load has a higher chance of being culture positive? And my understanding is these are your data, not the agency's.

DR. RUSNAK: We do have some data on infectivity, and if we could find that. It's backup slide 437, and if we could project that, please.

Here we look at the infectious status from the viral recovery at baseline in the HR data set, and as a surrogate for infectivity, we use a threshold of 5 $\log_{10}$ copies per mL, and as you can see -- I can't see.

DR. BADEN: Yes, we can see.

DR. RUSNAK: I'm sorry. I can't --

DR. BADEN: We see 437.

DR. RUSNAK: -- the negative and the positive are shown -- there we go. Thank you very much for making it larger for me. The negative and the positive infectious virus from baseline are shown here in the 5 $\log_{10}$ copies per mL as a threshold for surrogate for infectivity.

DR. BADEN: So these are exactly the data I was hoping to see, so thank you for sharing. There obviously is a distribution, but one can see where the 95 percent -- or whatever the confidence intervals were, there was clear separation, that at 10^{6}-10^{7}, the infectivity is higher, and below 10^{5}, the infectivity is lower.

DR. GREEN: Dr. Baden, can you just ask them to put the slide up for one more minute? They took it off quickly. Thank you.

DR. BADEN: No, these are terrific data, and we accept, Dr. Rusnak, your careful framing. This is infectivity of the cells. We cannot infer transmissibility -- that's another step -- but

these are the kinds of data that are helpful as we think about this problem, so thank you.

Did you have a question, Dr. Green, based on this?

DR. GREEN: No, no. I just wanted to -- I didn't absorb it quite as quickly as you did, Dr. Baden.

DR. BADEN: So my next question, Dr. Rusnak, is, understanding who's high risk -- and high risk initially had to do with age, being unvaccinated, and the factors we all were faced with in 2020-2021 -- now that vaccine or prior immunity is present in the majority of our community, this now puts more pressure on the other risk factors, and it seems like the dominant risk factor is BMI greater than 25.

Again, I may have missed this in the data, but do you have the outcome of interest, severe outcome, divided by BMI, 25 to 30 and above 30? I wonder if 25.1 is the same risk as a BMI of 35.

DR. RUSNAK: I believe that we do have that data. Dr. Jennifer Hammond will present it. But

it could be argued that the 25 to 30 is perhaps the lowest of the risk for what is called out for high risk in our clinical study.

Having said that, it is difficult to predict who is going to end up with a severe outcome. For patients with greater than a BMI of 25, we had a total of 11 patients that had an outcome of hospitalization and death. Ten of those were in the placebo group and one was in the active treatment group. We do have a further break out, and I will defer to Dr. Hammond for that.

DR. HAMMOND: Thank you.

If we could project backup slide 231, this is additional subgroup analyses of the primary endpoint based on age, gender, race, and BMI. As you can see in the lower portion of the slide, the difference from placebo is noted for BMI categories of less than 25, 25 to 30, and greater than 30; so you do see a gradual increase in risk as BMI goes up.

DR. BADEN: Dr. Hammond, terrific, but I want to then understand that -- I think this is

EPIC-HR data -- half of these individuals had baseline immunity and half didn't. Do we know how this shakes out dependent on baseline immunity?

DR. HAMMOND: Yes. Actually, if we could go to backup slide 245, please.

DR. BADEN: Very impressive in your command of the backup slide --

(Laughter.)

DR. BADEN: -- and appreciated.

DR. HAMMOND: Can we project the slide, please? This is a breakdown, a multivariate analysis among those patients whose BMI was greater than 30, and as you can see, if you look down below for baseline SARS-CoV-2 status, there was an absolute reduction in risk among the seropositive patients with a high BMI versus a 13.5 point reduction in risk for patients who are seronegative.

DR. BADEN: And this is with BMI greater than 30 --

DR. HAMMOND: Yes.

DR. BADEN: -- BMI 25 to 30 baseline

immunity. As we think about going forward who's at high risk, the seronegative group of individuals is such a small group now, so understanding the risk factors for the agency, for you all, for the community, which risk factors put you into a high-risk group; therefore the benefit outweighs the risk of the medication?

DR. HAMMOND: Sure. We have the same plot for a BMI less than 30. If we could bring up slide 246. Please project the slide.

So again, a very similar layout and plot. As we provided for the BMI greater than 30, this is looking at patients whose BMI was less than 30. Again, you can see in the seropositive patient population, we see 100 percent relative risk reduction against hospitalization or death, and, again, the event rate is 5 out of 310, so we're looking at an event rate of -- what is it? -- just under 2 percent.

DR. BADEN: Terrific. Thank you. Very helpful.

Dr. Green?

DR. GREEN: Thank you. This question might be for the applicant --

DR. BADEN: Actually, I apologize, Dr. Green. I see Dr. Hunsberger has a follow-on question. The green check doesn't rise to the top of the list in Zoom the way it did on Adobe Connect, so sorry that I missed that.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. I think the question was, did you do a multivariate analysis for the seropositive group to look at risk factors? That's the piece I didn't quite see. So in the seropositives, is there a multivariate analysis to look at risk factors?

DR. RUSNAK: I'll ask Dr. Hammond to address this question.

DR. HAMMOND: Yes, we did. If we could project backup slide 416, please. This is, again, a very similar layout, a very similar multivariate analysis, and these are among patients who at baseline were SARS-CoV-2 positive from a serology status.

You can see the breakdown of the placebo and Paxlovid rates, and, again, the point estimates here broadly favor treatment with Paxlovid, and we were showing relative risk reductions across each of these subgroups, ranging from 60 to 100 percent.

DR. HUNSBERGER: Okay. Thank you. That's helpful. Thank you.

DR. BADEN: Now, Dr. Green. Sorry for that.

DR. GREEN: Thank you. This is probably a question for the applicant, and may be a question for the agency. Certainly, the topic for today and the data that we have to review is really addressing those who have mild-to-moderate symptoms, who are at risk of progression to severe disease. But I note that we likely would see in labeling that you could use it up to day 5 because that's what the data really show.

I wonder if there are plans to look at -- or if there are thoughts from either you or the agency -- what one might do for individuals who don't have the stereotypically prestated risk factors but on whom day 2 or 3, and maybe even

day 4, really are having very, very prominent symptoms. And the data seem to show that this Paxlovid not only keeps you from going to the hospital or dying, but also mitigates those severe symptoms. Thank you.

DR. RUSNAK: Yes. We did conduct the EPIC-SR. In that study, the primary endpoint was not met, which was a symptomatic scale. The exact identical scale was actually measured as an alpha protected endpoint in EPIC-HR, and we did show that numerically the same 2-day outcome did result in a highly statistically significant finding. But to date, we don't have any data on that non-high-risk group that has significance associated with it in terms of symptom resolution.

I would also --

DR. GREEN: I just would add, do you think that that study was adequately powered to actually answer that question?

DR. RUSNAK: We believe that the scale that we used could be further refined. I think that we have learned that the resolution of certain

symptoms such as shortness of breath and fatigue are more important than the resolution of other symptoms such as gastrointestinal related symptoms. I think that there is potentially an opportunity to look at a symptomatic trial in this patient population at a further time as well.

I would also just like to take the opportunity to thank Dr. Harrington for his correction that all three patients that had the E166V mutation did occur on Paxlovid treatment. Thank you.

DR. TROY: I was wondering if you mind if we responded to that question, too.

DR. BADEN: Please do, Dr. Troy.

DR. TROY: Thank you.

First, I just want to reiterate what the applicant said, which is that in EPIC-SR, the endpoint of time to symptom alleviation was not met in the non-high-risk population, and there are also some limitations with the time to symptom alleviation and time to symptom resolution endpoints in EPIC-HR, and I'm going to defer to my

colleague, Dr. Jie Cong, who's a statistician, to discuss that more.

DR. CONG: Hi. This is Jie Cong. I'm the statistical reviewer for this application. We do consider the time to sustained symptom alleviation endpoint and time to symptom resolution endpoint. There are certain concerns even though it reached statistical significance in the EPIC-HR study.

These endpoints are heavily influenced by the hospitalization and death endpoint because those events of hospitalization and death in EPIC-HR and SR studies are considered symptom not resolved or alleviated in the symptom endpoints. Also, as stated earlier by Dr. Troy, the EPIC-SR study already failed the primary endpoint of time to sustained symptom alleviation. Also, those symptom-related endpoints have some drawbacks With data quality, including missing values, so we consider the day 28 hospitalization and death endpoint be the focus of the efficacy evaluation. Thanks.

DR. BADEN: Thank you.

DR. RUSNAK: We have done some sensitivity analyses around the hospitalization and death in how it relates to the symptom endpoints that Dr. Wayne Wisemandle could share with the committee.

DR. BADEN: Thank you.

MR. WISEMANDLE: Yes. Thank you. Wayne Wisemandle from biostatistics for Global Product Development. Could I get BU-458, please?

To assess the impact of the primary endpoints upon the time to sustained alleviation for the EPIC-HR trial, we did do a sensitivity analysis excluding those patients that have an endpoint, which was the 9 Paxlovid patients and the 64 placebo patients. That analysis is on the right side of this table here, and as you can see, we still see a meaningful treatment effect in the subgroup of patients that are excluding those people with those endpoints with a nominal p-value of 0.01. Thank you.

DR. TROY: Can I ask if you also have a backup slide showing the same thing for the time to

symptom resolution?

DR. RUSNAK: We do not.

DR. BADEN: Thank you.

Dr. Clark, did you have a follow-on?

DR. CLARK: I did. Thank you. I was going to ask about the missing data. There were FDA comments, I think, about missing data, and I wasn't sure if that was related to the EPIC-SR, where the primary endpoint was symptoms, or if it was just the HR study, and how that would affect the outcome.

DR. TROY: Thank you for that question, and I will, again, defer to Dr. Jie Cong.

DR. CONG: Hi. This is Jie Cong, the statistical reviewer for this application. We did look at the missing data percentage for both the EPIC-HR study and EPIC-SR study. For the EPIC-HR study, we used the population of all treated patients, mITT2. There are close to 20 percent missing data in the symptom diary data, and for the EPIC-SR study of 2021, which is a major part of the EPIC-SR, there are close to 15 percent missing data

for the e-diary. Thanks.

DR. TROY: Thank you.

DR. BADEN: Thank you.

It is 1:31, and I just wanted to mention that now would be the time for the open public hearing section; however, we have no open public hearing speakers. We will continue with our question of the applicant and the agency.

I think Dr. Hunsberger had some questions.

