FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING

(PADAC)

Virtual Meeting

Wednesday, November 9, 2022

9:00 a.m. to 4:51 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Takyiah Stevenson, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBERS

(Voting)

David H. Au, MD, MS

(Chairperson)

Professor of Medicine

University of Washington

Director

Center of Innovation for Veteran-Centered and

Value-Driven Care

VA Puget Sound Health Care System

Seattle, Washington

Scott E. Evans, MD, FCCP, ATSF

Professor & Chairman ad interim

Department of Pulmonary Medicine

Rebecca Meyer Brown and Joseph Mellinger Brown

Chair in Basic Science Research

University of Texas MD Anderson Cancer Center

Houston, Texas

Edwin H. Kim, MD, MS

Associate Professor

Division of Pediatric Allergy and Immunology

University of North Carolina School of Medicine

Chapel Hill, North Carolina

Janet S. Lee, MD, ATSF

Professor of Medicine

Director, Acute Lung Injury Center of Excellence

University of Pittsburgh Medical Center Chair in Acute Lung Injury

Division of Pulmonary, Allergy, and Critical Care Medicine

University of Pittsburgh School of Medicine

Pittsburgh, Pennsylvania

Susanne May, PhD

Director

University of Washington Clinical Trials Center

Professor, Department of Biostatistics

University of Washington

Seattle, Washington

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Dawn M. Carlson, MD, MPH

(Industry Representative)

Vice President

Clinical Pharmacology

Abbvie, Inc

North Chicago, Illinois

TEMPORARY MEMBERS (Voting)

Lindsey R. Baden, MD

Director of Clinical Research

Division of Infectious Diseases

Brigham and Women's Hospital

Director, Infectious Disease Service

Dana-Farber Cancer Institute

Professor of Medicine

Harvard Medical School

Boston, Massachusetts

CAPT Daniel S. Chertow, MD, MPH, FCCM, FIDSA
United States Public Health Service
Tenure-Track Investigator
Head, Emerging Pathogens Section
Critical Care Medicine Department
National Institutes of Health
Clinical Center and Laboratory of Immunoregulation
National Institute of Allergy and
Infectious Diseases
Bethesda, Maryland

Daniel L. Gillen, PhD
Chancellor's Professor and Chair
Department of Statistics
University of California, Irvine
Irvine, California

Jennifer A. Schwartzott, MS
(Patient Representative)
North Tonawanda, New York

Nitin Seam, MD

Associate Chief and Director of Fellowship

Critical Care Medicine Department

National Institutes of Health Clinical Center

Clinical Professor of Medicine

George Washington University

Bethesda, Maryland

Steven D. Shapiro, MD

Senior Vice President for Health Affairs

University of Southern California

Professor of Medicine

Keck School of Medicine of University of Southern California

Los Angeles, California

Pamela Shaw, PhD

Senior Investigator

Biostatistics Division

Kaiser Permanente Washington Health Research Institute

Seattle, Washington

Roblena E. Walker, PhD

(Acting Consumer Representative)

Chief Executive Officer

EMAGAHA, INC.

Atlanta, Georgia

FDA PARTICIPANTS (Non-Voting)

Joseph G. Toerner, MD, MPH

Deputy Director (Acting)

Office of Immunology and Inflammation (OII)

Office of New Drugs (OND)

CDER, FDA

Banu A. Karimi-Shah, MD

Deputy Director

Division of Pulmonology, Allergy, and Critical Care (DPACC)

OII, OND, CDER, FDA

Robert Busch, MD, MMSc

Medical Officer

DPACC, OII, OND, CDER, FDA

Rebecca Rothwell, PhD

Lead Mathematical Statistician

Division of Biometrics III (DBIII)

Office of Biostatistics (OB)

Office of Translational Science (OTS)

CDER, FDA

Karen Higgins, PhD

Supervisory Mathematical Statistician

DBIII, OB, OTS, CDER, FDA

Sai Dharmarajan, PhD

Senior Mathematical Statistician

Division of Biometrics VII (DBVII)

OB, OTS, CDER, FDA

C O N T E N T S

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

My name is David Au, and I will be chairing this meeting. I will now call the November 9, 2022 Pulmonary-Allergy Drug Advisory Committee meeting to order. Dr. Takyiah Stevenson is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

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

Dr. David Au?

DR. AU: Good morning. David Au. I am with

the VA Puget Sound Health Care System and the University of Washington.

DR. STEVENSON: Dr. Carlson?

DR. CARLSON: Hi. I'm Dawn Carlson. I'm the industry representative, and I currently work at Abbvie.

DR. STEVENSON: Dr. Evans?

DR. EVANS: Good morning. I am Scott Evans. I'm a pulmonologist at the University of Texas MD Anderson Cancer Center in Houston.

DR. STEVENSON: Dr. Kim?

DR. KIM: Edwin Kim, allergist/immunologist at the University of North Carolina Chapel Hill.

DR. STEVENSON: Dr. Lee?

DR. LEE: Janet Lee from the University of Pittsburgh.

DR. STEVENSON: Dr. May?

DR. MAY: Susanne May, professor of biostatistics at the University of Washington in Seattle, and director of the University of Washington Clinical Trials Center.

DR. STEVENSON: Dr. Baden?

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

DR. STEVENSON: Dr. Chertow?

CAPT CHERTOW: Dan Chertow. I'm a critical care and infectious disease physician at the NIH Clinical Center in Bethesda, Maryland.

DR. STEVENSON: Dr. Gillen?

DR. GILLEN: Yes. Dan Gillen, professor and chair of statistics at University of California at Irvine.

DR. STEVENSON: Ms. Schwartzott?

MS. SCHWARTZOTT: Jennifer Schwartzott. I'm your patient representative.

DR. STEVENSON: Dr. Seam?

DR. SEAM: Nitin Seam, pulmonary and critical care medicine, NIH, Bethesda, Maryland.

DR. STEVENSON: Dr. Shapiro?

DR. SHAPIRO: Hi. Steve Shapiro, senior vice president for Health Affairs, University of Southern California.

DR. STEVENSON: Dr. Shaw?

DR. SHAW: Hello. Pamela Shaw. I'm senior investigator of biostatistics at the Kaiser Permanente Washington Health Research Institute in Seattle, Washington.

DR. STEVENSON: Dr. Walker?

DR. WALKER: Good morning. Roblena Walker, acting consumer representative, chief executive officer, EMAGAHA, INC.

DR. STEVENSON: I will now introduce the FDA participants.

Dr. Toerner?

DR. TOERNER: Yes. Good morning. This is Joe Toerner. I'm the acting deputy director in the Office of Immunology and Inflammation at CDER, FDA.

DR. STEVENSON: Dr. Karimi-Shah?

DR. KARIMI-SHAH: Hi. Good morning, everyone. This is Banu Karimi-Shah. I'm the deputy director of the Division of Pulmonology, Allergy, and Critical Care in the Office of Immunology and Inflammation in CDER at FDA.

DR. STEVENSON: Dr. Busch?

DR. BUSCH: Hi. This is Robert Busch. I'm the medical officer in the Division of Pulmonology, Allergy, and Critical Care at FDA.

DR. STEVENSON: Dr. Rothwell?

DR. ROTHWELL: Hi. This is Rebecca Rothwell, statistical team leader in the Office of Biostatistics at the FDA.

DR. STEVENSON: Dr. Higgins?

DR. HIGGINS: Hi. This is Karen Higgins. I'm a supervisory mathematical statistician in the Division of Biometrics III, Office of Biostatistics, FDA, CDER.

DR. STEVENSON: Dr. Dharmarajan?

DR. DHARMARAJAN: Hey. This is Sai Dharmarajan, statistical reviewer at the Office of Biostatistics at CDER, FDA.

DR. STEVENSON: Thank you, everyone. I will turn it back to the chair.

DR. AU: 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. 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 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 topics during breaks or lunch. Thank you.

Dr. Takyiah Stevenson will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. STEVENSON: The Food and Drug

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

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal

employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the 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 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 discussion of the request for Emergency Use Authorization, EUA, 113, for sabizabulin oral capsule, a tubulin

polymerization inhibitor, submitted by Veru Inc., for the treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk of acute respiratory distress syndrome. A focus of the discussion will include the treatment effect size in the context of the high placebo mortality rate, the limited size of the safety database, and identifying the proposed population.

This is a particular matters meeting during which specific matters related to Veru's EUA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that

Dr. Dawn Carlson is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Carlson's role at this meeting is to represent industry in general and not any particular company. Dr. Carlson is employed by Abbvie.

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 participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you, and I will hand it back to the chair.

DR. AU: Thank you.

We will now proceed with the FDA opening remarks from Dr. Banu Karimi-Shah.

FDA Opening Remarks - Banu Karimi-Shah

DR. KARIMI-SHAH: Thank you, Dr. Au.

Good morning to you, esteemed committee members, the Veru team, my FDA colleagues, and members of the audience. My name is Banu Karimi-Shah, and I'm a pulmonary critical care physician and the deputy director in the Division of Pulmonology, Allergy, and Critical Care here at FDA. On behalf of the agency, I would like to welcome you to this Pulmonary-Allergy Drugs Advisory Committee meeting, where we will discuss the emergency use authorization request for VERU-111, for the treatment of adult patients hospitalized with COVID-19. I will now provide some brief opening remarks to begin our meeting.

VERU-111 is an oral tubulin inhibitor, not approved for any indication. It is a new molecular entity or NME. Veru Incorporated has submitted a request for emergency use authorization, or EUA, for VERU-111 for the proposed use of treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 and who are at high

risk for developing acute respiratory distress syndrome or ARDS. The proposed dose is 9 milligrams once daily for 21 days or until hospital discharge, to be administered orally or via nasogastric tube.

The FDA's authority to authorize a product for emergency use is a result of the declaration enabling FDA to issue EUAs as a part of the U.S. government response to the COVID-19 public health emergency. Based on this declaration, FDA may issue an EUA after determining that certain statutory requirements are met. These statutory requirements are outlined here.

The FDA may issue an EUA if, based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition that can be caused by SARS-CoV-2, and that the known and potential benefits of the product outweigh the

known and potential risks; additionally, there is no adequate approved and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

Further, the FDA may require appropriate conditions with respect to collection and analysis of information concerning the safety and effectiveness of the product with respect to the use of such products during the period when the authorization is in effect and a reasonable time following such period. For example, FDA can require additional trials as a condition of authorization, and this will be an area in which we will seek your input and I will outline in a later slide.

First, a few words about the COVID-19 pandemic. We acknowledge that there is a continued unmet medical need despite current standard-of-care therapy, including vaccination and the medications listed here. The World Health Organization reports over 600 million cases and over 6 million deaths worldwide. In the U.S., the Centers for Disease

Control report close to 100 million cases and over 1 million deaths since early 2020, with over 35,000 new cases, over 3,000 new hospital admissions, and over 300 deaths per day as of mid-October.

It is in this light that we bring this emergency use authorization request from Veru Incorporated to this advisory committee for discussion and input.