DR. HUNSBERGER: I guess this is for the agency, and if this is not an appropriate question, feel free to say so. But I'm just wondering, and I'm still struck, as Dr. Baden raised, about the relative risk in relation to the proportion of people that are actually affected or helped.

Are there examples of other medications that the agency has approved that would have this similar relatively good relative risk, but such a low proportion of people that are benefited?

DR. TROY: You know, that's a very good question. I'm trying to think of some, and I wonder if any of my -- no? We'll think about that

and try to get back to you after the break.

DR. HUNSBERGER: Thank you.

DR. TROY: Thanks.

DR. BADEN: Thank you.

I will ask another question, and I'll ask this question both to the agency and the applicant.

How satisfied are each of you, given your analyses; is 5 days the appropriate duration of therapy? What is your view, Dr. Rusnak, and yours, Dr. Troy? How confident, given the state of the data, that 5 days is the correct duration?

DR. RUSNAK: Yes, 5 days was selected, in part, based upon other antiviral therapies used for upper respiratory infections, as well as a quantitative systems pharmacology model. With the dose that we selected and with the treatment duration that we selected, we had, as you saw, a very robust relative risk reduction, as well as an absolute risk reduction in EPIC-HR. For most patients, more than 80 percent of the patients, they have no incidence of symptomatic rebound or viral load rebound. For those that do experience

symptomatic rebound, they're generally mild, self-limited, and do not result in severe outcomes.

For the patients that do have symptomatic rebound, we have an ongoing trial looking at retreatment, so patients would have to have a documented treatment course of Paxlovid, and then followed up by resolution of symptoms, rebound of symptoms, and then a positive rapid antigen test within the first 14 days following cessation of the first 5-day course. That trial is ongoing. It will be reported out in the third quarter of this year, and it's about two-thirds of the way recruited.

For the highest unmet medical need, that really comes back to the immunocompromised patient population, and for that we have the ongoing study. And I think that we can continue to understand what's the optimal treatment duration for that particular population, but we have a high degree of confidence that 5 days is right for the general population.

DR. BADEN: Dr. Troy, the agency's reaction?

DR. TROY: Thank you. I would agree that we do have a high degree of confidence that for the general high-risk population, 5 days is the optimal duration, and we do have the data that 5 days of treatment from the clinical trials showed a significant benefit in terms of reduction in hospitalization and death. I also agree that the biggest group with the unmet need, the highly immunocompromised patients, that we still don't know if a longer treatment duration would be better, and that hopefully we'll be getting that data this year.

I also, just really quickly, wanted to go back to the prior question because I thought of a response since then, which is the point was made that the absolute risk reduction is low but the relative risk reduction is high, but I just wanted to, again, stress that we're talking absolute risk reduction in hospitalization and death. So in my mind, a 1-to-2 percent reduction, absolute risk reduction, with that endpoint is still a big deal; so I just wanted to say that.

DR. BADEN: Thank you.

Dr. Hardy?

DR. HARDY: Hi. This is David Hardy from Los Angeles. My question is for both the agency and for the applicant. It's looking like, as I continue to read and understand these data better, that one of the most practical concerns about the safety of this medication is its concomitant use with contraindicated medications, even for a short, 5-day course; and the fact that, as you pointed out, it is prescribed primarily by primary care physicians, internists, family practitioners, et cetera, who oftentimes have very little, if any, experience with using ritonavir-boosted medications. And in fact, not even many HIV providers these days are using ritonavir and remember how it has drug-drug interactions.

So to that point, how do you plan to mitigate these drug-drug interactions by educating or somehow having prescribers best understand how not to run into problems with those patients who have a high concentration of comorbid diseases,

which is overlapping with the highest risk group for COVID, and these particularly detrimental drug-drug interactions? How do you plan to mitigate those problems by education?

DR. RUSNAK: I will ask Dr. Merchant to address this, but of course of paramount importance here is that physicians need to make the determination of the patient's ability to comply with modifications, whether it's an interruption or dose reduction of their concomitant medication, as well as the severity of the consequences of the DDI should they not be able to comply with that.

Dr. Merchant?

DR. MERCHANT: Thank you. Lubna Merchant from Risk Management Center of Excellence. Can I have slide CC-58 projected, please? Thank you.

As outlined on this slide, we have implemented a comprehensive and robust risk mitigation plan that targets multiple stakeholders. In terms of communication and outreach, we've had multiple DHCP letters, healthcare provider letters, that raise awareness to the DDIs for the

prescribers and provides them with recommendations, and tools, and resources, where they can go find these resources to manage the patients successfully on all these concomitant medications.

We also have multiple other point-of-care solutions like the Drug Interaction Checker that is provided by Pfizer, as well as there are non-Pfizer interaction checkers available as well. We've also developed a healthcare provider dosing card which is available in digital and print, which outlines all the recommendations and, again, points to the resources for healthcare providers on how to best manage the patients in drug-drug interactions.

In terms of your question regarding the population of prescribers that are prescribing this and how this differs from the other HIV medications, well noted, we acknowledge that the majority of the prescriptions are to primary care practitioners, and social media and medical outreach is targeting and increasing the communication of the awareness of DDIs to this particular group. Thank you.

DR. TROY: Hi. Is it my turn?

DR. BADEN: Please, yes.

DR. TROY: Okay.

First of all, I just wanted to clarify one thing because the initial comment said that a lot of these were due to contraindicated drugs, and I just want to clarify that actually most of the serious adverse reactions are not due to the contraindicated drugs; they're due to some of the drugs that would require dose adjustment or close monitoring. For example, tacrolimus is not contraindicated but it requires very close monitoring of tacrolimus levels to give Paxlovid safely. So that's one of the concerns, I think, is that there might be a misconception out there that it's just the contraindicated drugs that are the problem, but that's not the case.

I agree with everything that the applicant said about the risk mitigation and all the different efforts. I'll add that if Paxlovid were to receive marketing approval, we will make sure that the risk of serious adverse reactions due to

DDIs will be described appropriately in labeling. We've also taken a number of efforts, even under EUA, to try to get out this message. We have the Prescriber Checklist that we put out with things they could check off and what they have to do in order to prescribe Paxlovid. We've done a number of webinars. We've done a number of CRER statements. We've worked with the applicant to put out Dear Healthcare Provider letters, et cetera. Thank you.

DR. HARDY: Thank you. That's the end of my question, Dr. Baden.

DR. BADEN: Thank you.

Dr. Scarsi?

DR. SCARSI: Hi. Kim Scarsi from University of Nebraska Medical Center. I have a question that follows on to that, and then one other question.

Related to the drug interaction mitigation strategies, it's great to have all of these different resources, but sometimes they can get confusing for providers when there are different recommendations and different resources; then often

it's a bit of a moving target.

So I guess for the applicant, I'd ask how frequently you plan to actively update and maintain the drug interaction resources that you're providing, and how you'll be making sure that the places that you're referring providers to for drug interaction resources -- to ensure that those are also being updated?

For example, you use the NIH and Liverpool drug interaction resources, who are working closely together to align recommendations, but then you also have recommended the CDC, which may be a bit more static in their recommendation. So can you just speak to how you're going to make sure that providers don't get overwhelmed or confused by the number of different resources?

DR. RUSNAK: Thank you for the question. I will ask Dr. Merchant to answer that.

DR. MERCHANT: Thank you for the question. Lubna Merchant with the Risk Management Center of of Excellence. In terms of the resources that are available, first and foremost, we would direct the

healthcare providers to the labeling. The labeling is updated as soon as information is available and is evaluated by the agency. That information is updated. That information is also updated in real time on the Pfizer website as well. In terms of the interaction tools, the Pfizer interaction tools are updated, again, in real time or as soon as possible, with the most recent information that's updated, and the EUA fact sheet will be updated in the USPI.

In terms of updating the other resources, we would communicate that to the responsible -- I guess the other non-Pfizer resources who govern that, but we can't guarantee at what time those resources will be updated, but we do monitor to ensure that it's updated according to the labeling. Thank you.

DR. BADEN: Dr. Troy, did you did you want to respond?

DR. TROY: I guess I would just say that that's an excellent question and an excellent point, and that's one thing that we struggled with

quite a lot here, is how to keep all these updated. So if you have any recommendations, we would love to hear them.

DR. SCARSI: Thanks. And I will acknowledge that the FDA does has have a representative on the NIH panel, and we are working to align everything.

I guess a point of clarification also on that is in the applicant's briefing document, it was often mentioned that the ritonavir product labeling would be used to inform the drug interaction tables, which I think is what was done with the initial EUA, but the FDA and the applicant have worked to refine the EUA over time to, I think, also more closely align with other guidance documents out there.

So I just wanted to confirm with the applicant did you mean that it will still be in the proposed labeling and it would revert to the Norvir packaged insert information, or will it more closely reflect the EUA labeling?

DR. RUSNAK: It would be the EUA labeling.

DR. SCARSI: Thank you.

Since I don't see any other hands, can I ask one additional?

DR. BADEN: Yes, please, Dr. Scarsi.

DR. SCARSI: Sorry.

Going to the conversation that we plan to have about the use in patients with immunocompromising conditions, I believe in the FDA briefing document, it mentioned that some further information on drug interaction management would come from that study.

I guess, first, I want to ensure that the study is allowing broadly inclusive common medications used for patients with immunosuppression. Then secondarily, I didn't see any secondary objectives or specific objectives on clinicaltrials.gov that would actually assess the interaction with Paxlovid as a perpetrator for those medications. So are there specific plans to assess drug interactions with those immunosuppressants in EPIC-IC?

DR. RUSNAK: BU-235 shown. So we do have a number of other secondary endpoints. We didn't

call that one out as a specific secondary endpoint, but certainly we can use that as an exploratory endpoint in the trial. Because we didn't have a broad population of immunocompromised in EPIC-HR, and most of them were immunocompromised based upon the use of TNF inhibitors or corticosteroids, we, again, did cap that at 25 percent of this population. We are recruiting patients with B-cell depleting therapies, as well as transplantation patients and HIV patients, so we do anticipate that we will have a patient population where we can further understand DDIs within this complicated group.

DR. SCARSI: Thanks. That's the end of my questions.

DR. BADEN: Thank you.

Dr. Murphy?

DR. MURPHY: Hi. Richard Murphy. I also want to ask the FDA, now that we're in this era of potentially somewhat diminishing gains from Paxlovid with pre-existing vaccination and immunity, I think it becomes even more important

that when we give the drug, that we get it within the right time frame, within 5 days of symptom onset; otherwise, the patient assumes all the toxicity and drug-drug interactions with very little benefit.

So would the FDA plan to put a time stamp on the recommendation for a window period, for the use of the drug? Thanks.