The sponsor conducted two trials in COVID-19, Trials V0211901 and V3011902, which the agency will refer to as Studies 901 and 902, respectively. This table summarizes the characteristics of both trials, and you will see this again in the agency's presentation. You will note that Study 901 enrolled a total of only 39 subjects, therefore, the agency will focus our discussion and review primarily on Study 902, which was a 2 to 1 randomized, double-blind, placebo-controlled, parallel group study in 204 adults hospitalized with COVID-19. The primary endpoint was all-cause mortality at day 60.

The primary endpoint results are summarized in this table. We see that when looking at the proportion of subjects alive at day 60, both at the interim analysis and when considering all 204 subjects, that the odds ratio for staying alive was 3.2 in favor of COVID-19 VERU-111 treatment at interim, and for all subjects, the odds ratio for staying alive was 2.77 in favor of treatment, with the corresponding 95 percent confidence intervals as listed in this table.

Secondary endpoints included proportion of patients alive and without respiratory failure at various time points, days on mechanical ventilation, and days in ICU. Because of the influence of the mortality results on these secondary endpoints and the importance of the all-cause mortality endpoint to the overall regulatory decision making regarding VERU-111, the agency's briefing materials and presentations focus primarily on the analyses of all-cause mortality.

The FDA review team acknowledges that Study 902 met its prespecified primary endpoint of

all-cause mortality at day 60. We believe that all-cause mortality is an important and clinically meaningful endpoint in hospitalized patients with COVID-19, however, we also note several uncertainties with the data provided in the VERU-111 development program.

We will go over these in detail during the course of our presentations today, but to briefly summarize here, these include a high placebo mortality for baseline severity; potential unblinding events with enteral tube administration; differences in application of standard-of-care therapies; differences in timing of enrollment between treatment arms; uncertainties around the effects of goals of care decision making on all-cause mortality; and that the efficacy results of other microtubule disruptors do not support the finding in the VERU-111 program. There's also an uncertainty around how the study population was defined.

In addition to the uncertainties in the efficacy is the limited safety database for this

new molecular entity. To be clear, many of these issues might not influence the overall interpretation in a very large trial but lead to uncertainty in this small trial with a 2 to 1 randomization ratio, where any effect on the mortality of even a few subjects in the placebo group may have exerted an exaggerated effect on the overall results.

So as you listen to the presentations today, we ask you to focus on how these uncertainties influence the robustness and reliability of the treatment effect; the patient population in whom this might be appropriate if authorized; and whether the data we have is enough to conclude that the known and potential benefits of the product outweigh the known and potential risks for the EUA statutory requirements.

As I mentioned earlier, even with authorization, additional clinical trials can be required as a condition of authorization, and we will ask you to discuss what such a study should look like. To help with this discussion, I have

provided some considerations for an additional trial in this slide. These include the study population, the proposed study design, and additional study elements to deal with the uncertainties that we have raised with the VERU-111 data. I will revisit these discussion points during my charge to the committee, but I preview it here to set the stage as you listen to the presentations this morning.

Before I conclude my opening remarks, I would also like to share the questions which we will be asking you to discuss this afternoon. I will go over them now and present them again during my charge to the committee.

Question 1 is a discussion question. We ask the committee to discuss the strength of the all-cause mortality data, specifically considering the uncertainties raised by the agency in Study 902, including those that I have outlined in the previous slide.

Question 2 is also a discussion question. We ask the committee to discuss your level of

concern regarding the limited size of the safety database for this new molecular entity.

Question 3 is a voting question. We ask, do the known and potential benefits of VERU-111, when used for the treatment of adult patients hospitalized with COVID-19 at high risk of ARDS, outweigh the known and potential risks of VERU-111? If yes, we ask you to discuss the appropriate population in which VERU-111 should be authorized. If you vote no, we ask you to discuss what additional data would be necessary to assess the benefits versus the risks of treatment.

Finally, Question 4 is also a discussion question. We ask, if authorized, the agency believes that additional data are necessary to understand the benefit-risk assessment as a condition of authorization. Please discuss the proposed design aspects of a study to provide this additional data.

Thank you for your attention. I will now turn the meeting back to Dr. Au as we proceed with today's meeting.

DR. AU: Thank you.

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 sponsor, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based on the outcome of the meeting.

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

We will now proceed with Veru's presentation.

Applicant Presentation - Mitchell Steiner

DR. STEINER: Good morning. I'm Dr. Mitchell Steiner. I'm the CEO and CMO of Veru. I'm a urologic/oncologic surgeon, and I've been in drug development now for the past 25 years, including in oncology and gene therapy.

When the COVID-19 pandemic started, sabizabulin, the novel agent that targets microtubules, was a phase 3 clinical study to advance prostate cancer. Dr. Barnette, who's our chief scientific officer, and I knew that microtubules also play a critical role in viral infections and the overexaggerated immune response responsible for ARDS and death, suggesting that sabizabulin could be a novel therapeutic against COVID-19.

In the face of a public health emergency, we felt duty-bound to redirect our company's efforts to prove out this hypothesis. I'm so glad we were persistent, and we really, really appreciate the

FDA's guidance in the development of sabizabulin in hospitalized COVID-19 patients at high risk for ARDS and death, and I'm pleased today to have the opportunity to share with you our sabizabulin COVID-19 program.

This is the agenda for this morning. First, I will provide an overview of the program, and furthermore, I will discuss some of the company's perspective with some of the points raised by the FDA. Next, Dr. Gary Barnette will provide a summary of efficacy and safety of the COVID-19 program, and then that will be followed by Dr. Lee-Jen Wei, who will provide a robust analysis of the primary and secondary endpoint. Dr. Wei is a professor of biostatistics at Harvard University. Dr. Wei has extensive working experience in regulatory science with developing and evaluating new drugs.

Next, Dr. Christian Sandrock is a division vice chief of internal medicine, director of critical care, and professor of medicine at the University of California, Davis. Dr. Sandrock is

on the frontline of managing severe COVID-19 patients. His specialties include emergency infectious diseases, outbreak management, sepsis, and critical care medicine. He will go over the benefit-risk assessment of our program, and then I'll come back and end with some concluding remarks.

As you heard, over a million people have died from COVID-19 in the United States, and even with current standard care treatments, COVID-19 infection is responsible for over 350 deaths each day. This is unacceptable. We can do better. Another surge in new COVID-19 cases is expected this fall and winter in the United States and has already begun in Europe. We need effective and safe treatments to reduce deaths in the hospital, the greatest threat of the COVID-19 pandemic.

By way of background, Veru is a biopharmaceutical company focused on developing novel medicines for infectious disease and oncology. Sabizabulin, as you heard also referred to as VERU-111, is a novel oral microtubule

depolymerization agent, and sabizabulin was in phase 3 clinical development for advanced prostate cancer when the COVID-19 pandemic started. As I mentioned in my comments, the mechanism of action suggests that sabizabulin could be both an antiviral and an anti-inflammatory agent, and a novel treatment for COVID-19.

Based on this, we initiated a COVID-19 program. We worked closely with the FDA to design the phase 2 and phase 3, and you can imagine the chaos that was going on when thousands of companies were scrambling to figure out what is the best way to go after something that we didn't know much about, and how do you study it. The FDA was the best source because it had the best access to new and developing and emerging information, and that's how we designed our phase 2 and phase 3.

Based on the positive phase 2 study in hospitalized, critical COVID-19 patients, we received fast-track designation. Ultimately, we ended up with a completed phase 3 study, and sabizabulin treatment in the phase 3 study

demonstrated clear clinical benefit in hospitalized COVID-19 patients at high risk for ARDS and death, and was published in the New England Journal of Medicine Evidence.

How is it that a single agent could have both dual antiviral and anti-inflammatory activities to treat COVID-19? Well, the mechanism of action is actually central. Sabizabulin targets and disrupts rapidly forming microtubules, and that's why we were developing it in oncology because it can arrest dividing cancer cells, but it can also halt virus transport and suppress cytokine production release, and let me show you how that's done.

If you look at the cartoon to your left, this is a viral infection of SARS-CoV-2 in a lung cell. What you see is that the microtubules play a critical role throughout the viral replication lifecycle, and you'll see SARS-CoV-2 being internalized, and it has to latch onto the microtubule to move within the cell -- and that's called microtubule trafficking -- to get to the

endoplasmic reticulum. And the endoplasmic reticulum is where the virus replicates, gets packaged -- the new viruses get packaged -- go through the Golgi, and then it is placed onto the microtubules for export, for release, and spread.

Furthermore, what's important about this process, where you see the microtubules play a key role, this is not the virus itself. The drug is not attacking the virus itself. The drug is attacking a cellular process, and that cellular process allows even greater advantage, and that is that this mechanism is variant independent, agnostic, and furthermore, potentially other viruses can be treated with VERU-111, sabizabulin.

Let's turn our attention now to the immune response. In the immune response, you see a T-cell, and even though we're using microtubules, it's a very different process. What you see is the most important component of the immune response is the innate immune system that's trying to fight off a pathogen it just doesn't understand. And the way that's done, and central to that, is the

inflammasome. But the inflammasome has to be put together, and it's sample.

As soon as its virus triggers the innate immune response, the individual components of the inflammasome come together by microtubules to be assembled. When it's assembled, it then sets off a cascade of activating inflammatory proteins, and these activated inflammatory proteins have packaged, put back onto microtubules, export release, and are a part of that cytokine storm that leads to ARDS, and death.

So as you can see now, even though it has what appears to be different end and activities, sabizabulin had dual antiviral and anti-inflammatory activities by going after the same central process, which is the microtubule.

Now, we have evidence from preclinical studies that confirm sabizabulin's dual mechanism of action against COVID-19. We have an antiviral activity that was observed in an infectious viral titer assay in SARS-CoV-2 infected cells in vitro. We have an anti-inflammatory activity that was

demonstrated in a septic shock model in vitro, and I'll show you these data.

Again, now that we understand that we're affecting microtubules, the way to judge that is to test and measure the release of infectious virus particles in the cell itself, so that is the endpoint that you look forward to see whether or not you're affecting viral production.

In this assay called the infectious viral titer assay, the way this is done, in step 1, which you see, is you can incubate cells with the virus by itself or virus plus our drug. And what's happening in that period of time when it's incubating is a viral cycle's taking place and new virus is being released into the media, and now you want to measure that new virus that's in the media to see whether your drug has an effect or not.

The way you do that is you take the media, the supernatant, and you replate it on fresh cells, and what you're looking for as an indicator of infectious disease particles is you're looking for dead cells, and if the cell gets infected, it dies.

And you can measure that; you can actually measure the cell viability.

When you look at the graph to the far right, this is measuring viable cells versus the supernatant diluted, diluted, diluted, to a point that you have enough viable cells that you can see 50 percent of your cells alive. So by way of example, if you did the straight virus, you have to dilute that supernatant a million-fold to see 50 percent of those cells alive, whereas with VERU-111, sabizabulin, and 1 nanomolar and 10 nanomolar -- which incidentally is easily achievable with a 9-milligram dose -- you see 80 to 100 percent of the cells are viable even at their your first dilution. So what this suggests and indicates is that there is a marked reduction in infectious viral particles released by the cell with sabizabulin incubation.

How about anti-inflammatory activity? We use what's called an endotoxin septic shock model in vitro, and what we're trying to do is simulate the cytokine storm. And the way you do that is you

take mouse spleen cells and shock it with an agent called LPS. What this does, it releases a bunch of cytokines into the media, and you can measure it if you add your drug, for example.

So in this case, sabizabulin at 40 nanomolar, which is, again, easily achievable with a 9-milligram human dose, you see that we were able to reduce cytokine production, not just IL-6, but across the cytokines that were produced by this septic shock model, and this suggests that sabizabulin has broad anti-inflammatory activity.

Now, this has come up several times, and the reason for it is -- and this is looking at colchicine as a proxy for a potential drug that is exactly the same as sabizabulin, and of course it's not. First of all, colchicine is originally indicated for acute gout and a Mediterranean familial fever.

Sabizabulin is not colchicine, and colchicine has not fared well in COVID-19 studies. But again, it's not the same molecule. It's a different chemical structure, as you can see to the

right, and it targets microtubules differently. So you can't put microtubule inhibitors into one bucket. That takes away the complexity of why there's so many microtubules today being used for different diseases. In this situation, it's very specific. Sabizabulin binds to beta tubulin and alpha tubulin to crosslink alpha and beta tubulin, whereas colchicine binds only to beta tubulin.

So the biology is different. The pharmacology is different. The pharmacokinetics is different. The therapeutic index is different. In fact, it turns out sabizabulin is a much more potent inhibitor tubulin polymerization, so sabizabulin does not fit into p-glycoprotein or CYP3A4, which CYP colchicine does, and is the reason why colchicine has a narrow therapeutic index; we just don't fit.

In fact, if you look at the biology -- and I call your attention to the right-lower side of the slide -- you'll see this cell proliferation assay, where we're looking at human triple negative breast cancer cell lines, and the Y-axis is the mean

inhibitory concentration 50 in nanomolar. You'll see the green, which is VERU-111, is very effective in inhibiting human triple negative breast cancer cell lines, but colchicine is not. Ultimately, ultimately, clinically, sabizabulin did show in phase 2 and phase 3 clinical studies that it was a strong mortality benefit in hospitalized patients at high risk for ARDS, and for death.

Now, the program, the sabizabulin clinical program, consists of the phase 2 and phase 3 COVID-19 studies that were done during the pandemic period, from June 2020 to June 2022, so we really overlapped the pandemic period, and we allowed standard-of-care treatment. And you can see in the blue these are the two studies that support efficacy and safety, and we used as our patient population hospitalized COVID-19 patients who are at high risk for the development of ARDS, and death.

Supporting safety data comes from our prostate cancer studies of which we have a phase 1b/2 and a phase 3 that's ongoing. Advanced

prostate cancer patients are relevant because in this patient population, we use doses of 32 milligrams, which is about 3 and a half times higher, and chronic usage, in some cases as much as 3 years. So we believe that prostate cancer patients that have the same comorbidities and of similar age, and the fact it was well tolerated, is useful information.

The sabizabulin proposed EUA indication is exactly the patient population we treated. These are patients with hospitalized moderate to severe COVID-19, who are at high risk for ARDS. The dose in administration is a 9-milligram oral capsule, once daily for up to 21 days or discharged from the hospital. And the reason that's important is a capsule can be opened and used in an ICU setting. Secondly, the patient doesn't get to go home with the drug, so this is a hospital-controlled drug.

Now, you're going to be asked to consider the observed high placebo mortality rate in our phase 3 sabizabulin study and put that into context. But I would argue we have to also put

into context the observed placebo rate that we got; and furthermore, once we understand that, what was the result of our drug in that setting?

So first of all, to be clear, we purposely designed our study to enroll very sick patients, and this was done in consultation with the FDA. And furthermore, we selected mortality as the most objective and important primary endpoint. In fact, we went one step further and said mortality at day 60.

So what did we learn by having a clinical trial with the inclusion/exclusion criteria that focused on selecting out the sickest patients is we found out that sicker patients die at a higher rate, and we have two lines of information -- evidence -- that supports the context of our observed high placebo rate.

One is contemporaneous studies, and what we did is we took 15 contemporaneous COVID-19 studies, and we plotted out the mortality rates of placebo plus standard of care, and these are the studies that either have an EUA or they're part of the NIH

COVID-19 treatment guidelines, and compared it to our phase 3 sabizabulin study.

Next, very recently, the CDC has real-world data, where they reported the mortality risk in hospitalized severe COVID-19 patients during the Delta to Omicron periods, from July 2021 to June 2022, which again is where our studies overlap, from the Premier Healthcare Database Special COVID-19, and this database captures 678 hospitals and 25 percent of the annual hospital admissions.

So what did we see? Well, again you just can't put the death rate side by side; you have to put context to the death rates. And what we did here is we plotted the placebo mortality rate with standard of care, plus against the proportion of patients that have severe disease defined as non-invasive ventilation, high-flow oxygen, and mechanical ventilation; so these are sick patients. And it makes sense, and what we showed is that the higher proportion of sick patients you have, the higher the death rate.

This follows and is highly correlative with an R squared of 0.7702. So the black dots form that line, and you recognize these studies. These are the common studies and viewed again through the lens of the proportion of patients that have severe disease.

Now when you add the overall study from Veru, which is 29.4 percent at day 30 -- and we picked day 30 because this is how all of these studies have reported -- you see that the red dot falls in line. Again, you would imagine at day 60 you would have even a higher death rate.

Now let's look at the real-world data. The real-world data that was reported -- and I draw your attention to the blue table -- this table shows you the mortality rates of the high-risk COVID-19 patients based on variant. So to pause for a moment, I'm not talking about all the patients that come into the hospital and that are admitted, and those are the patients you're treating. No. We're talking about the patients at high risk for ARDS, so those are the patients on

this chart: ICU, WHO 5, WHO 6, WHO 5 being forced oxygen, WHO 6, mechanical ventilation.

What you see whether you look at Delta or early Omicron, they're the patients that are contributing to the high mortality rate, then and today. In fact, if you look now at the phase 3 COVID-19 sabizabulin full study that was enrolled in this same period of time, the overall placebo rate of 29.4 percent at day 29 and 39.7 percent at day 60 is in line.

So now when you understand the context of the high placebo rate, based on the severity of the patients that were enrolled, now let's look at the mortality benefit of the sabizabulin study.

Well, the mortality benefit shows the strong effect size was robust and clinically meaningful in every subgroup or sensitivity analysis of the primary endpoint regardless of the placebo mortality rate. In fact, the hospitalized COVID-19 patients at high risk for ARDS and death then and now are the same patients who are dying, and will have the same benefit from sabizabulin's treatment.

How about our safety database? We acknowledge it's small, but we also acknowledge the safety database supports the EUA. The overall safety population database is 266 patients, which consists of the COVID-19 patients and the prostate cancer patients. There were no remarkable safety findings in our safety population. It was well tolerated at 3 and a half times dose higher, and up to 3 years duration in prostate cancer studies.

To put in perspective, sabizabulin has a short half-life. Five and a half hours it's quickly cleared, and you have a short course of therapy, 21 days or discharge from the hospital; again, because it's a hospital-controlled drug. Any potential safety risk is minimized, as the indicated population will be hospitalized and under direct care. We're committed to working with the agency to collect additional clinical information under the EUA to support the continued use of sabizabulin.

We also ask to consider the proposed population. Well, the patient population we put in

our proposed fact sheet is the patient population we studied. We propose that sabizabulin be indicated for the treatment of hospitalized adult patients with moderate to severe COVID-19 who are at high risk for acute respiratory distress syndrome. This matches our inclusion/exclusion criteria for the phase 2 clinical trial, and this is the population where sabizabulin treatment resulted in a robust, statistically significant, and clinically meaningful mortality benefit.

A serious unmet medical need still exists when you look at patients who are on supplemental oxygen with comorbidities, WHO 5 with forced oxygen, and WHO 6 from mechanical ventilation.

Now, I would like to ask Dr. Gary Barnette, our chief scientific officer, to provide a summary of the efficacy and safety of our COVID-19 program.

Applicant Presentation - Gary Barnette

DR. BARNETTE: Thank you, Dr. Steiner.

My name is Gary Barnette, and I'm the chief scientific officer at Veru. I'm a PhD clinical pharmacologist by training. I'm a former FDA

reviewer in three different divisions.

In March 2020, we were starting this pandemic, and as you know, there was a lot of information, misinformation, disinformation, and patients and people just didn't understand what to do, and I started getting calls from people from my hometown in Lost Creek, West Virginia, as well as folks from church, "So if I get this virus, what do I do?"

With the knowledge that we have, a phase 3 asset of sabizabulin, a micro tubulin depolymerization agent, and then looking at the biology and the microtubule trafficking, and the inflammatory response that the virus induces, it became very apparent to Dr. Steiner and I that sabizabulin had, or could have, a potentially incredible important effect on this pandemic.

Initially, we called the FDA immediately. The FDA has been very responsive. We were in a pre-IND meeting. Very quickly we went to the IND and collaboratively designed the phase 2 study that Dr. Steiner has mentioned and that I'll go over

briefly.

That phase 2 study was a proof-of-concept study to look at this very novel mechanism and way of attacking a virus, a viral infection. The study indeed only included 39 patients as per the discussion with the FDA. The key efficacy endpoints, as you can see on the left, we showed an 82 percent reduction in mortality in this small study. We showed a reduction in days in the ICU and a reduction in the mean days on mechanical ventilation.

Turning to safety, in the right box, this is a summary of adverse events that occurred in at least 2 patients in either group in the study. As you can see, there's no adverse event that was over represented in the sabizabulin group. As a matter of fact, the adverse events associated with COVID progression looked like they were higher in the placebo group than they were in the sabizabulin group.

We took these data back to the FDA for an end of phase 2 meeting; again, had an incredibly

collaborative discussion about the design of the phase 3, discussed and decided upon the primary endpoint of mortality, all-cause mortality, at day 60, and ultimately, based on the data that you see on the screen, the FDA granted fast-track designation for the program.

Now, the phase 3 clinical study that we designed was a double-blind, placebo-controlled study, 2 to 1 randomization, and frankly, the 2 to 1 randomization is because ethically it became difficult for us to include a number of patients on a placebo arm when you had, potentially, an 82 percent reduction of mortality, as you saw in the phase 2.

The study was designed with an estimated placebo rate of 30 percent, a mortality rate of 30 percent, with approximately 50 percent reduction in the sabizabulin group. The alpha was 0.05 two-sided and the power was greater than 92 percent.