DR. TROY: Thank you for this question. Labeling discussions are probably something that are ongoing, so we can't discuss labeling recommendations too much at this point. But I can say that at least in instructions for how to take it, there would be something in there about taking within 5 days, most likely.

DR. BADEN: Thank you. Yes, most likely covers you, and gives you the flexibility needed to craft the label properly.

I have another question while my co-panelists see if there are additional questions to ask. This gets to rebound.

To Dr. Rusnak, it looks like the data from

EPIC-HR show rebound in the 1 to 2 -- it's a couple of percent range. And this is a question I've gotten from many, many colleagues, and we've seen it in high profile members of society who have been infected and then have rebound and got second treatments. How should we harmonize the low rate of rebound seen in your EPIC-HR study, for example, with what many of my colleagues see in practice, or think they see in practice, being a much higher rate of rebound?

The second part to the question -- which I think you've answered, but just wanted to have you re-answer -- is, this rebound doesn't appear to be associated with significant illness, therefore, one, we need to understand the rate for the community is in surprise and, number two, what one should do with a non-immunosuppressed patient. So the average at-risk person without significant immunosuppression has rebound; how should we think about that therapeutically?

So the first question is, the frequency of rebound and why is the clinical impression that

it's 20, 30, 40 percent, yet the systematic data appears to be 5-10-fold lower? How do you think about that?

DR. RUSNAK: Yes. I think it's a great question. In the core presentation, if I could have the slide that addresses the rebound with the active treatment group, as well as some of the TriNetX data, please.

Overall, we did have a variety of different definitions for viral load rebound. The symptom rebound, as Dr. Hammond indicated -- and if I could have that slide CC-63 projected, thank you -- was collected on a daily basis. I think what we see here from the ACTIV-2 study is that the placebo rate for symptomatic relapse was actually 26 percent there. I think as one begins to have a broader understanding that symptom relapse can occur, that it can occur with or without treatment, that the extent by which it occurs probably varies dramatically by the recording tool.

If you remember, whenever we have our symptom rebound, it's around consecutive days of

being symptom-free, which doesn't necessarily reflect -- it did in the ACTIV-2 trial because it's the same scoring system but doesn't reflect necessarily all of the real-world experience. The range of symptomatic rebound is rather broad, but it's very consistent, that whether patients were treated with placebo, or active, or different antiviral therapies, as shown here by the TriNetX database, it is not related to antiviral therapy.

DR. BADEN: So just to explore that further, it looks that placebo versus active treatment have similar rates. The rates vary by how it's measured and how one makes the definition of rebound. But it looks like -- and I think this is what you all presented -- those who have rebound, there isn't severe illness and there isn't retreatment; because again, I'm trying to think through for our community if this may be a frequent event, particularly depending on how assays are done in the community, how should patients and providers react to the presence of a positive test at day 10 or day 15.

DR. RUSNAK: If I can have backup slide 236 presented. Thank you.

This is another ongoing trial that we have addressing the retreatment of the use of Paxlovid for patients that have had an initial course of Paxlovid and then have a symptomatic rebound with a positive RAT test within 14 days. We are exploring the retreatment with nirmatrelvir versus placebo in this group just to ensure the safety and efficacy for those patients that need to be retreated can be safely and effectively retreated with Paxlovid.

DR. BADEN: Fair enough, but in the data already collected, it looks like the rebound occurred at some frequency, whether it's 5 percent and 26 percent, and those patients weren't retreated. And if I understand your comments correctly, none of them went on to serious illness --

DR. RUSNAK: That is correct.

DR. BADEN: -- which is reassuring for the community in thinking about this issue of rebound, which, in part, is impacted by how rebound is

defined and what testing is available.

DR. RUSNAK: Yes, and that general statement around that there were no severe cases was also reflected in the CDC statement on rebound with Paxlovid use.

DR. BADEN: Thank you.

Dr. Green, you have a follow-on?

DR. GREEN: Yes, and I think this is clear to the committee, but just for those that might be listening, and just to clarify, there was no difference; whether it was symptomatic rebound, asymptomatic rebound with a positive load or positive virologic test, or the combination, in all cases, it was pretty limited, very mild, and didn't progress; correct?

DR. RUSNAK: That's correct. And if I could just have CC slide 62, please, and if we could project that, please.

This, again, just shows that about 80 percent of patients have no rebound whatsoever. Whether it's symptomatic or asymptomatic viral load rebounds, symptom rebound in EPIC-HR was somewhere

between 12 and 16 percent, numerically higher on the placebo group. Viral load rebound was a little less common in the intersection of the combination of symptom and viral load rebound was quite uncommon.

DR. GREEN: Thank you.

DR. BADEN: Very helpful.

Dr. Siberry?

DR. SIBERRY: Thank you, Chair. I'm going to shift directions. This is for the applicant.

We were discussing before about the importance of highlighting the greatest benefit coming from starting as soon after onset of symptoms as possible, within 5 days. The other observation I've made is I've heard well-meaning health professionals counsel patients, "You're not sick enough. If you start to get sicker, call me back, and then we can start Paxlovid."

So I think it would be helpful, in the same vein as making sure the advice in the label emphasizes starting as soon as possible and within 5 days, to make as clear as possible that starting

when symptoms are at their mildest is preferable, and it's not advised to wait until symptoms start to progress in order to initiate Paxlovid. I have had several observations where this was advice given by a variety of health professionals, again, well-meaning but not understanding, I think, of what the data would support.

Is that something that you could consider in the labeling advice?

DR. RUSNAK: We are in agreement that if a patient is at high risk, it is very difficult to determine which patient will progress and which patient can be safely observed. So if a patient is at high risk, we would make a recommendation that they start Paxlovid as soon as possible to intervene with the viral replication cycle as quickly as possible. And for the labeling discussions, I will defer to the agency.

DR. TROY: To say again, the labeling is under discussion right now, so we can't talk too much about labeling, but we do agree with you that treatment earlier, I think, is preferable.

DR. SIBERRY: Thank you so much, and I had one additional for the agency.

I would like to ask if you could consider that the decision-maker adults about this approval would also be relevant for adolescents 40 kilos and over, rather than continuing to have adolescents at 12 years to adult age, which I assume would be 17 or 18, be held under an EUA status, which I think limits access and availability in the way that biologically I don't think is well justified. So I'd like to recommend considering that the decision apply not just to adults but also in this for adolescents 40 kilos or greater. Thank you.

DR. TROY: Thank you for the comment, and I'm going to defer to Dr. John Farley to answer.

DR. FARLEY: Thanks, Dr. Siberry, and I certainly hear your concern. The agency is committed to work with the applicant to complete pediatric drug development as quickly as possible, but at the moment we anticipate that we will need to have the EUA remain authorized to both facilitate adolescent treatment, as well as address

other access issues. Thanks.

DR. SIBERRY: Thank you, Chair. That's it for me.

DR. BADEN: I'm going to take, Dr. Siberry, a rare chair moment, in that I think we have to be careful about recommending thinking about broad approval beyond the data available, even though it makes sense. We all, as clinicians, as investigators, and the agency as well, and the applicant, need to balance where the data are versus what we want, so I don't have a good answer either, but I do think there is a premium on actually having data.

The amount of data may be proportionate to the pre-existing data set, but at least -- and I'm making my own editorial comment, and, Dr. Siberry, you shared yours -- how we balance what we think should be true versus what we have measured. I'm a big believer in measuring because I worry we're not as smart as we want to be.

DR. SIBERRY: Agreed. Thanks, and I know this is not the place for debate, but we want to

make sure that we're not protecting people from something that actually they would benefit from with well-meaning but misguided approaches, so thank you so much, a very helpful discussion.

DR. BADEN: And your your point is well taken as well, and appreciated.

Dr. Carvalho?

DR. CARVALHO: Thank you, Dr. Baden. I have a quick follow-up question for the applicant, again, on EPIC-IC. One thing I'm curious about is my previous question was how long is viral load going to be assessed, which is approximately a little bit over 6 weeks, I believe.

What I'm wondering is with the longer courses, like the 15-day course, will there be any evaluation for protease inhibitor resistance development?

DR. RUSNAK: Yes. We will be looking at all of that within the context of the EPIC-IC study.

DR. CARVALHO: Thank you so much.

DR. BADEN: I'm looking to see if any of my colleagues have additional clarifying questions to

understand the data, and I do not see additional questions at this point in time.

(No response.)

DR. BADEN: If not, then we can proceed with the charge to the committee from Dr. Birnkrant.

I would like to thank Dr. Troy and Dr. Rusnak for guiding such an important discussion and bringing in the appropriate colleagues.

Dr. Birnkrant, please?

Charge to the Committee - Debra Birnkrant

DR. BIRNKRANT: Good afternoon. My name is Debbie Birnkrant. I'm the director of the Division of Antivirals, and I'm pleased to present the charge to the committee.

This morning we heard from both the applicant and FDA about the data contained in NDA 217188 for Paxlovid, for treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19, including hospitalization and death. Briefly summarizing years of work, COVID-19 is a serious and potentially life-threatening disease that has

evolved since the beginning of the pandemic; we all acknowledge that.

To date, remdesivir in the form of a 3-day infusion is the only FDA-approved therapy available for mild-to-moderate disease in adults and the pediatric population at high risk of disease progression. Paxlovid and molnupiravir are available under emergency use authorization also for treatment of mild-to-moderate disease, and the Paxlovid NDA was submitted on June 29, 2022.

For this NDA, three phase 2/3 trials supported safety and efficacy. EPIC-HR was a pivotal clinical trial that was conducted in 2021 with Delta predominating. EPIC-SR was conducted in 2021 and 2022 with Delta as the variant of concern in 2021 and Omicron as the variant of concern in 2022. EPIC-PEP was conducted in late 2021 and early 2022 with both Delta and Omicron as variants of concern. Notably, there was also limited vaccination of participants in these trials.

Fast forward to 2023, where we have a changing landscape with the Omicron subvariants

circulating and most U.S. patients having some immunity either from vaccination or naturally occurring infection So how did we fill in the gaps handed to us by the changing landscape?

The review team and the applicant explored various review issues that we identified that also framed the questions for voting and the discussion points. The review issue, related to efficacy of Paxlovid in individuals with some pre-existing SARS-CoV-2 immunity, was evaluated in the seropositive and referenced seronegative subgroup in pivotal trial EPIC-HR, as well as the high-risk vaccinated cohort in supporting trial EPIC-SR. Regardless of vaccination status or evidence of prior infection, trial results support the efficacy of Paxlovid for the treatment of high-risk adults with mild-to-moderate COVID-19.