As Dr. Steiner outlined, these are sick patients. I mean, these are the most progressed

patients. These are WHO 4's. And just to remind you, a WHO 4 is a hospitalized patient that is on supplemental oxygen or passive oxygen. In our study, these patients had to have at least one comorbidity that made them at high risk for development of disease. WHO 5's we recruited. A WHO 5 is forced oxygen and WHO 6 mechanical ventilation with innervation. The patients in our study did have to have an SpO_2 of less than 94 percent on room air prior to oxygen support.

The study was done under current GCPs and was conducted rigorously. The study had an adequate informed consent process, and as far as the differences in goals of standard of decision making that the FDA mentioned earlier and we'll ask you to opine on later, the patients that came into the study made an informed decision to participate in this study when they were progressed, and they made the decision that they wanted to give this drug a shot because they wanted to live. And we believe that that is the basis of this particular program; keep patients alive.

The patient disposition, we screened 244 patients for the study. We randomized 204. The 2 to 1 randomization worked fairly well with 134 in the sabizabulin and 70 in the placebo group. As you can see from the bottom line, the proportion of patients that completed the study in the treatment group was fairly similar with 93.3 treated group versus 94.3 in the placebo group.

Key demographics, the mean age of the patients was similar. The proportion of gender distribution was similar. The WHO score at baseline was similar. One of the uncertainties that the FDA will ask you to discuss later on is the standards of care. The standards of care that we applied to the study is distribution. Here again, as Dr. Steiner mentioned, patients were allowed to have standard of care in the study, and in the placebo group as well as in the treated group.

As you can see, dexamethasone is a little higher in the treated group, but when you look at

any corticosteroid, there's no difference. Remdesivir is approximately similar, and then of course the IL-6 and the JAK inhibitor used appears to be higher in the placebo group than the treated group.

As has been mentioned many times, the primary endpoint of the study was all-cause mortality or the proportion of patients who died on study up to day 60. Some key secondary endpoints were proportion of patients alive without respiratory failure at varying time points; days in the ICU; days on mechanical ventilation; days in the hospital; proportion of patients who died on study at other time points other than day 60; and then change from baseline and viral load, and we'll go over these as we go through this presentation.

As has been mentioned, we did have a planned interim analysis. The planned interim analysis was the first 150 patients randomized into the study. On April 8th, an independent data monitoring committee reviewed the data that you're seeing on the screen and made a decision that the study

should be unanimously stopped; a unanimous decision, or recommendation, to stop the study early for clear evidence of benefit.

As you can see in the graph on the right, the placebo cumulative mortality curve starts separating from sabizabulin almost immediately and continues to widen as the study progressed up to day 60. The p-value on the bottom-right, this is using a logistic regression with the covariate analysis and the multiple imputation. The p-value is 0.0042 with an odds ratio of 3.21. This is very consistent with the data that Dr. Karimi-Shah presented in her introduction.

At the time that the interim analysis was completed, we had enrolled 204 of the 210 targeted patients into the study, and the rest of the data that I'm going to present today is focusing on this data set. As you can see in the curve to the left, the top-left, the mortality benefit was maintained in the overall population. Again, the placebo group, from a cumulative mortality standpoint, separates quickly and continues to separate over

the 60-day treatment period or follow-up period. The p-value of this overall analysis, again, very rigorous and robust at 0.0046 using the planned primary analysis.

We did some sensitivity analyses, and you can see those in the blue box. The take-home method, whether you look at it from a time to event Kaplan-Meier perspective, or a Cox proportional, or a logistic regression proportion, the p-values are very strong with basically less than 0.005 across the board. Dr. Wei in a few minutes will provide an independent analysis of these data that he did that also demonstrates statistical significance and benefits of sabizabulin in reduction in death compared to placebo.

Now again, some of the uncertainties that the FDA has commented on earlier, and we'll ask you to discuss later, are related to demographics, standards of care, and these kinds of things. We did subgroup analyses, using the primary endpoint, of the demographics. The males/females, you can see age 60, various standards of care, WHO score,

and geography.

Let me orient you to this slide very briefly. The vertical line in the middle means anything left of that vertical line means sabizabulin is better in absolute risk reduction. Anything to the right, or any dot to the right of that, means placebo was better. As you can see across, all these subgroup analyses, the dots are all to the left of that line, meaning the absolute risk reduction, regardless of what subgroup analysis we look at, shows a benefit in sabizabulin in deaths compared to placebo.

Now I'll focus you on the standards of care, specifically vaccine versus unvaccinated; use of remdesivir, no remdesivir; dexamethasone, no dexamethasone; tocilizumab, no tocilizumab; JAK inhibitor, no JAK inhibitor. I want to point out, whether they got the standard of care or they did not, the dots are all to the left of that vertical line, meaning the absolute risk reduction clearly demonstrates that sabizabulin reduces death compared to placebo.

Another potential uncertainty the FDA mentions is the comorbidities, so we did a number of analyses of comorbidities, again, looking at the overall death rate up to day 60. You can see on the left the subgroup analyses of various comorbidities, as well as constellations of comorbidities, meaning multiple comorbidities, and strings of comorbidities that patients could have had in the bottom two sections, just hypertension plus 3 comorbidities, et cetera, and then the bottom three lines are just the sheer number of comorbidities that the patients had coming into the study.

The take-home message from this slide is the right two columns, and your eye can go down those two columns and see negatives. So in every comorbidity or every constellation of comorbidity, the absolute risk reduction in mortality with sabizabulin is observed and the relative reduction in mortality is observed across every analysis we have conducted.

Now, to further investigate this, we did a

backward logistic regression analysis, where we basically eliminated, or took out in a step-wise fashion, all of the comorbidities and all of the covariates that you would consider that's possibly affecting this mortality and the observed effect size.

You can see them listed here. I know it's busy and complicated, but suffice it to say if you look at the bottom-right, the p-value -- and we did this -- and looked at the effect of all of these covariates combined and separately, the p-value is 0.0050, again, in favor of sabizabulin.

Now one of the other questions that is often asked is around variant. Now remember, the mechanism of action of sabizabulin is independent of variant and, frankly, it's independent of virus, and this data here demonstrates that. I think everybody would agree that -- well, our study was conducted through the Delta and Omicron variants, and I think everybody would agree, or most people would agree, that prior to December 15, 2021, Delta was the predominant variant that was circulating,

really, around the world. And you can see that top line; the relative reduction in mortality of patients that were randomized prior to that date was 41.3.

I think we could argue about the transition from Delta to Omicron, but regardless of whether you look at after 12-15-2021 or after 1-15-2022, whenever you feel the Omicron took over, basically, as the predominant variant, the mortality benefit is maintained, 59.1 percent relative reduction in death, an absolute reduction of 21.1 or 16.6, both, of course, clinically relevant.

Now, the FDA has brought up, and we acknowledge, that there was the potential for an unblinding when a patient went on to an NG tube, and the capsule was opened. We also investigated this extensively, and we investigated this down to the site level, and we could not find any evidence of unblinding or conscious unblinding. We don't see any difference or change in standards of care administered, or adverse event, and so on and so forth.

We also did a statistical analysis. This is a Kaplan-Meier analysis where we used mortality or initiation of dosing via NG tube as the censored event. And as you can see in this analysis, a relative difference of 43.4 percent, but a log rank -- a p-value log rank -- on the Kaplan-Meier analysis of 0.0179, or using Wilcoxon, 0.0228, both show robust statistical significance. So while it could have happened, we don't believe it affected the study at all.

Key secondary endpoints, when we look at the first secondary endpoint, which is proportion of patients alive and free of respiratory failure at day 29, you can see the blue box in the middle of the screen. At day 29, we showed a 32 percent increase in patients who were alive and did not have respiratory failure at that time point. This resulted in a p-value, at the bottom-right, of 0.0186; again, robustly statistically significant.

Looking at the other secondary endpoints, days in the ICU, days on mechanical ventilation, days in the hospital, again, all the way to the

right you can see each one of these met statistical significant rules.

Now I want to point out in this particular analyses, as per FDA direction, we attributed the worst possible outcome for every patient who died on study. What that means is the worst possible outcome would be 60 days in the hospital. So for every patient that died in the study, we attributed 60 days in the hospital, 60 days in ICU, and 60 days on mechanical ventilation to those patients. That's the analysis you're seeing on the screen. Dr. Wei, here in a bit, will be talking to you about an independent analysis he did that looks at it differently that also shows statistical benefit of sabizabulin in these parameters.

The bottom secondary endpoint is viral load. This did not reach statistical significance; very highly variable and didn't reach statistical significance. But when you compare the mean values at baseline versus the mean values at last on study up to day 9, you see an approximately 43 percent reduction in sabizabulin viral load and

approximately 412 percent increase in placebo viral load; again, not statistically significant, but certainly this observation is intriguing.

So what are our efficacy conclusions? Sabizabulin demonstrated a very robust 20.5 percent absolute risk reduction at 60-day mortality. This was also analyzed as a 51.6 relative risk reduction. Every sensitivity analysis, every subgroup analysis, when we looked at every parameter that we could outline, they all confirmed the overwhelming benefit of sabizabulin in reduction of death. The secondary endpoints also consistently demonstrate statistically significant and clinically meaningful efficacy of sabizabulin.

Now the number to treat, or NNT, this is the number of patients that we need to treat to save a life, and this is an incredible finding or an incredible way to look at this. For every 5 patients treated in the clinic with sabizabulin in the phase 3 clinical study, we saved one life.

Now, I have not gone over one of the other points the agency is going to mention and ask you

to opine on, is the timing to enrollment. I do not have data on slide, however, I do have it in a backup if you'd like to see it. We did have 6 patients in the sabizabulin group that were in the hospital for greater than 14 days prior to entry into the study. Now, one could argue whether that patient would be more likely or less likely to die because they're in the hospital, but the bottom line, it was different, six in the treated group versus zero in the placebo group. When we eliminate those 6 patients from the analysis and do the analysis again, the p-value is still 0.0046. So the time coming into the hospital prior to entry into the study does not appear to matter.

I'm going to continue to discuss our safety database. As Dr. Steiner mentioned, the overall safety population is 266 patients and growing. We have 149 patients in the two COVID-19 studies, 117 patients in the ongoing phase 3 study at the time of this data cutoff. I'm going to focus this discussion on the phase 3 study, and specifically the safety data set, meaning patients who actually

got at least once dose of study drug, and that's 199 patients or 130 in the sabizabulin group and 69 in the placebo group.

The first slide is the treatment-emergent adverse events, and this table represents the adverse events that occurred in at least 5 percent of the patients in either treatment group. The first thing I'll point out is that this is a 2 to 1 randomization study, so you have to focus on the percentages in the middle, in the parenthetics in the table, to understand the difference between the treatment groups.

The proportion of patients that experienced any treatment-emergent adverse event was 24 percent higher in the placebo group compared to the sabizabulin treatment group. The adverse events above that blue line really represent adverse events that are associated with COVID-19 progression. As you can see, they virtually all are more highly represented in the placebo group than the sabizabulin group.

Below that line is our other adverse events

that meet the criteria for this slide and, really, not much that shows an imbalance against the treatment arm. I would point out urinary tract infections at the bottom is 6.2 and 1.4. I would say additionally that when you look at bacterial infections overall, there's no difference between the treatment group, and when you look at infestations and infections as a system organ class, it's actually 33 percent higher in the placebo group than in the treated group. This is an observation we make, and we will follow this in our fact sheet, as well as the patients being treated with sabizabulin.

When you look at treatment-emergent adverse events leading to the treatment discontinuation -- this is an important aspect -- there's no difference between the treated group, 4.6 percent versus 4.3 in the placebo group. The other thing that you notice is that there's no individual adverse event that's more than 1 in either group, meaning there's nothing, again, that has represented anything -- overrepresented in the

sabizabulin group.

Switching our attention to serious adverse events, again, this table is the serious adverse events that occurred in at least 2 percent of patients in either treatment group. Again, the proportion of patients that experienced any serious adverse event was 59 percent higher in the placebo group compared to the sabizabulin treated group.

These adverse events, as you scan down the left side, are all adverse events, or serious adverse events, that are associated with COVID progression and COVID death. I could point out that virtually all of them are overrepresented in the placebo group versus the sabizabulin group. I point out the bottom one, respiratory failure, a key serious adverse event in this population, is 20.3 percent in the placebo group versus 10 percent in the sabizabulin group.

Adverse events, fatal adverse events, of course we had more deaths in the placebo group than the sabizabulin group, so certainly it's overrepresented in the placebo group. But the

take-home message from this slide is that there's no individual fatal adverse event that's overrepresented, again, in the sabizabulin group compared to the placebo group.

So what are our safety conclusions? Sabizabulin was well tolerated in our COVID-19 studies. The most common treatment-emergent adverse events were respiratory failure, acute kidney injury, and pneumonia. All three of these events were experienced in a higher proportion of subjects in the placebo group than in the sabizabulin group.

The most common serious treatment-emergent adverse events were respiratory failure, acute kidney injury, and acute respiratory failure. Again, all three were experienced in a higher proportion of subjects in the placebo group compared to sabizabulin, and interestingly, the safety observations -- because of all the adverse events associated with COVID progression -- appear to be higher in the placebo group than the treated group confirm the efficacy findings of sabizabulin

in the treatment of COVID-19.

The safety findings, I did not discuss these, but the safety findings from the prostate cancer program, at a dose of approximately 3 and a half fold higher than the dose we're using in the COVID-19 studies, showed sabizabulin is well tolerated even when administered chronically daily for up to 3 years.

We agree with the FDA that additional data is needed, and these are planned clinical trials that we intend to conduct. The three, the first one is V3011903. This is in hospitalized adult patients with less severe COVID-19 than we studied in the completed study, meaning WHO 3, that's hospitalized patients not on supplemental oxygen, and then WHO 4, patients without a comorbidity.

We believe and propose that this patient population would be an ideal population to assess the true effect of any adverse events associated with sabizabulin because these are less sick populations and will be less complicated by progressing disease.

Incidentally, as we've mentioned multiple times, the method of action of sabizabulin is agnostic to variant and, frankly, it's agnostic to virus. We do have nonclinical information of the positive effect of sabizabulin on H1N1, or influenza, as well as pox viruses or vaccinia viruses.

We do intend to initiate two phase 3 studies, one in influenza, adult influenza patients hospitalized, and then also hospitalized adult patients with viral-related ARDS. We do look forward to discussing these proposed studies with the agency. We do have protocols written for these and ready to initiate.

We're discussing this, but it looks like each one of these studies will actually have approximately 500 patients in each or more, so this should give us a lot of safety data to augment the knowledge of sabizabulin. Of course, additionally, we will collect safety data under the EUA as we have to and as regulated.

So what is the benefit-risk from the

sponsor's perspective? The benefit-risk assessment really shows overwhelmingly positive in favor of sabizabulin with reductions in mortality and death. From COVID-19, we're not worried about getting the sniffles; we're worried about dying. And overall, sabizabulin reduction in mortality in the overall population and in all subgroup analyses and sensitivity analyses is robust.

Sabizabulin, again, is intended for use only in hospitalized patients that are high risk for death, or to use the FDA's terminology, "non-negligible risk of death," and they're under constant surveillance. Therefore, any adverse events that are observed can be addressed very quickly and mitigate any further risk.

As I mentioned, additional safety data will be obtained under the EUA for this indication, including the spontaneous reporting under the regulations, as well as a pregnancy registry that we have put in place. Through the additional planned clinical studies with sabizabulin that I outlined in less severe COVID patients, influenza

and virus-related ARDS, we do propose that we will collect a significant amount of safety and efficacy data on sabizabulin as we go forward in a very short time frame.

Now, I'd like to introduce Dr. Lee-Jen Wei from Harvard. He's a professor of biostatistics at Harvard. He has done independent analyses of our efficacy data, both primary and secondary endpoints, and we'd like him to present that today.

Dr. Wei, the floor is yours, sir.

DR. WEI: Thank you, Dr. Barnette. Can you hear me alright?

DR. BARNETTE: Yes.

Applicant Presentation - Lee-Jen Wei

DR. WEI: Thank you.

This is Lee-Jen Wei. First, I want to make disclosures. I have to admit there are probably limited numbers we served in the industry because I've been doing clinical trials for 40 years. Most of the time we served data monitoring, we probably served like 50 or 60 committees in the past. So I apologize if I missed any of those companies

involved in the past.

I joined Harvard 1991 during this HIV epidemic. I was told I was hired because they needed someone who knows a little bit about survival analysis to handle HIV. Our department actually is a data center for HCTG [ph] Network. Since then, I've gotten involved with infectious disease quite a bit. Now, our center actually also sponsors for several COVID-19 trials.

In the past two years, our group published several papers in the clinical journals for methodology and discussion, for example, of statistical methods. For example, the New England Journal of Medicine, Annals of Internal Medicine, et cetera, and myself right now has got involved in a couple of ARDS trials involving COVID-19.

Now, for the current study, the primary endpoint is day 60 survival, which is a binary endpoint; either the patient survived on day 60 or died. The sponsor told me, "Well, the results are so impressive." They just wonder if my group can actually analyze data independently to see if

anything they actually -- this is very unusual. They told me, "Anything you can poke into to find out our results are not robust, we will be happy to hear it," and this is very unusual from a sponsor from industry. So I said, "Okay. Let's try the following. Send the data to us." So we had raw data, survival data, and also had secondary endpoints, so I'm going to share with you very quickly what we did.

Now, everybody knows now, the FDA has some concern about the 902 study may be a small size, and maybe there is some imbalance in the patients' baseline level, what we call covariates, so that's one of the concerns we're going to discuss today. Before I present in a robust way to analyze day 60 survival with covariate adjustment, allow me to show you what is exactly the same that the sponsor presented in the survival analysis Kaplan-Meier curve. You notice the blue curve is for the treated arm. The brown curve is for placebo or control arm patients. You notice the curve, the blue one, is always about the brown one, so

numerically we know the patients' survival profile is much better in the treated arm than the control.

Now remember there are 6 patients, four in the treated arm, two in the control arm. We don't know their survival status because they withdrew from the study. In the Kaplan-Meier, we actually assumed those 6 patients are censored, the survival data, which is a very popular way to handle this censored observation.

You notice they are only treating 60 days, so you use the Kaplan-Meier curve. You're using on the right-hand side the 60 days. You're reading the blue curve's value against the brown curve. That's what we interpret, 60 days survival rates between the two arms.

This is not adjusted with the baseline covariants at all. It's unadjusted. You notice with the treated arm patient, on average, 60 days survival is at 80.9 percent. The placebo is 60.7 percent. The difference is 20 percent. I have to say this. Even without adjustment, I never saw this kind of mortality benefit. This is not

relatively a reduction of mortality; this is absolute reduction. I don't think any trial -- so far I haven't seen -- in the COVID-19, we have such a dramatic difference in absolute sense.

In any event, the risk difference, or mortality, or survival difference is 20 percent, and you notice that the lower bound is 7 percent, upper bound is 33 percent, and the p-value, again, 0.0028, as Dr. Barnette showed us. The odds ratio is 1. That means there is no difference, and the lower the better in this case, but the FDA uses it the other way around, like flipping over or something. Again, it's highly significant.

Next, the method we used, we actually started to use the covariate information from the patient; that means the patients at baseline variable information. This is all prespecified in the protocol, and you notice the sponsor used the logistic regression because of the binary data with those covariate adjustments.

Another thing that's very interesting is because we had 6 patients without a survival

status, the sponsor used multiple imputations to figure out what's going on with the day 60 mortality for 6 patients. I believe the statistical method was actually shared with FDA. I believe FDA agreed with this plan, but in survival analysis, this is a little bit unusual.

We usually don't impute those censor observations, also we actually use a logistic regression covariate adjustment we call ANCOVA. It's very popular, but nowadays people start wondering, maybe we can relax this modeling. Instead of using logistic regression, can I do better? That means I don't use any model, model-free. I notice we have several experts in survival analysis on the committee today. We'll be happy to discuss it a little further.

So what we did is the following. We actually used a method called augmentation method, which also was recommended by FDA guidance for the covariate analysis and recently actually was published in 2021. It's very impressive. Actually FDA recommended also thinking about using

non-parametric, use a model-free method instead of logistic regression.

Of course, logistic regression still is one of the analyses that we usually do anyway, but if we do this in a non-parametric way, make adjustments for patients covariates, the first one, because we have 6 patients, we didn't know their survival status. So let's first drop the 6 patients because we don't know how to do this imputation, which I think is to ignore the imputation method [indiscernible]. How are we going to do it with 6 patients?

First, we ignore the 6 patients and the data and say, what happened? If we use this non-parametric augmentation method and adjust it, again, the difference is 20 percent and the p-value is still pretty impressive. In fact, this is a very interesting methodology. In fact, FDA asked the sponsor to perform such analysis I think maybe a month ago, so we did this augmentation method to actually answer FDA's questions about the augmentation method. Anyway, unadjusted is also

20.5 percent.

Now, because we didn't want to drop the 6 patients, what are we going to do with these 6 patients? Then we said, "Well, why don't we do the following?" You have 4 patients that were in the treatment arm and 2 patients in the control arm. We didn't know the survival status on day 60. Why don't we just put this in 4 patients, assign the treatment group, the old debt [indiscernible] at day 60. On any hand, those 2 patients in the control arm, we assume they survived on day 60, so we try to penalize the treatment group and saying, "Look. I gave you the worst case." What happened in this case?

Again, we used this augmentation method. If you noticed, without adjustment, you have 16.9 percent difference and the adjusted one, 16.8. They're almost identical. Look at this confidence interval p-value. The p-value for adjusted is a little bit larger, 0.0136. Now, remember this is a penalty against the treated arm.

Now, of course if you have survival data, we

usually use a Cox model instead of logistical regression, then we way, "Okay. Let's do a Cox model." I think the sponsor also did this Cox model. Again, if you do the Cox model, you don't have to worry about the 6 patients anymore because they are censored observations. If you look at this hazard ratio at 0.432 and the covariate adjusted for Cox model at 0.38, this is really very impressive, clinically speaking. Don't even worry about this p-value anymore. We ask ourselves, clinically speaking, do you think you have a survival benefit? I would say yes.