In addition, to address the review issue of efficacy in the setting of the SARS-CoV-2 Omicron variant, review of nonclinical virology, genomic surveillance, and clinical virology data from nasopharyngeal swabs in EPIC-SR showed that

Paxlovid is expected to retain clinical efficacy in high-risk adults with COVID-19 caused by the SARS-CoV-2 Omicron variant.

Another area we assessed was viral and symptomatic rebounds following treatment with Paxlovid or in placebo recipients that likely reflects natural COVID-19 disease progression and/or technical variability in virology assessment.

There was a brief discussion on the immunocompromised population. We know that the immunocompromised trial is enrolling, and we hope to get definitive answers related to treatment duration in the near future. Although Paxlovid was well tolerated in clinical trials, FDA identified as a review issue the potential for significant drug-drug interactions primarily based on the ritonavir component of Paxlovid.

We will turn to the voting question first, and then specific discussion points. We would like the committee to first address the voting question, which is on the screen and reads, "Is the overall

benefit-risk assessment favorable for Paxlovid when used for treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization and death? If yes, please provide your rationale; if no, please provide your rationale and list what additional studies or trials are needed." We will then turn to discussion points that address pragmatic issues.

On the next slide, we have two discussion points for you. Discuss the strength of evidence for use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, in the following populations: individuals who are vaccinated against COVID-19 or previously infected with SARS-CoV-2; individuals infected with Omicron subvariants; and individuals who are immunocompromised. We are particularly interested in any ideas for future research or additional suggestions for acquiring data where there are

gaps.

Lastly, please comment on the strength of evidence for an association between use of Paxlovid in the treatment of mild-to-moderate COVID-19 and COVID-19 rebound. Again, please comment if additional data are needed to describe this phenomenon. Thank you very much, and we look forward to your deliberations.

Questions to the Committee and Discussion

DR. BADEN: Thank you, Dr. Birnkrant.

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 all of the comments that we have heard, and public comments that have been posted as well.

We now will 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 questions or comments concerning the wording,

and we will proceed with discussion of the, first, question before we vote to make sure the issues have been properly aired among the committee members.

Can we make it gallery, so we can see each other?

(Pause.)

DR. BADEN: The question before the committee, is the overall benefit-risk assessment favorable for Paxlovid when used for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death? If yes, provide your rationale; if not, please provide your rationale and what additional studies are needed.

DR. FRIMPONG: Dr. Baden?

DR. BADEN: Yes?

DR. FRIMPONG: I will provide the panel with the voting instructions.

DR. BADEN: Okay.

DR. FRIMPONG: Our first question is a voting question. If you are not a voting

participant, you'll be moved to our breakout room. Voting members will use the Zoom platform to submit their vote for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

A voting display will appear where you can submit your vote. There will be no discussion during the voting session. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will announce that the vote is closed. Please note, there will be a momentary pause as we tally the results and return non-voting members into the meeting room.

Next, the vote results will display on the screen. I will read the vote results from the screen into the record. Thereafter, the

chairperson will go down the list, 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?

MALE VOICE: So this radio button will just pop up on our screen?

DR. FRIMPONG: Yes, that is correct, with the question, yes.

MALE VOICE: Okay. Thank you.

DR. FRIMPONG: No problem.

Back to you, Dr. Baden.

DR. BADEN: Are there any questions about the question?

(No response.)

DR. BADEN: If not, then I guess -- Dr. Green?

DR. GREEN: Yes. Hi. Thanks, Dr. Baden.

I just want to clarify -- because once we

roll down this process -- that after we vote and we're providing our answers or our vote into the record, the rationale that we're going to provide is really limited to specifically this first question, and should not address the discussion point number 2, or rather, item number 2, discussion point number 1, and item number 3, discussion point number 2; is that correct?

So when we read our vote, we're only going to put our statement, and we're really going to restrict it to just question 1; is that correct?

DR. FRIMPONG: Yes, that is correct.

DR. BADEN: Dr. Murphy?

DR. MURPHY: Just a question on who will ultimately define a high risk?

DR. FRIMPONG: Dr. Baden?

DR. BADEN: I welcome Dr. Farley and Dr. Birnkrant, but my view of it is, Dr. Murphy, that goes to 2A. 2A, we will then as a committee discuss some of those issues for the agency to hear how we are struggling with that issue. That was my read of how this was positioned, but I welcome your

perspective, as well as Dr. Farley or Birnkrant that we should look at it differently.

DR. TROY: Dr. Baden --

DR. FARLEY: If I may --

DR. TROY: -- sorry. This is Stephanie Troy from FDA again. I just wanted to clarify that in the EUA fact sheet for healthcare providers, we reference the CDC website for the medical conditions and factors associated with increased risk for progression to severe COVID-19, and we also say that healthcare providers should consider the benefit-risk for an individual patient. So I just wanted to throw that out there in terms of defining high risk. Thank you.

DR. BADEN: Thank you. Yes, that was in the documents, and thank you for highlighting again. Many of us will debate the adequacy of the guidance, but that, again, comes to 2A.

Any other questions?

(No response.)

DR. BADEN: Then I think we are at the time to vote, and then there will be lots of discussion

as intimated in all of the prior commentary.

DR. FRIMPONG: We will now move the non-voting participants to the breakout room.

(Voting.)

DR. FRIMPONG: Voting has closed and is now complete. After I read the vote results into the record, the chairperson will go down the list, 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.

(Pause.)

MR. ELEY: The voting results are displayed.

DR. FRIMPONG: There are 16 yeses and 1 no.

Dr. Baden, I hand it off to you.

DR. BADEN: Thank you.

We will now go down the list and have everyone who voted state your name and vote into the record. You may also provide justification of your vote, if you wish. We will in addition have the additional discussion of questions 2 and 3, so

this is focused on the voting question.

We will start with the first on the list, so we'll start with Dr. Green.

Please state your name and how you voted for the record, and then comments on subparts to the question and rationale.

DR. GREEN: Thank you, Dr. Baden.

This is Michael Green, and I voted yes. Both clinical trial data and real-world experience support the efficacy against the critical endpoints of hospitalization and death in an at-risk population at a 28-day time point. The data regarding resolution of symptoms globally are encouraging, but they were not significant, and as noted, the rates of new infection and emergence of variants remain dynamic and a major concern, and having Paxlovid approved I think is very reassuring, as is the absence of significant resistance concerns, at least so far.

Clearly, labeling and mitigation efforts relating to drug-drug interactions will be critical, and I personally hope to see special

mention of tacrolimus and perhaps cyclosporine on this, and at least pending the more prospective data that we're going to get from the EPIC-IC study. Then finally, I want to thank the agency for maintaining -- or the plan to maintain -- the EUA for adolescents, and hope to see data and consideration of approval for both adolescents [inaudible - audio fades].

DR. BADEN: Thank you.

Dr. Adimora?

DR. ADIMORA: Hi. This is Ada Adimora. I vote yes. My reasons are similar to those of Dr. Green, and specifically I would add that given the severity of the outcome of interest here, hospitalization and death, the demonstration of reduction of both the absolute and certainly the relative risk is quite important.

This is clinically meaningful for most individuals, although clearly it's important to weigh the drug-drug interactions and the risks that those pose. It's also clinically meaningful for the population as a whole, given the high incidence

of COVID-19 in the U.S. that's ongoing, and is especially important given the limited availability of effective oral agents. Thank you.

DR. BADEN: Dr. Carvalho?

DR. CARVALHO: Thank you, Dr. Baden, and thank you to the panel. I agree with the comments by Drs. Green and Adimora.

This is Paula Carvalho, and I voted yes. The reason is, I feel also that the clinical world and real-world data are both appropriate in order to give that response. The additional thing is that there are future studies that are already designed, and some are ongoing by the applicant, that are going to be available, hopefully shortly, for us to be looking at the right targets such as symptomatic rebound and additional data on immunosuppressed patients. That concludes my comments. Thank you.

DR. BADEN: Thank you.

Dr. Patel?

DR. PATEL: Yes. This is Nimish Patel, and I voted yes. I think the presentation by the FDA,

they walked through the numbers of the number of current cases of COVID that are currently occurring, and just walking through the math I think was very compelling. The data from EPIC-HR in a high-risk group who were unvaccinated was also very compelling.

DR. BADEN: Thank you.

Dr. Hardy?

DR. HARDY: Hi. This is Dr. Hardy from Los Angeles. I voted yes also because I'm really in agreement with the previous speakers. I think that the applicant has shown that as the COVID-19 pandemic has evolved with new and different variants of interests, of concern I should say, that while the benefit is not at the 90 percent relative risk reduction, it's still, even at 50 percent, as demonstrated by the EPIC-SR study, is demonstrating continued benefit in terms of the most severe outcomes of hospitalization and death.

So although that study did not reach its endpoints, it is still showing, I think, a degree of benefit that is necessary. And the fact that it

has been shown to work with some of the Omicron clinical and with the almost completely up-to-date in vitro Omicron subvariants, is also very important to really best understand the lack of resistance that seems to be occurring with this agent as the virus continues to change, which I think is very important.

I would just emphasize that we underscore the importance of risk mitigation to the prescriber, primary care physician, and other prescribers in terms of drug-drug interactions. That's where I think we may get into trouble -- or I should say where they would get into trouble -- with prescribing this medication without a good knowledge of what ritonavir does to other medications. That's it.

DR. BADEN: Thank you.

Dr. Siberry?

DR. SIBERRY: Hi. George Siberry. I also voted yes. I think the applicant and the agency presented the full data in a way that convinced me of the evidence of efficacy, including over time as

levels of background pre-existing immunity increase, even if the absolute magnitude of benefit decreased in that setting.

Safety data I also thought was adequate, noting and appreciating what others have said about high importance of clear information about DDIs, and then just thinking that the studies ongoing in pregnancy, pediatrics, and immunocompromised are on target, and urge the applicant to complete them with urgency. Thank you.

DR. BADEN: Thank you.

Dr. Murphy?

DR. MURPHY: Richard Murphy. I voted yes. I'd say besides oxygen, Paxlovid has probably been the single most important treatment tool in this epidemic, and it continues to be. And we still have many groups that stand to benefit from the use of Paxlovid, including unvaccinated persons, undervaccinated persons, elderly, immunocompromised; and the other treatment options that we have, have significant disadvantages, including a lack of oral formulation for remdesivir

and the low efficacy of molnupiravir.

So I would support it, and I think it should have an indication that states that it should be used within 5 days of symptom onset.

DR. BADEN: Thank you.

Dr. Waterman?