I finished the primary endpoint analysis, and we know, under the sun, any method we did, we have a treatment effect, and statistically and clinically very meaningful. The next one, the sponsor says, "L.J. Wei, why don't you try to analyze the secondary endpoint?" I said, "Fine."

Now, the first one, we are dealing with the hospital staying time. For example, the patients stay in the hospital 15 days and check out, so these patients are 15 days in the hospital. They

wanted to know, based on the time in the hospital, in this endpoint, what would happen between the two groups?

You notice the sponsor did an interesting analysis. Suppose a patient died at 10 days in the hospital, and we said, well, what would be the patients in the hospital days? The patient died. Then the sponsor actually imputed this number by 60 days. That means, "Sorry. I give you the worst number." But on the other hand, if you think about it, the patient died at 10 days, the in-hospital days shouldn't be 60 days. It's a very artificial number.

That's one of the methodology papers we published in Annals of Internal Medicine last year. For COVID-19, we encouraged people to think a little bit differently. We traced this endpoint a little bit. We said, "Hey, listen. Why don't you think it the other way around? You have 60 days of follow-up time. How about we say hospital-free survival days during the 60 days?" So I said, "What do you mean?" I said, "Well, if the patient

is in the hospital for 15 days and checks out alive," and we said, okay, 60 days minus 15, that's 45 days. So this guy, again, 45 days, happy days. On the other hand, you have a patient who died 10 days in the hospital. I said, "How many days did this guy survive checking out from the hospital?" Zero days.

So clinically speaking, this is a much better way to quantify this concept. So we use this endpoint slightly different from the sponsor, and you notice in the table, the treatment arm patient, on average, 36.1 days hospital free, and then they also survived. The placebo is 28 days. The difference is 8.11. Again, you can see it's statistically and clinically very interesting. In fact, if you notice in remdesivir, the original trial, those products probably give us 1.5 days, on average, for 28 days, but this is 8.11 days for 60 days.

For ICU-free survival days, we used the same definition, then we compared the two arms. You notice the treatment arm, 44.2 days, placebo,

34 days; again, statistically, clinically very meaningful. The next one is mechanical ventilation-free survival days. The difference is 9.29 days, and again, it's a pretty interesting result.

So I think that the concern about imbalance of covariates, I think FDA in the briefing document is kindly saying, "Well, maybe there are some differences among those patients between the two groups." They have some kind of a small discrepancy between the two groups. That's probably due to the small data set. But on the other hand, the FDA also claims, no matter what analysis -- and we made an adjustment any way we wanted to, and we couldn't find anything that would discredit this impressive mortality benefit.

Another thing I think FDA also mentioned is maybe there are some unobserved covariates. We didn't collect, so we cannot make an adjustment, so what are you going to do with this? They believe a large trial is probably ok, but in my humble opinion and so many years experience, you have so

many unobserved covariates, but those covariates are probably all highly correlated with observed covariates.

So if we make an adjustment with observed covariates, I don't think there's a big issue with those unobserved covariates. So in summary, I believe the efficacy of the treatment is solid, and I would emphasize clinically and also statistically very meaningful.

Allow me to introduce the next speaker, Dr. Sandrock, for further discussion. Thank you very much.

Applicant Presentation - Christian Sandrock

DR. SANDROCK: Great. Thank you, Dr. Wei, and nice to meet you all today.

I'm Christian Sandrock. I'm an infectious disease pulmonary and critical care physician here at the University of California, Davis. I'm actively involved in both clinical trials, as well as clinical care. I'm actually the ICU attending on this past week and this current week right now, which makes for things to be very entertaining. So

thank you for your time this morning, and I'll talk a little bit about risk-benefit assessment here as we move forward.

My disclosure's listed here. I don't have any equity or capital in any companies. I do have some grant funding, which is NIH, CMS, and CDC sponsored. I've been both a principal or sub-investigator in a number of clinical trials over the prior five years, and I have a number of speaking and advisory roles predominately within the antimicrobial world.

As we manage these patients here in the ICU and as a clinician at the bedside, unfortunately, the risk of death and serious illness from COVID-19, unfortunately, remains persistently high. I was just on this past weekend. We had a death directly from COVID-19. Yesterday, we had to place somebody on mechanical ventilation for COVID-19, so it still persists, unfortunately, a few years into this pandemic.

When we manage these patients in the hospital, as you can see, up to a third of them

that are hospitalized have some signs of acute respiratory distress syndrome, or ARDS, and that may be those patients on the floor with minimal oxygen support and they have some signs of ARDS. But, unfortunately, as they migrate into the more critical areas, into the ICU, requiring more ventilatory support, whether it's high-flow nasal cannula or non-invasive mechanical ventilation, or unfortunately, if they require mechanical ventilation, their mortality rate increases greatly, and that's predominantly due to ARDS.

What we're seeing now is that, at least in September and October, we have an average of 4[00] to 500 deaths per day still from COVID-19. So unfortunately that's still acceptably high, and it's really driven by these patients in our ICU with severe COVID-19 and severe COVID lung disease.

Now, Dr. Steiner did a nice job of highlighting some of the changes by variant of crude mortality, and I want to draw your attention over to the right-hand side. This is sort of the world we kind of live in as a clinician, and we're

really grateful for the interventions that have happened over the last couple years, whether it's been newer therapeutic options, vaccinations, other public health measures, and certainly as the variants have progressed.

Patients that are unhospitalized, we've seen certainly less severe disease in hospitalization, and for those that are hospitalized, particularly as you can see in that top table, there has been a decline from Delta, to early Omicron, to later Omicron. But as we move down that table, particularly in our patients in the ICU and those more severe patients, it still remains persistently high. Although it declined, this is still a persistently high mortality rate.

The second table below that really highlights, again, those WHO class 4, 5, and 6 patients, which make up the majority of the patients that are dying from COVID-19 now, they either have multiple comorbidities, they're over the age of 65, and they're in our ICU either requiring some form of advanced oxygen support,

whether it's high-flow nasal cannula or non-invasive mechanical ventilation, or they're on mechanical ventilation themselves.

You can see in that bottom table this subgroup, which is the subgroup study, is really the ones that are persistently still dying from COVID-19 and what we're seeing at the bedside. So it highlights that we still have this hole or this unmet medical need around these difficult-to-treat patients, which we're still seeing in our institutions on a regular basis.

Now, I really wish I had a crystal ball that can predict how this pandemic's gone and where it's going to go. I certainly in the last couple of weeks would have loved a crystal ball to predict where RSV are going. We're getting quite inundated with RSV here, mostly in pediatric, but definitely in our adult population.

So we, unfortunately, have to prepare for both ends of the spectrum, a best-case and a worst-case scenario. This is data from the COVID-19 Scenario Modeling Hub at the University of

Massachusetts Amherst, and you can see on the left-hand side a best-case scenario which we both at the bedside and both as a medical institution have to really focus in on, and we hope this is the direction it goes in.

Ideally, we have boosters that are now available, and most of our patients are taking up those boosters. Immunity and natural immunity, as well as vaccination booster immunity, remains the same, and that the severe risk infection remains unchanged. Even despite that, we're still looking at modeling predicting roughly, on average, 1600 new deaths per week towards the end of the calendar year.

Unfortunately, we still have to prepare for a worst-case scenario, and in this case there's a high immune Escape variant. This variant, even though we have reformulated boosters, doesn't quite provide the same immune protection with those boosters, and there's a 40 percent immune Escape that leads to roughly a 20 percent increased risk of hospitalization and death with this new variant,

and that could push our new deaths weekly towards the end of the calendar upwards of 4700.

So we really need to be ready, both clinically at the bedside, both from a pharmacy and therapeutics standpoint at our institution, but also as an institution and a community as a whole for both ends of these spectrums. So that's kind of how we approach a lot of our planning and treatment options, by looking at both of these. And I will admit, I'm a bit nervous as we enter into winter here with the way RSV has been going as well.

So when we look closely at the treatment landscapes and some of the limitations, again, we're expecting these COVID-19 surges to continue and to create a new strain in our hospital, or hospital capacity, to impact our ability to do some of our regular daily operations, but also to really make it difficult to manage some of these patients at the bedside. And our existing therapies, as far as numbers and as absolute and relative benefit, are modest at best.

So obviously, as I manage these patients at the bedside, they require moderates amount of oxygen, and they're in my ICU. We have some treatment options. Some can be antiviral like remdesivir, anti-inflammatories such as baricitinib, tocilizumab, and dexamethasone. All offer modest benefits at best, which we'll show you in a second. Unfortunately, a lot of the monoclonal antibody treatments are not indicated in these patients, and they're also very strange specific, so we don't have that option available to us as well. So again, there's really this unmet need for managing this subgroup of patients.

This outlays what we sort of do on a daily basis, and I can tell you, for all of our patients that we manage, this patient I just mentioned that we intubated and placed on mechanical ventilation yesterday, remdesivir, tocilizumab, dexamethasone, these are all things we're going to do on a regular basis at the bedside with all of these patients, and you can see that modest, absolute risk reduction as we move from left to right across the

screen, particularly as we get into tocilizumab and baricitinib.

Sabizabulin on the right; this is the New England Journal interim analysis data showing that 25 percent absolute risk reduction. This is the kind of unmet need that we certainly would like to have here at the bedside, so we can provide that sort of support. And this is just kind of a nice slide that lays the landscape of where we are as we manage these patients every day, and certainly how we can layer that treatment from remdesivir to dexamethasone in managing these patients. We certainly need something more than a modest reduction in death as we move forward.

As we look at this risk-benefit analysis, and as I sit at the bedside managing these patients, what are some of the things that attract us to this? What are these benefits in this hole that can be filled? And really, as Dr. Barnette and Dr. Wei outlined very nicely, there's a 20 percent absolute risk reduction and a 50 percent relative risk reduction in death at day 60. And

that's one, certainly as a critical care physician at the bedside, that really jumps out, and that's really spread throughout all of this meaningful subgroup analysis. And as the imbalances were analyzed nicely, and Dr. Wei did a good job of explaining this, there was still a clear benefit favoring sabizabulin across those different imbalances and subgroups.

If the patient survived, the other portion which really gets us interested is that the secondary end -- whether time in the ICU, days in the hospital, and time on mechanical ventilation -- those all showed improvement. So this is really that unmet need that we're looking for currently for these persistently difficult patients to manage.

Dr. Steiner did a nice job outlaying the phase 3 study placebo mortality that was roughly a little under 30 percent, and how this was in line at both 30 and 60 days with contemporaneous studies, and I think that's key for us. So really, this stubbornly high group of patients in our ICU,

in our hospital, with moderate to high risk for COVID death, they're still difficult to manage, and this is this unmet need that would really help support our therapy at the bedside.

How do we approach this risk-benefit analysis when we're sitting here at the bedside? Well, if we look at the benefits -- and I have a patient like this one that we just intubated, or one that's coming in and admitted with oxygen therapy, which I probably will get in the next day or two -- really what stands out for us is, obviously, the 50 percent relative risk reduction in mortality compared to standard of care. So that is the first and foremost, and secondary to that is we obviously get fewer days of mechanical ventilation; fewer days in the ICU.

All the data that we saw this morning, looking at both the trials specifically for COVID, as well as the cancer studies, show that it is really well tolerated. It's efficacious and independent of vaccination status and virus variant. Then when we have newer agents and we use

these at the bedside, one of the things we really like to see is that it's short term and that they're in the hospital. So this is 21 days or until discharge, so this is a short-term therapy, which is provided in the hospital, so that provides that added support.

Then lastly, not to be minimized but lastly, sabizabulin is a new chemical entity. It's its first in class, and then it works in two mechanisms. Number one, it decreases viral replication, and secondary, it's an anti-inflammatory. So it has two mechanisms of action in this subgroup of patients that we like.

So those are the benefits we look at, and we balance those out very closely with the risks. And we saw with Dr. Barnette's data a very nice description of the adverse events and serious adverse events in the phase 2 studies that were on the minimal side and certainly don't at all approach what the benefits would otherwise be.

Then secondarily, if we are going to see some safety risk that's associated with this drug,

they're with us in the hospital or they're under observation. We have ways to manage this, and manage them through direct care. So it's clear when we lay this out at the bedside, that the benefits for us as clinicians certainly outweigh any of the risks that we see, and that's very important for this unmet need that we have at this time.

So to sum everything up from our side of things at the bedside, I'm still seeing patients clinically here in our hospital. We still know that there are many deaths globally, greater than 6 million in total. We're still seeing greater than 400 deaths per day here in the United States. Our treatment options currently available to us have moderate benefits at best, whether it's remdesivir, baricitinib, tocilizumab, steroid therapy with dexamethasone, and having sabizabulin with 20.5 absolute risk reduction, a greater than 50 percent relative risk reduction at 60 days as far as mortality, with secondary endpoints reducing time on the mechanical ventilation and the ICU, is

really that unmet need that we're looking for at this time, and it really shows clear efficacy and a favorable risk-benefit profile that we would really like to have at our bedside.

I'm happy to take any questions later, and at this time I'll turn it over to Dr. Steiner for any further questions, and we can move to the next slide. Thank you.

Applicant Presentation - Mitchell Steiner

DR. STEINER: Great. Thank you, Dr. Barnette, Dr. Wei, and Dr. Sandrock. I appreciate it.

COVID-19 is still a public health emergency. We're still trying to understand and continue to be surprised by the public health implications of its evolving nature and potential threats. Death remains the greatest fear from getting COVID-19 in hospitals where patients are dying. The number of deaths remain unacceptably high. We want to do better. We need more effective tools.

Sabizabulin treatment and mortality benefit was robust and clinically meaningful, including in

every subgroup or sensitivity analysis of the primary endpoint conducted regardless of the observed placebo mortality rate. Further analyses, the small imbalances, and the constellation of these imbalances still supports sabizabulin's clear clinical benefit. The mortality benefit and secondary outcomes observed in our phase 2 and phase 3 COVID-19 sabizabulin studies were generalizable to today, as these high-risk patients studied are the same population that have the highest mortality rates today.

Sabizabulin has a strongly favorable benefit-risk ratio to prevent deaths in hospitalized patients with moderate to severe COVID-19 and high risk for ARDS, and death. Our program supports an EUA. We are committed to working with the agency to allow these patients in greatest need access to sabizabulin under the EUA and to collect additional clinical information post-EUA.

I would like to thank the committee for your attention and the FDA for the valuable advice and

collaboration on this project. We look forward to your questions and comments. Thank you.

Clarifying Questions to the Applicant

DR. AU: Thank you.

We will now take clarifying questions for Veru. Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

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

We'll start with Dr. Chertow.

CAPT CHERTOW: Okay. Thank you. This is Dan Chertow, and I appreciate all of the excellent

presentations.

My question is for Drs. Barnette and/or Wei, and it is really a simple and straightforward question as it relates to the various statistical approaches to determine a reduction in 60-day mortality in the drug group, and my question is this.

How many deaths would have to switch from from drug to placebo; in other words, reduce deaths with drug versus placebo? How many cases -- how many deaths would have to switch from one group to the other in order to erase the statistically significant difference in 60-day mortality using your various statistical methods?. That's the end of my question.

DR. BARNETTE: Hello. This is Gary Barnette. We've done some analysis on that, and it would be a fair amount. I mean, we would need -- we did the sensitivity analysis and the tipping-point analysis, where you move 4 and 6 deaths, and so on and so forth, and the p-values remain robust.

I would ask Dr. Wei to continue and answer this question.

DR. WEI: Thank you for the question. This is L.J. Wei. In our group, we didn't do this tipping-point analysis like you described, but in my presentation we did one sort of similar to what you described.

We have 6 patients, and we didn't know the survival status on day 60. Four were in the treated; two were in the control. So we were saying those four treated, we're assuming they were all deaths on day 60, but on the other hand, two in the placebo arm were alive day 60. I think that's the only penalty we considered, is a tipping-point analysis.

I think you raise a good point. Unfortunately, our group hasn't narrowed down to exactly what. Sorry about that.

CAPT CHERTOW: I'll just make a follow-up point to my question, which is that if one just simply does the proportion of cases that died in drug versus placebo, and you just swapped, and you

made your way down the line, and you swapped deaths in the placebo group into the drug group, and for the full study, that included all the 200 and some patients, in order to become equivalent proportion of deaths, it would be 9 patients that would have to switch. So presumably, the statistically significant difference in mortality outcome would be meaningfully less than 9 patients. Thank you. That's the end of my comment.

DR. AU: Thank you.

Dr. Evans?

DR. EVANS: This is Scott Evans at MD Anderson. I suppose this is for Dr. Steiner. I understand that the sponsor considers this intervention to be a strain agnostic intervention, and I see on applicant table 15 and on slide 31, assessments of the timing, the predominant strain different points. But nonetheless, an unanticipated imbalance in strain could have a significant impact on your patient outcomes.

So my question is, whether the sponsor has any sequencing data or other strain-related data to

demonstrate whether you have an actual balance between your patients?

DR. STEINER: This is Dr. Steiner. I'm going to ask Dr. Barnette to answer that question.

DR. BARNETTE: This is Gary Barnette. At the time of the initiation of the phase 3 and leaving the phase 2 study, we made a decision not to collect the actual variant because it was very difficult. We didn't know where we were going and what variant was going to show its face over the time, so we do not have the actual variant, but we do believe and propose that the timing analysis we've conducted addresses that fairly well.

DR. EVANS: Okay. I have additional unrelated questions, so I'll just allow my colleagues the opportunity to speak first. I'm going to lower my hand, and I'll re-raise it. That's just notice to the chair. Thanks.

DR. AU: Thank you so much.

Dr. Gillen?

DR. GILLEN: Yes. Thank you, and I'm going to stick to a clarifying question. I would just

like to get some feedback from the sponsor.

DR. AU: Dr. Gillen, I'm sorry to interrupt you. Can you please state your full name for the record, please?

DR. GILLEN: Oh, I'm sorry. Daniel Gillen.

DR. AU: Thank you.

DR. GILLEN: UC Irvine.

Again, a clarifying question to the sponsor, and this is with respect to the protocol amendments, and specifically with respect to the changes in the interim analysis and monitoring plan and the rationale behind those.

There's limited information in the briefing document on the original design assumptions that were made that defined the 300 patients that were originally planned, but I'm going to try and piece things together in terms of the timeline, and if I can get the sponsor to clarify some things for me.

So according to the FDA document, on January 9th of 2022, the interim analysis timing had changed from 67 percent maximal information -- in other words, occurring at 200

total patients to a 50 percent maximal information at 150 patients -- and the rationale behind that that's stated in the FDA briefing document was to limit the amount of alpha or type 1 error that was spent at that moment in time. I think that they phrased it as to conserve alpha at the final analysis.

Then 2 months later, the sample size then was changed from 300 total to 210. And one question I have there is, based upon what data and rationale -- because the FDA briefing document states that this is because it was difficult to recruit patients, and yet we're applying for an emergency use authorization. So those two things seem to not really coincide with one another.

Then I believe that very shortly after that -- but I can't understand the timing of it -- there was an interim analysis that was actually done because there was 198 patients totally enrolled by March 29th, so that interim analysis must have taken place on or near March 18th.

So one of my big issues is what was prespecified in terms of the interim monitoring plan; what were the guiding principles in changing the interim monitoring plan; and what data, if any, were those changes based upon?

DR. BARNETTE: This is Gary Barnette. Your timeline is accurate. The study was initially designed with 300 subjects enrolled, and the alpha level of 0.05 and the power in that particular was greater than 99 percent. As we moved forward, we were -- you know, recruitment into a clinical study, of a placebo-controlled clinical study, is always difficult, especially when you have hundreds of studies also going on at the same time.

So our original design was 300 subjects with a power greater than 99 percent. We do use the 60-day absolute mortality as the primary endpoint, and as Dr. Wei outlined, that's a difficult endpoint to hit. So we did adjust the interim analysis number down to 150 because we felt like that would be a sufficient number of patients in the interim analysis to make a judgment of whether

we should continue the study or not and whether the drug had effect. So that's why that analysis -- or that protocol amendment was executed.

There wasn't any data, or unblinding, or knowledge of any kind of unblinded data in that particular decision. As we were going forward into the spring, it became apparent that while recruitment was still ongoing, it was slowed. It significantly slowed at the sites that we had. As we all know, the recruitment in these kinds of studies waxes and wanes heavily, and we were making a projection that it would take us somewhere between 9 and 24 months to finish enrollment out to to 300 and, frankly, we felt like as an organization we made a business decision that we had to make decision earlier. And remember, we were way overpowered at 300.

So we made a decision again, prior to any interim analysis and any unblinding of the data, we made a decision to drop that N back from 300 down to 210. The interim analysis, the planned interim analysis, was conducted on April the 8th, and at

that time -- and, again, that was the analysis of the first 150 patients randomized into the study. And at that time, we had 204 patients randomized into the study, but at that time, also, we only had one patient in that group that was continuing on treatment, and we allowed that patient to finish out treatment, the last few days on treatment, and then finish the follow-up, the 60-day follow-up, in the full 204, and that's the data that we've been presenting today.

DR. WEI: Dr. Barnette, this is L.J. Could I make some comment to answer Dr. Gillen's question?

DR. BARNETTE: Please. Yes, sir.

DR. WEI: Dr. Gillen, a good question.

I don't know exactly the history of the interim analysis plan. I read it like you read it, from the post-documents. But in my humble opinion, the interim analysis was based on the data from 150 patients only, but even though they enrolled 204 patients at that time, they didn't use the rest of the patients beyond 150, so they got a very

interesting result. The DMC people were just doing according to the book. They said, "Well, we have to terminate a trial." That's what they decided.