DR. WATERMAN: Hi. This is Paige Waterman. I also voted yes. As has been said, I agree that the clinically relevant primary endpoints are supported. I would comment that it does assume labeling and prescribing information will be clear and easily accessible, again, as has been discussed and described.

DR. BADEN: Thank you.

Dr. Swaminathan?

DR. SWAMINATHAN: Yes. This is Sankar Swaminathan. I voted yes. I thought that the efficacy data were clear and convincing. The safety concerns are derived mostly from the drug-drug interactions, but these should be addressable and minimized. I think the benefit in partially immune patients is not as clear, but I

think it's important to have this treatment available for any high-risk patient because it's not possible on an individual level to know how effective someone's immunity is, even if they've been vaccinated fully or if they've had COVID in the past.

I think that the fact that the drug has retained activity against various evolutionary strains of the virus is also reassuring and gives hope that this will continue to be useful going forward. Thank you.

DR. BADEN: Thank you.

Dr. Perez?

DR. PEREZ: Thank you. I'm Federico Perez, and I voted yes. I want to thank the professional staff of the agency for their excellent summation of the evidence, and I did vote straightforward, and echo the comments of others to remain vigilant about the impact of the drug-drug interactions in the population, pending the [indiscernible] study.

DR. BADEN: Thank you.

Dr. Clark?

DR. CLARK: Hi. It's Nina Clark. I voted yes. I would say I was also influenced by the benefit on the serious outcomes of hospitalizations and deaths, and particularly relevant of course in people who may not respond optimally to vaccines, as has been mentioned, and the fact that we can't always perfectly predict who's going to do poorly with COVID. I feel that Paxlovid is worth it for that, especially since it seems that the toxicities are manageable. I also had concerns about future variants and the ability to evade immunity. Thank you.

DR. BADEN: Thank you.

Dr. Scarsi?

DR. SCARSI: Hi. Kim Scarsi. I also voted yes. I agree with all of the comments made so far. I think we were fortunate, but in addition to the clearly presented clinical trial results, we had broad use of this drug that reflected clinical trial results and gave us good assurance about the benefit-risk of the medication.

I really appreciate the agency's and the

applicant's, really, attention to drug-drug interactions and focusing on appropriate management, but I also agree that these can be managed appropriately through support of prescribers through some of the ongoing efforts, and really applaud and encourage the continued collaboration between the guideline committees, the FDA, as well as the sponsor to support providers going forward to adequately assess the individual risks-benefits.

DR. BADEN: Thank you.

Dr. Shankaran?

DR. SHANKARAN: I'm Shivanjali Shankaran. I voted yes. As the prior speaker mentioned, both the study results, as well as real-world data supported my decision.

DR. BADEN: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I voted yes. I thought the company and the FDA both did great analyses, very thorough and very helpful to understand. I think the relative risk clearly

shows that it's beneficial, and I think we just still have work to do to figure out who this is benefiting, which is reflected in the absolute benefit. But I think, overall, it is definitely beneficial. Thank you.

DR. BADEN: Thank you.

Dr. Baden. I voted yes as well, and in addition to the comments already made, I think the data demonstrating activity are clear. I think the safety with a large population treated also is very reassuring. I am concerned that the strength of the data in those with pre-existing immunity are much thinner, and as the absolute rate of benefit changes, the static rate of adverse events of concern may approximate the meaningful benefit, and that's something we will have to pay attention to, to make sure that the risk-benefit ratio stays favorable to the patients we treat.

I also think it's important that we understand who's admitted with COVID and who's admitted to the hospital for COVID, and the same thing with mortality. So as we look at benefit, we

need to understand the data we're drawing from because I think there's a lot of testing going on, and we're not as careful, I think, in understanding, given the effort needed to understand cause and effect in terms of the diseases COVID causes. And I think the preservation of activity across coronavirus species, as well as variants of concern is very reassuring. Thank you.

Dr. Walker?

DR. WALKER: Hi. Dr. Roblena Walker, and I voted yes. Ditto to what all the other panel members have said. But more importantly, as the consumer representative, it's important for me to fully be able to go back to the community and encourage them on certain drugs. So based on the clinical data that was provided, specifically amongst the population that are deemed immunocompromised, that's why I voted yes.

So I want to say excellent work to the applicant, as well as to the FDA, and this long journey that we've all been in, and moving the

needle, and fighting through the battle of COVID as we try to get everyone back to what was once being the normal life. Thank you.

DR. BADEN: Thank you.

Dr. Gillespie?

MS. GILLESPIE: Yes. I voted no, and here's the reason why I voted no. I agree with all of the things that everyone said, but I had COVID. I have one lung, and I'm overweight, and I've had COVID 4 or 5 times, and never once was Paxlovid even offered to me. I was hospitalized only one time, so I'm kind of concerned about the doctors knowing actually when to prescribe it to somebody, say, like me. Now, I normally am very breathy. I normally can't breathe well, but when I call a doctor and say, "Hey. I think I have COVID," and I test for COVID, it's never offered for me.

Then with the interactions with other medications, maybe it's not such a great thing; however, we need something. So I voted no because of that reason, because I don't feel that the doctors really know how to use this, and that's it.

DR. BADEN: Thank you.

MS. GILLESPIE: Umm-hmm.

DR. BADEN: So let me summarize the comments from our 17 panel members. The overwhelming sense of the committee is that efficacy and safety have been demonstrated. It is important to understand who's at high risk, which we'll discuss shortly, to understand who's likely to benefit.

The issue of viral resistance emerging seems to be low, at least given the available data, which does not show such a concern, as different variants have emerged, which is reassuring. The lack of alternative therapies that are easy to give oral outpatients and effective also increases the importance. The heavy use in the community is reassuring over the last year in terms of safety. The drug-drug interactions is a significant concern, and that has been discussed and requires continued attention.

The issue of both those who said yes and our colleague who said no is how do we support patients and providers to understand where this fits in, and

our colleague who voted no expresses a concern that the community doesn't understand where this fits in, who will benefit, and therefore being able to access and use this in an appropriate and timely manner.

I think that summarizes the comments of the committee for question number 1, and I welcome anyone from the committee if I misrepresented any key points.

(No response.)

DR. BADEN: If not, we can take a quick 10-minute break. Please, panel members, remember there should be no chatting or discussion of the meeting, and we will resume at 2:51, in 10 minutes, and we will then have discussion on the other two questions. See you in 10 minutes.

(Whereupon, at 2:41 p.m., a recess was taken.)

DR. BADEN: It is now 2:51, and we shall resume for the two discussion questions. Can we move to the next question, please?

Question 2, which is a discussion question,

please comment on the strength of evidence for use of Paxlovid for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19, including hospitalization or death, in the following populations: A, individuals who are vaccinated against COVID-19 or had prior SARS-CoV-2 infection; B, individuals infected with Omicron subvariants; C, individuals who are immunosuppressed.

Please comment if additional data are needed in these populations.

Are there questions about the discussion question wording?

(No response.)

DR. BADEN: If not, Dr. Swaminathan?

DR. SWAMINATHAN: Sure. So I'll kick this off. I think the first point, A, I think we don't really know how effective this is going to be and how useful it's going to be in people, and this is really the majority of people who have some level of immunity. I have seen people who have been vaccinated as many times as they could possibly

have gotten vaccinated and have had infections, who have nevertheless had severe subsequent infection, and who that's going to be is, I think, unclear.

So I think there clearly are patients who have some level of immunity who are nevertheless at high risk, and I think we're in a position where we often use drugs where we're not sure how effective they're going to be, but they have laboratory and clinical evidence that it could be effective, and we use it -- you know, we do this on a routine basis in patients who are hospitalized. We empirically use certainly antibacterials and antivirals, where we have no really hard data on how effective that intervention is going to be.

So I think without much more extensive data on people who have prior immunity, we're in that position of making what we call a clinical judgment decision, and I think we do this having the humility to know that we don't know the answer.

DR. BADEN: What I would like to do is discuss each of these individually, so we can focus the discussion, as you have done, Dr. Swaminathan,

on A, and then we'll work through the others. But I think each of these points require a full discussion, just as you started off for us, Dr. Swaminathan.

Dr. Green, on 2A?

DR. GREEN: Thank you, Dr. Baden. This is Michael Green. I absolutely agree with Dr. Swaminathan, particularly because I think we're seeing an increasing number of individuals that have had some vaccines but may not be getting an ongoing booster. And we have no idea about the persistence of benefit from vaccines, both over time as we get remote from when we receive our vaccines and also, as was mentioned, I think, earlier -- and certainly it comes out with each new variant -- the concerns of immune escape; so that we don't know that either vaccination or prior infection is necessarily going to leave you as protected as we would want.

I would also just say that time from COVID infection, like time from COVID immunization, is an unknown in terms of the persistence of protection

that you may get from that. So I think that the preliminary data that we saw showed that while the benefit was perhaps reduced, it was still in the same direction; and if the denominator is huge, the overall public health benefits should be maintained, and I think we should do it independent of vaccine status or prior history of infection. Thank you.

DR. BADEN: So I just want to explore this conversation a little bit more, in that the data in the vaccinated were small, 300 on the order of hundreds per group with zero or three hospitalizations versus five or seven. The evidence there are intriguing, encouraging, and pointed in the right direction, but they're kind of thin.

I do understand the comments, Dr. Green and Dr. Swaminathan, and look forward to the other committee members' comments, but I'm trying to think about in a fully vaccinated population, a 25 year old with a BMI of 25.1 versus a 90 year old with multiple comorbid illnesses -- heart disease,

on low-dose glucocorticoids -- are we really looking at them as the same because we don't know? Is that what's being suggested?

DR. SWAMINATHAN: Sorry. I didn't raise my hand.

DR. BADEN: No, no. Please, Dr. Swaminathan.

DR. SWAMINATHAN: I think that's a very good question, but the 25 year old who has the only risk factor of a high BMI is actually somewhat rare because they tend to have diabetes, and many of them, in my patient population that we see, have asthma, and the DDI, which is the main risk as I see it, is often limited in those younger patients who are not on 8 medications like that 90 year old, or whatever, that you exemplified there. So I think it's an opportunity to prove that infectious disease doctors are still useful for their ability to make clinical decisions, and we just have to make an individual risk-benefit analysis for every one of those patients, and take into account that they may have some level of protection.

I would also add that I was looking, during the presentations, at the CDC data on -- the phrase "fully vaccinated" was an unfortunate one, I think, which really is a level of vaccination that currently is completely really quite inadequate, and the percentage of people who have had a booster who are eligible is as low as 20 percent of the population in many states. So the previous level of possible immunity I don't take into account as much as the individual assessment of their risk of progression.

DR. BADEN: Dr. Green, I see you have a comment.

DR. GREEN: Yes. I agree with Dr. Swaminathan, and I would say that this is certainly an argument for personalized medicine, and perhaps an analogy would be, there has been some level of controversy within the pediatric community about the management of otitis media; and in particular in the child that's perhaps a little bit older, can you do watchful waiting as opposed to giving therapy to all? And it is surprising to

see that there isn't a consensus that supports one or the other really because the data are not definitive.

One of the added problems here is that watchful waiting may not be the right answer for the 25 year old with a low level BMI who might be the one that progresses because this is a medication that we heard earlier is probably best used when used earliest. So if you wait until their symptoms are worsening, one may have lost the benefit of the medication, which I think makes the challenge.

I do think that decisions should be individualized. Physicians should consider the risk, which in this case probably would be drug-drug interaction, the potential benefit. It's a relatively easy regimen to take twice a day. You're taking 2 pills twice a day. They're different pills. But the other side effect profile, besides drug-drug interaction and the inability to completely predict who within those meet risk criteria will be the ones who progress,

really makes it sort of challenging to finalize decision. And I think it should be left to the physicians who are prescribing, in conversation with their patients, and to do shared decision making in that setting within the context of having an existing risk factor. Thank you.

DR. BADEN: Dr. Hunsberger?

DR. HUNSBERGER: I agree it needs to be left to the physician for personalized medicine, but we still need more data to help the physician. I think what Dr. Baden was talking about is there's just so few events at this point to really be able to pick out who is benefiting, and I think in the future we need to have that data. That's what's reflected in the absolute benefit versus the relative risk.

So there is something going on, there is a benefit, but we haven't identified who. So I think to this question, we need to have more data to be able to figure out who it's benefiting so that the doctors can do the personalized medicine. Thank you.

DR. BADEN: Dr. Clark?

DR. CLARK: Yes. Thanks.

I would say that the real-world evidence, those studies did seem to support the benefit in vaccinated persons, but I'm not sure how much data were collected. And this goes to my first question that I asked about the EPIC-SR study, whether they collected time since last vaccine dose or how many vaccine doses people got. So I think those would be helpful data and maybe could contribute to stratifying risk.

DR. BADEN: Drs. Clark and Hunsberger, I appreciate the support on the perspective in that the EPIC-SR study did not demonstrate benefit. Subgroups showed benefit consistent with EPIC-HR; at least that's my understanding of the data we've been able to see. So I do share the concern about absolute rate because there are side effects, and as the agency mentioned through their reporting system, there is anaphylaxis and Stevens-Johnson and other issues, the rate of which we don't know. But there is a rate, and that rate needs to be

weighed against the benefit, which I think, Dr. Hunsberger, you were getting at. We have to understand that benefit in the right population.

Drs. Green and Swaminathan, as you both raised, the strength of the protection from vaccination is not fixed in time, so that we have a moving parameter that we don't fully understand as to how strong is vaccination-elicited protection over time, and how is that reflected in whatever boosting strategy is recommended or whatever uptake there is by the community; so complicated moving parts.

Dr. Hunsberger?

DR. HUNSBERGER: Just to add that you said that way better than I did, so I totally agree with what you said.

DR. BADEN: To amplify your other point, Dr. Hunsberger, having systematic data will allow us to be more informed. So I don't think the issue is whether or not there's benefit; it's understanding of who/when, and mitigating the risk, which is not zero, but it's small.

DR. HUNSBERGER: Exactly, yes.

DR. BADEN: Per discussion on point A, Dr. Murphy?

DR. MURPHY: Yes. I just wanted to say that I think the understanding of which risk factors are meaningful today in the context of vaccinations to inform the use of Paxlovid is probably not going to come from clinical trials. I'm thinking that it's going to come from large health systems that can isolate specific risk factors and match them with patients who have the same risk factors and don't benefit from Paxlovid or don't receive Paxlovid. So I think more research needs to be done, but I don't think it's going to be clinical trials on this issue.

DR. BADEN: The point is well taken. What I was getting at in a clumsy way is I'm not convinced a BMI of 25.1 has the same weight in terms of risk as age of 90. But that's an impression, and how to generate the data to inform that, Dr. Murphy, may well need to come from large health system data sets, albeit complicated, by individual choice

in terms of who's health seeking and who isn't, and how that bias can be mitigated.

Dr. Waterman?

DR. WATERMAN: Yes. I don't know that I have anything necessarily new to add, but I guess I would just agree with those that said the evidence isn't as compelling as in those that are unvaccinated, but as has been said, it suggested a benefit. I would point out I don't think we're ever going to have a fully vaccinated population, whatever fully vaccinated means, as you said, although taken together with prior infection, I guess it would give us decent numbers.

I agree with the points made about individualized decisions, and yet, as we're saying, physicians need to recognize the indication, who meets the risk criteria, as was noted by Ms. Gillespie, for example. So the bottom line, risk appears relatively low, but the indication -- in other words who is at the highest risk -- is less clear, and that really is the area that we're all saying, I think, needs more study.

DR. BADEN: Thank you.

To the committee members, this conversation -- and I encourage all to share your viewpoint -- is incredibly useful to the agency as they weigh these different competing uncertainties that guide us in this drug, whether it should be approved; and if it is, how to guide discussion about to improve its potential use. So I encourage committee members to share your thoughts on these points, as it's incredibly useful to the agency to hear how we think about and are trying to weigh these issues that are well beyond the data available, but incredibly practical to decision making in every clinic across the nation today.

Dr. Swaminathan?

DR. SWAMINATHAN: Yes. I have more concerns in a way, not that the drug is being overused in populations where the risk-benefit calculation is not positive, but rather as our panelists who voted against approval. I think there's a broad lack of understanding not only among the physicians, but among patients, and it concerns me that not only

are there patients that she described who are not offered the drug, who would clearly be candidates for it, but I've had many patients who I've seen for other reasons who have told me that they had COVID, and I always ask them, "Were you treated, and how did that go?" And there have been a distressingly large number of patients who told me, "Oh, I was told that I shouldn't take it because of rebound," and these are patients who some of them had cancer. Some of them clearly should have been offered it. And knowing their medical history, they really had no contraindications to its use.

I'm concerned that there's not a good understanding among the medical community and actual dissuading of patients from taking an effective and safe drug that could save their life. This has been reinforced to where we're in a situation now where social media and journalism have more of a say in what people believe than their doctor, and there's been a very quite dramatic acceptance among the journalists that rebound is a thing, and it's a bad thing. And as

we heard today, we don't have evidence that it's either of those.

That's just an editorial comment. I don't know if that's helpful to the FDA, but I do think that making calculators for DDIs more clear, more accessible -- I mean, we have the AI to do this so that every doctor who prescribes or is thinking about prescribing Paxlovid can just press a button and know whether or not there's a problem with giving it to a particular patient.

DR. BADEN: Thank you.

Dr. Gillespie?

MS. GILLESPIE: I totally agree with everything he said. When I mentioned people getting Paxlovid, they said, "Oh, no, I don't want it," because of the rebound, and also that the people who did take it said, "Oh, yeah. I had a rebound," or people are telling people about the rebound. So that's a big thing.

When I asked my doctor why I wasn't prescribed it, she said, "Because the rebound might be worse than the original infection." So it's

misconstruity [ph] between patients, doctor, and social media.

DR. BADEN: Thank you, Ms. Gillespie. I think that's very important.

I think the issue of rebound, as we've discussed today, the more data we have, the better it's understood, the lower the concern that it's an issue because the data to date, as discussed, does not demonstrate a medical issue with the rebound, or at least as far as the data go in terms of what's available. And that's very important to know in a systematic way so we can reassure each other that this concern has been mitigated and may not even be a clinically relevant concern, but the data will help guide that discussion.

Other comments about vaccinated individuals, or those with prior immunity, and how to think about the Paxlovid use, which is really, who's at high risk?

Dr. Scarsi?

DR. SCARSI: Hi. Kim Scarsi. I just wanted to add on to Dr. Swaminathan's comment, more about

just making sure that we're finding the right people and not avoiding it in people unnecessarily.

I will say a little bit about creating the online checkers that just refer to the product labeling because, as I tried to get to in some of my questions, sometimes the labeling isn't able to give us, really, clinically applicable how long does it need to be discontinued for, before and after Paxlovid treatment and what kind of dose directions are needed. It's there for some of the drugs, but not all of the drugs.

So I think there's a real need for actionable items that the practitioners who are not familiar with ritonavir can really apply, and I think there are other resources that try to do that. So I don't know if there's a way that we could kind of integrate those so that people don't just circle back always to broad recommendations about just don't combine them, because then I worry people will not be selected appropriately.

Then if I could add that, obviously, the biggest concern is about safety related to drug

interactions. One point I was also trying to get across is there is information in the label that would propose that Paxlovid causes significant effects on commonly used medications. I'll use hormonal contraception as an example.

Over half of the world's population may use hormones at some point for either contraception, or gender-affirming therapy, or menopause. So recommendations within the labeling that infer that there's going to be significant reduction in efficacy of those products without having specific data that really strongly back up that recommendation will be a deterrent for people who may not want to take the risk for an additional risk of pregnancy. So I think we have to be comprehensive in making sure that we're understanding the broad spectrum of the interaction.

DR. BADEN: Thank you.

Dr. Walker?

DR. WALKER: Yes. For whatever it's worth, I just wanted to comment on the comment made by

Dr. Swaminathan and the other panel member regarding social media and the evidence of mistrust, especially among communities of color. We could sit here and talk about how do we encourage that and how do we dismantle social media. We can gather all the data in the world. I don't think that's the real issue as it relates to helping communities understand how this particular drug can help them, based on whatever may be going on with them biologically, but I think it's just really helping them understand what the data is saying.

So I just wanted to make that point because I know that it was brought up about social media, and it's nothing new under the sun as it relates to the lack of mistrust as it relates to doctors and specific communities of color. So I just wanted to point that out.

DR. BADEN: So Dr. Walker, I want to explore that a little bit to make sure I'm understanding it properly. What I hear you saying is we have to have the data and we have to communicate it to the

relevant communities appropriately.

DR. WALKER: Absolutely, because think about a person of color who may only have a high school education. They don't understand what data means. So when you are trying to convince them or encourage them to take any drug, even this one or any other drug that may be on the table for discussion, it's all about ensuring that you communicate the information to them at the level in which they are able to understand because we'll have to battle against social media. You have to battle against, "Oh, I'm not doing this because my grandmother took this, and this is what happened to her," et cetera, et cetera.

So gathering the data is good, but making sure that the data is shown in a way in which communities understand it is another battle in which I think we've all been fighting for a very long time.

DR. BADEN: So we have to engage the community where they are, not where we are.

DR. WALKER: Absolutely.

DR. BADEN: In terms of the data, do we also need to generate the data that represents a community we're trying to reach or can we extend the data we have to all the different communities?

DR. WALKER: No, and I'm glad you brought that point up because when we talk about this particular study here, I think it was – I can't remember exactly – 4 percent of African Americans who participated in this study. So how can I, as the consumer representative, as an African American female, go into my communities and encourage individuals, "Hey. If this drug is offered to you by your doctor, you need to take it," and only 4 percent of the data shows that African Americans or people of color participated in the trial?

DR. BADEN: No, I think that's a very important point, is that the data need to come from the communities so it can then be applied to those communities.

DR. WALKER: Yes.

DR. BADEN: And we have to reach individuals in communities where they are, not where we are --

DR. WALKER: Absolutely.

DR. BADEN: -- in terms of the education.

This also gets to my earlier comments -- and I apologize to Dr. Siberry -- about how we have data when we talk about communities, to communities younger than 18. We don't want to not make drugs available to communities that could benefit, but we also want to have data from those communities that reassure us we got right.

I think that's what Dr. Siberry was getting at as well. In that case, it's the 12-to-17 year olds, but I think we need to think about all of our communities, and I share your concern, Dr. Walker, that if we don't have data from the African American communities, it's hard for us to reach out to those communities and say, "Trust us this will work."

You're on mute, Dr. Walker. Thank you.

DR. WALKER: I was just saying thank you.

DR. BADEN: Without seeing other hands on this point, I would like to move to 2B -- and I welcome comments; I don't want to cut off any

discussion because there's so many important viewpoints across the committee members -- what is the reaction of the committee to the utility of Paxlovid for individuals with Omicron subvariants; given [indiscernible] the data available to us, reactions, thoughts?

(No response.)

DR. BADEN: I'm happy to break the ice. I think the in vitro data were very valuable looking at the Mpros and the activity at nanomolar concentration for the different variants for Paxlovid, and I found that very reassuring; add then in the clinical studies, particularly in the breakthroughs, not seeing obvious clinically meaningful resistance, however, the numbers are small clinically, but I find the in vitro data very reassuring.

Dr. Green?

DR. GREEN: Thank you, Dr. Baden.

I think that I agree with you. I actually would say that I don't think we should be speaking about individuals infected with Omicron subvariants

and end our conversation there because we don't know what Greek letter is going to be responsible for SARS-CoV-2 infections in the fall, a year from now, or what-have-you, as we've gone through so many different variants, both within one lineage, and then within another.

But I find, one, at least the statement that they made that it's active against many, if not all, of the coronavirus tested to date, that's exciting, particularly when we think about MERS and what could be SARS-CoV-3, God forbid. But I also think the fact that it's a highly conserved region for which resistance doesn't appear to be easily selected and have viable virus is encouraging.

Having said that, there certainly should be ongoing efforts by the applicant. I think it would make sense to sponsor the kinds of ongoing studies in treated populations to identify the potential emergence of resistance because perhaps with the exception of penicillin resistance in group A strep, I don't know that we have an example of a pathogen that doesn't become resistant to therapy

after some prolonged period of use.

So we have to keep looking for it, but I think at least for the moment, what we have is exceptionally reassuring, and we should press forward. We as a committee deal with new antibacterial agents that are active against multidrug resistant organisms, suggest their approval, and then only we find out that a year after we approved it, the substantial burden of resistance has emerged.

So we are, to some extent, limited to the data we have, but the database that they've shared with us to date, I think as you said, Dr. Baden, is very reassuring, and the more conserved the target is, the more likely we're to have durability, although it may not be permanent. So I thank them for asking for comments, and those are mine.

DR. BADEN: Thank you, Dr. Green.

Dr. Hardy?

DR. HARDY: Hi. This is David Hardy. I'll be brief. I think you summed it up in both of those comments very well. From what the applicant

has done so far in terms of attempting to study the Omicron variants, at least at the early part of when they became common in the global viral swarm, and what they've done for in vitro up to a very recent Omicron subvariant, everything is looking great so far.

They obviously picked a good target. It seems to be molecularly conserved, and that does forbade the fact that it's going to probably be a good and stable non-resistant sort of way to go. So I think where we are at this point, the technology that we can have available to us is saying that everything looks good so far, but definitely have to keep looking.

DR. BADEN: Thank you, Dr. Green and Dr. Hardy; very helpful.

I think what I'm hearing is we have to pay attention to the emerging variant, and as already commented on earlier, XBB.1.5 perhaps has more escape from vaccine-elicited immunity, and therefore does that increase the need for oral agents as rescue? But also as new variants emerge,

as Dr. Green said, we need to make sure they remain susceptible to this agent, and that will require an ongoing pharmacovigilance plan or in vitro vigilance plan to ensure that the new emerging dominant variants, we have an understanding of drug activity.

Dr. Carvalho?

DR. CARVALHO: Thank you, Dr. Baden. One of the things that I was going to follow up on your comments, which yours and some of the other panel members comments are extremely valid with these upcoming variants, is one that's particularly potentially troublesome, the CH.1.1. It has a piece of Delta, and we don't know that much about it. I agree the target that the applicant picked is quite clever and hopefully will be long lasting, but I would like to see some very good surveillance with new variants, particularly this upcoming one. Thank you.

DR. BADEN: That should be baked into the forward-looking plan, is maintaining vigilance on the activity of this Mpro inhibitor on future Mpros

in dominant variants.

I think that largely covers the Omicron subvariant conversation. Now to look at 2C, which we've already hinted at lots of discussion earlier, what are committee members' thoughts on how this medication should be positioned in those who are immunosuppressed? How comfortable are we in how this should be used in that setting?

Dr. Carvalho?

DR. CARVALHO: Thank you, Dr. Baden. We had several questions earlier for the applicant about this, and it seems as though their plan is quite comprehensive with data gathering that's upcoming in these immunocompromised patients. We're hopeful that the HIV population is well represented there, as they're certainly particularly high risk and have overlapping medications, as well as the concern of resistance emerging in the future.

So I'm pretty satisfied with their plan, and I hope that the studies can be done in a timely way because we need this information pretty badly. Thank you.

DR. BADEN: Thank you.

Dr. Swaminathan?

DR. SWAMINATHAN: Yes. I think this is interesting because I think it was late last year, in November or so, that there was a paper published where they did a very high-profile journal -- I can't remember which one -- where they passaged the virus with the drug and generated a whole variety of mutants that became resistant in vitro. They were able to identify many of these mutants as naturally occurring even though many of them did not have that much replicated fitness, presumably explaining why they didn't spread more widely in the population.

But I think in this immunocompromised population you have a situation -- somewhat similar to what we have with CMV, that's refractory even though it's sensitive -- of a very highly immunosuppressed patient, and it's almost a matter of time until you generate not only a virus that's resistant to the drug but is also fit in terms of replication. We are aware of that. We give the

antiviral to the highly immunosuppressed patient with CMV, but we monitor them for resistance, especially if they seem to be relapsing, and we can monitor their viral load.

Now, the problem with SARS-CoV-2 is that it's a much more fraught situation. You're generating a highly transmissible virus, not one that's relatively easy to prevent transmission like CMV, for example. Further, the measurements of viral load is not as easily correlatable to more virus replication necessarily or more infectiousness. So I think it's a ticking time bomb in some ways if you have a patient who continues to be either symptomatic or shedding large amounts of of detectable virus, who despite the antiviral does not control the infection.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thank you, Dr. Baden. I think one issue, in thinking about answering item C, is recognizing just how diverse the heading of immunocompromised really is because it can go from

a patient on steroids or on anti-TNF to a patient with cancer, or it can go to the organ transplant patients that I'm very involved in the care of, who may or may not have risk, depending upon their own history of rejection, how close they are to transplant, and whether they're a pediatric or an adult organ recipient; but also then the likely dependence upon a calcineurin inhibitor, which, again, from the data that's been presented, is perhaps the number one drug-drug interaction of concern being associated with more deaths and the number one cause of the SAEs.

So while I'm excited that the applicant is doing their study EPIC-IC, and I'm remembering a little bit their slide presenting the design, and they said it was open to organ patients, I'm not sure that they'll get enough numbers by just having them all lumped together. And since we're supposed to comment on additional data, they need a particular study in there. We also could benefit from really having guidance on how to manage tacrolimus because I've heard people who are given

a single dose of Paxlovid and had tacrolimus levels go above 20, and stay that way for a sustained period of time.

So we really do need to think about immunocompromised as a more global term, and then hone in on what immunocompromised state they are. And even within organ recipients, there are some who are being managed not on calcineurin inhibitors, although most on calcineurin inhibitors; and then we get to HIV, and we can get to autoimmune, and we can get to cancer, et cetera. And they're probably all deserving of individual attention, so the one study may not be enough to fully inform decision making that we're going to do. Thank you.

DR. BADEN: Thank you, Dr. Green.

I think what I'm hearing, and also my own reflection, is what does immunocompromised mean, and from interferon, infliximab, or the TNF blockers to anti-CD20, to our patients with HIV with low CD4 counts, as Dr. Adimora raised earlier, there really is a spectrum of what

immunocompromised means. Then in the setting of a profoundly weakened immune system, then we've seen many patients who can clear the virus, and that puts incredible drug pressure or stress on a medication. So the concern, Dr. Swaminathan, as you raised, is that is an environment that can allow the emergence of drug-resistant organisms, and if they are transmissible, then can also have broader impact.

I enjoyed slides 235 and 237 that Dr. Rusnak presented several times to us. The issue of how to really understand what immunocompromised is, and CD20 given repeatedly over the last month versus completing therapy a year ago, may be different, and that has to be thought through carefully as we think about the patients who aren't able to clear the virus, and therefore, where additional medications can make a difference. So I think those are complicated issues but very important to sort out; otherwise this may well be a place where more difficult variants emerge for us to manage.

Dr. Perez?

DR. PEREZ: Thank you. I just wanted to say that when using Paxlovid in general, as just mentioned on question 1, I think that more strongly those who are immunocompromised, there are very few alternative options, and they have considerable limitations of their own. Although this does not increase the strength of the evidence, I do think that it increases the strength of our recommendation and the therapeutic area, although all of these recommendations [indiscernible] are momentary. Thank you.

DR. BADEN: Thank you.

I'm not seeing additional comments from the committee members, but I do welcome the agency, if you want to probe the committee on additional issues raised from our discussion. I'm sure the members would be happy to further share their thinking on the matters if they weren't clear.

Dr. Swaminathan?

DR. SWAMINATHAN: I just wanted to say one thing, and it might be a little bit too detailed for this, but to the agency, I'm not sure, in the

studies that they're doing with the immunocompromised, exactly how and what data they're collecting, but it is a wonderful opportunity to do at least, in a few selected highly immunocompromised patients, a serial deep-sequencing analysis to monitor the emergence of small populations of resistance mutations, which may not be immediately reflected in clinical worsening. This essentially would be an in vivo analogous study to the studies that have been done in vitro that show the selection of resistance mutants in cell culture.

DR. BADEN: Dr. Swaminathan, to take that to the next step, one, is to look at the emergence of minor swarms. The other is, in those individuals who failed to clear, whether it's 10, 15, 20, or however many days of treatment -- because it wouldn't surprise me if this were available duration of therapy maybe beyond 2 weeks in some patients who are really immunosuppressed -- if they failed to clear, or if they lowered the viral load and then it goes up again, to really go after those

isolates to understand their mutation pattern.

DR. SWAMINATHAN: I think it's a great opportunity to understand what the risk is of selecting from mutants.

DR. BADEN: Thank you.

Dr. Clark?

DR. CLARK: Yes. Thanks. I was also wondering if there are any plans to look at combination therapies, especially in immunocompromised patients like with molnupiravir, or if there are other drugs that could help with treatment and hopefully preventing resistance.

DR. BADEN: So the issue is combination therapy, be it to oral agents, remdesivir, or convalescent plasma if monoclonals re-emerge as having value, depending on the isolate. So what is the value of combination therapy to either enhance clearance in those who can or to blunt the potential emergence of resistance if that turns out to be a bigger concern?

DR. CLARK: Right, exactly. Thanks.

DR. BADEN: That would be, obviously, beyond

any one company in that the compounds live in different companies. But it is a very important clinical issue to be mindful of and to strongly encourage as we try to help our most vulnerable patients get through very difficult medical conditions because if one has an underlying oncologic condition and receiving cancer chemotherapy, having COVID on top of that is an incredible burden; and then the complexity of the therapy and potential persistent virus only further complicates care that's desperately needed.

Other comments from the committee?

(No response.)

DR. BADEN: If not, then I think we should move to question number 3. And I do encourage the agency to probe that committee as helpful, given the many issues we have raised and discussed in different levels of completeness.

Question 3, please comment on the strength of evidence for an association between the use of Paxlovid in the treatment of mild-to-moderate COVID-19 and COVID-19 rebound. Please comment if

additional data are needed.

Any questions about the wording of the question?

DR. PEREZ: Is it worded [indiscernible] backwards? Is it the lack of evidence of an association between Paxlovid and the rebound?

DR. BADEN: I think the question as stated, Dr. Perez, in our discussion you should make that point.

So let me open it to discussion, and please, Dr. Perez, make that point because I think that is part of what the agency is asking us to debate and to explore.

DR. PEREZ: Yes. I refer to the presentation by both the agency and the applicant, where I think it was clearly shown that in the placebo group, for all the studies there were similar dynamics of the virus that matched the phenomenon of rebound. Therefore, the use of Paxlovid is not a determinant of this. The rebound is part of the natural history of COVID-19.

DR. BADEN: Dr. Perez, on that

point -- because many of my colleagues, as I'm sure your colleagues, ask us in infectious disease how often they see the rebound in clinic -- how do we square the perception from what the data are that were shared with us?

DR. PEREZ: Yes. I agree the phenomenon of rebound is not rare from that data. I think that, so I'm going to be honest, close to 10 percent, close to 20 percent, and that is not a rare phenonmenon, therefore.

DR. BADEN: Agreed, and I think that, to me, one of the important observations is in the context of rebound, without retreatment, there was no disease progression, at least severe disease, and that to me is very reassuring. I think the frequency of rebound depends a bit on the measurement assays of what is checked when and by whom, and not necessarily what is a clinically determinant of severe illness.

DR. PEREZ: No, I agree the question's not completely answered, and I think it was very encouraging to know about a planned

randomized-controlled trial, and some people with COVID rebound would be treated with an additional 5-day course of the medication. So the additional data is needed and actually will come [indiscernible].

DR. BADEN: Agreed, and I think, as previously mentioned, this is also where large databases, healthcare system data, may be helpful in looking at who after treatment, in the weeks after treatment, have significant illness emerge, and there, one would be able to capture admission and other kinds of significant healthcare utilization based upon who's treated and time.

Dr. Swaminathan?

DR. SWAMINATHAN: Yes. I think the company representatives may have made a comment about how the term "rebound" has implications, and I think it does. It makes it sound as if what you get after taking the course is potentially worse than what you would have had if you hadn't taken the drug. It's not just semantics; I think it's what you perceive when you hear that.

I have always been very, very skeptical about this because even physicians are susceptible to confirmation bias. There are so many people who've had COVID who haven't gotten treated, who haven't seen a doctor, and they've had a relatively mild case. And then they told me, "Yeah, but then it really kicked me. A week later, I was back coughing again, and I was not feeling good, and I couldn't go to work for a couple of days."

This denominator of people who have sort of waxing and waning symptoms for 2 weeks is, I think, not really known, so a lot of what's in the media and what we all think is the plural of anecdote; it's really not data.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thank you, Dr. Baden. I think what Dr. Swaminathan just brought up, first off, raises a question of are all the rebounds the same or of the same mechanism? We became very aware in the early side of the pandemic that where you really got sick was not at the beginning of your

illness, but perhaps later when the immune response kicked in. And the scenario that he just described makes me think quickly whether his patients on day 7 or 8 really started to get kicked in, and if that was a mild version of what used to put patients into the ICU and get them steroids.

So that as opposed to a virologic rebound where numbers go up, and symptoms recur, are those the same? Are they different? We don't know. I think that having natural history studies that maybe come from databases from third-party payers or what-have-you might be of value, but we don't know how well the information's being documented; so that, really, a sponsored study to really get at this both in those treated and not treated would be important.

Having said that, they showed from both the agency and from the applicant really substantial data, really putting this in context in terms of the frequency, the lack of association, or definitive association, with being treated versus not, and also progression. And yet I have to say,

although I'm someone who tries to keep up on this literature, although we're all a little tired of reading about COVID, I don't think that this has really gotten out there, so one wishes that someone would publish these data in a highly respected journal. One worries that if it came from the applicant, that people might discount it.

I don't know that the FDA ever publishes these kind of analyses or whatever, but maybe they could consider that and have a conversation with the appropriate journals, or whatever, to really get this information out because I think it's correct that people say, "I don't want to be treated" because they're worried about a rebound, either A, because they have a planned trip to see their elderly mother in two weeks, and they don't want to have a rebound and become symptomatic and or contagious again; or because they're afraid that the second episode may be worse than the first episode that was discussed before.

So I think we need to get this information that already exists into the literature and really

shine a light on it, but also to get larger amounts of data that are sponsored so we can do the right kind of natural history studies with large numbers to prove that these points are real and true. Thank you.

DR. BADEN: So what I'm hearing, and I encourage other committee members to chime in, one is we're not talking about the immunocompromised where they have prolonged persistent infection. We're talking about those who are able to clear infection, and what does it mean if there is a blip at 1 week or 2 weeks. The denominator issue is very tricky here, and the numerator gets a lot of attention, which is Dr. Swaminathan's anecdote ad infinitum as opposed to systematic data because the systematic data, as Dr. Perez said, seems very reassuring.

Then I think the issue of communication is so important because our lexicon of rebound, Dr. Swaminathan, as you raised, has implications of graver concerns when that's not the biology of what's going on. And this, again, is science,

data, health practice, communication in real time because when this was first identified some time ago, we didn't know what it meant, and up until very recently, and even some of the data shared today, have helped me understand what it means.

So we are seeing data in real time that are systematic and more informative, so how do we as a community and the FDA as an agency communicate these observations in a way that puts them into proper perspective as to what they mean so that we don't ignore things but we also don't worry about things that may not have health import? And as others have said, we don't want this to be reasons for those who would benefit from treatment to shy away from the treatment because they heard something of concern that's not fully understood.

I tried to weave in the comments that I heard from everybody in this arena for question 3. Are there other comments from committee members to make sure the agency hears all of our different thoughts? I think it's the issue of data needed, or more data to show how often this occurs and the

lack of clinical consequence, separating immunocompromised, where I think it's a very different biology, as we already discussed, from those who are getting better, and we're really dealing with the issue of how fast and quickly you get better, both symptomatically but also virologically.

Any other comments from the committee?

(No response.)

DR. BADEN: Seeing none, I think we have discussed the matter that the agency has asked us to discuss.

Before we adjourn, I'd like to thank the applicant and the agency for tremendous presentations and sharing lots of very important data. We all wish there were more complete data from so many different perspectives, but we are thankful we have the data we have to guide a reasoned path forward, and we look forward to the generation of the data that we have been talking about to further inform practice, so we can find the right treatment for the right patient,

balancing risk and benefit, as it will vary across different clinical arenas.

I also would like to thank the colleagues who have made this platform work and for us to be able to communicate, and to the committee members for really reading a lot of material and participating in quite a robust discussion.

Before we adjourn, any last comments, Dr. Birnkrant?

DR. BIRNKRANT: Thank you so much.

I just wanted to also add my thanks on behalf of our review team and our other FDA staff. Dr. Baden, as usual, you did a phenomenal job. We greatly appreciate how you were able to get answers for us that are needed so that we can then apply that information to make this product and provide the public with answers to important questions.

So thanks to the committee for all of their useful comments and for the review of all these complex materials. We greatly appreciate the discussion and, as I said, the suggestions that the committee made, and we will take them under strong

consideration. I would also like to thank the applicant as well.

Lastly, I would like to thank our FDA staff who have worked tirelessly on all products since the beginning of this pandemic, not only on products for COVID, but other products that have trickled in, like for Mpox as well. In particular, this team that reviewed Paxlovid, not only did they do a thorough job, they asked the right questions because they asked the questions that the public wanted to hear about.

I will say this has undergone a continuous review, not only the NDA application, but the EUA as well, because our goal is to be able to provide thorough information to the public so that they fully understand how to use these important products.

So again, thank you very much, and we look forward to having our paths cross again. Take care.

Adjournment

DR. BADEN: Thank you, and thank you for

putting all the effort into this process, as it is critical to building the trust with the public, which is so needed in this day and age.

We will now adjourn the meeting. Thank you all for your participation.

(Whereupon, at 3:56 p.m., the meeting was adjourned.)