Now, an interesting part, we can't always claim or say the interim analysis, based on 150 patient data, may be too small. Maybe just by chance you are lucky to get this extremely interesting result. On the other hand, afterwards they followed the 204 patient data, and still the benefit is still consistently very impressive. I think that's sort of like we double checked if the first interim analysis, the results are really by luck, or really something's cooking here? So let me stop here. Thank you.

DR. GILLEN: Thank you, Professor Wei. I appreciate that. My question really revolves around what was prespecified. I know that you know that one can sample to a foregone conclusion in trials, and you can certainly change the inference that's accrued through a trial by moving that first initial analysis back in time if that's done in the observation of an effect, and then changing the

maximal sample size to then lower what the critical value would need to be.

So I'll take the sponsor's word for it. I just wanted to clarify exactly what the decision-making process was. I do have one comment, though.

If your interim analysis on April 8th was on 150 completed patients, and I give you, I'm going to say, 30 days for a data lock, on March 29th you had already enrolled 198 patients, but then probably within 60 days, you guys had enrolled 48 patients approximately, if I'm doing this math correctly, 60 to 90 days maybe, depending upon how long it took you for the data lock and cleaning, which doesn't seem like very terribly slow enrollment to me on your projections. But maybe you can clarify that later for me.

DR. AU: Great. I enjoy this robust discussion.

In the interest of time, let's continue to move on, and then we can maybe have the sponsor come back or we can further discussion later in the

session.

How about Dr. Shaw?

DR. SHAW: Yes. This is Pamela Shaw. May I have a clarification from the chair? I have three clarifying questions. I do believe they're short, but is it okay to ask them one after the other? May I just have clarification on that?

DR. AU: Yes, please go ahead and do that.

DR. SHAW: Okay. Thank you.

My first question is for Dr. Steiner, and I believe it's slide 14 or 15 of your presentation. It was the graph showing the mortality rates of different trials, I believe, on the placebo arms.

I don't know if you'll get a chance to put that up, but I'll just ask my question which is, I'm trying to understand how comparable these different trials are, and they're being labeled as contemporaneous. I guess I'm wondering for that graph -- maybe the slide before this; I believe it is the slide before this -- how many of those trials would have been contemporaneous from the point of view that the overwhelming majority of

patients would have been during the same time frame, which was roughly Trial 903, roughly May 2021 to June 2022? Because I know that the case fatality rate was really changing over time, and was really high at the beginning of the pandemic.

To boil my question down, I want to make sure that it's the similar eligibility criteria and similar time frame. So for the severe patients, for Trial 903, we have an 8-point WHO scale, that to be eligible, it excluded WHO 7. So I'm kind of wondering amongst all these dots, which of these trials would have excluded WHO 7 and would have had patients at the same time as Trial 903? Because that's kind of what we're trying to compare this placebo mortality rate to.

Do you have a sense for which were contemporaneous and not including that most severe group amongst all these trials?

DR. STEINER: This is Dr. Steiner. All of these trials were overlapping. I mean, we're only talking about the pandemic occurring for 2 and a

half years, so within the scope of the months, they were very close to each other in months, and many of these trials were overlapping.

But your point's a good one. What we did is we didn't look at WHO score because WHO scores changes. As you know, in some cases, WHO 4 is a patient without oxygen. So we went back for the studies that actually laid out who was on mechanical ventilation and what was the patient population that was on non-invasive forced oxygen. We need to know that information because some of these trials, as you mentioned, you just kind of lumped it together, and you can't really tease that out.

So a second test for this analysis -- and that's why there's 15 -- is they had to specifically tell us what that patient population was, not whether the WHO score was a 5 or a 4 because there was some overlap.

I'm sorry. I didn't mean to cut you off.

DR. SHAW: No. That's alright. I appreciate your response. So my understanding is

it is a little hard, like that WHO 7 or the most severe of the mechanically ventilated --

DR. STEINER: Yes.

DR. SHAW: -- which also -- you can't really tease that out.

DR. STEINER: What I can say is that, particularly, there are some of these trials where they may have had -- for example, we were calling that WHO 7, which is ECMO, but they were less than 2 percent. So we had another version of this slide where we put that in, and we felt it would be distracting, so it would be unfair not to include that trial if 2 percent of those patients were an ECMO because 98 percent were either going to be mechanical ventilation -- WHO 5's as we're calling it now -- and that was the group that we're trying to get.

So I think the importance here is the number of trials and getting concrete information about the severe patients, and whether there is a correlation. So that gave us comfort that we were in range.

Then the real-world data from the CDC, which was the second slide I showed, that again shows you all hospital -- and my slide doesn't have this, but Dr. Sandrock's slide has it. And it shows, yes, we're doing a much better job with all patients in the hospital, but when you focus on the ICU patients, the WHO 5's and WHO 6's, we're still going down, but these are the patients that are contributing to the death rate, and this is the patient population our drug is indicated for.

DR. SHAW: Thank you very much for that response. I agree with you that perhaps the WHO 7's are a small percent, so while they do have an elevated death rate perhaps because they were a small percent, it's not clear how much they would have elevated.

DR. STEINER: Yes, it would have been small.

DR. SHAW: Yes. But I wanted just two quick comments. One is, according to table 30, some of those trials were published before 903 even started because RECOVERY, for instance, those were really quite quick, those early [indiscernible] trials.

So some aren't overlapping, I believe, and I am a little hesitant to compare the EHR or the nonclinical trial population because, as we know, individuals and clinical trial populations tend to have less social disadvantage and be a different racial mix than other things, so a little harder to compare. But I do really appreciate that graph, and I think you've answered my questions regarding the clinical trial populations. Thank you.

DR. STEINER: Thank you.

DR. SHAW: My next two questions are probably shorter. The next one, I believe it's for Dr. Barnette. This is just a quick question, clarifying question, regarding the 6 individuals who were lost to follow-up, who's mortality status at 60 days was unknown.

Can you say whether or not those 6 patients, the censoring was related to the discharge, where they discharged from the hospital?

DR. BARNETTE: This is Gary Barnette. The censoring was related to our last contact with them, or last known, vital status was known. These

6 patients were doing very well, were discharged from the hospital, and I think one of them was the last contact we had was at discharge, but a lot of them, we were making follow-up calls with them, so the decensoring is the last point of contact.

DR. SHAW: Okay. Great. Thank you. I think you answered my question, which is they were all discharged, and maybe some of them got followed a little bit later. Thank you. That answers the question. Thank you.

My final question is for Dr. Wei. I'm very interested in all the sensitivity analyses, and I had a quick question. I think it was slide 53, which is the worst-case scenario, I like to call it, where you you think about those 6 patients for whom you don't know of that 60-day survival status, and the worst-case scenario in terms of the drug efficacy would be you think about the four that were unknown status on the drug arm and you impute has died, and the two unknown survival status on the placebo arm you impute as alive, and you see how much that might degrade the observed treatment

effect.

My question for this analysis -- I believe [indiscernible] the exact slide -- is I think I understood you to say that this was an augmented analysis. That's a bit of a black box since we can't unpack here, but I wondered how much that augmentation really mattered, and if you had done the p-value from just a standard analysis where you would have done this imputation, how different would that p-value really be, if you knew that?

DR. WEI: Sorry. This is L.J. If I understand your question, ma'am, you're saying if I'm imputing those 6 patients, either they died at day 60 or not, what is the usual way we analyze this data?

DR. SHAW: Yes.

DR. WEI: As you know very well, if you use survival analysis, and we can easily handle this patient, assuming those guys -- like Gary is saying, we take this last contact date as a [indiscernible] observation. We do Cox regression stuff, and you can actually --

DR. SHAW: But can I --

DR. WEI: Sorry, ma'am. Go ahead.

DR. SHAW: I was just going to say, actually, in a severe population, there are many people who aren't willing to do the usual survival analysis, knowing that you know that they've been discharged. I'm actually interested in the logistics. Just because it's 60 days, that's very standard to do a 60-day mortality of logistics. So just for the logistics, making it super simple -- I'm a simple person -- just a super simple analysis, you've done imputations, there's no missing data, this worst-case scenario, is the p-value much different from this or is it similar? Because I understand this is an augmented p-value; this isn't a standard p-value.

DR. WEI: I'm sorry, Dr. Shaw. Could you repeat your question? I'm sorry, because of my age, probably I don't understand what you're asking.

DR. SHAW: My confusion is around this idea of augmentation. Were these p-values -- was this a

logistic regression p-value here?

DR. WEI: Oh, I see what you mean. I'm sorry, Dr. Shaw. Yes. If you use just regression doing this, you get the same result. It's almost identical.

DR. SHAW: Okay. Thank you, a very simple question. Thanks, Dr. Wei.

DR. WEI: Sorry about that. Thank you.

DR. SHAW: That's it.

DR. AU: Thank you so much.

Dr. Baden?

DR. BADEN: Yes. I have two clarifying questions. I can ask one, and then get back in line. Just building on Dr. Lee's question, really trying to understand who's in the study, what I'm getting at in particular is the WHO 4 with oxygen and at least one comorbidity, and this is probably to Dr. Barnette or Steiner.

Am I supposed to understand that we think there's a 45 percent mortality for WHO 4 with 2 liters of oxygen? Because I want to understand the benefit based on the risk of who entered the

study and is it that the WHO 4's, 5's, and 6's all behaved identical, then I need help to understand what that baseline staging -- how it tells us who was enrolled.

DR. BARNETTE: This is Gary Barnette. Who we enrolled were WHO 4's with at least one comorbidity. Now, let me clarify. The average number of comorbidities between the treatment groups is about 3 and a half, so it wasn't like a patient came in with just one comorbidity; usually it was multiples, as I showed in that one distribution slide.

The placebo mortality rate that we observed in the study, again, the 45 percent at the interim analysis and 39 percent in the overall analysis was an aggregate of all the WHO 4's, 5's, and 6's. We did stratify randomization by WHO 4, 5, and 6's, and it worked fairly well, and that's who we enrolled.

Now, what you'll see if you look at the WHO 4's independently, the WHO 5's independently, and the WHO 6's independently, is you see a

relative reduction in mortality across all three of those groups. As a matter of fact, the reduction in mortality in the WHO 4's is about 82 percent and the reduction in mortality in the WHO 6's is approximately 50 percent. So you see the benefit across all WHO categories that were enrolled.

DR. BADEN: But the WHO 4 mortality, how did that behave in relation to WHO 4 mortality in the literature, in the placebo group? I'm trying to understand the WHO 4's in relation to what we would expect their mortality to be for who these patients are.

DR. BARNETTE: This is Gary Barnette again. This is a difficult question to answer because this is not just a simple WHO 4, it's a WHO 4 with multiple comorbidities in this situation, and many of the publications in the literature don't really outline it that way. We had approximately a 30 percent mortality rate in this population in our study as we demonstrated in the placebo group. It was 27 6 percent at day 60.

Yes, slide up. Table 12, slide up. Here's

WHO 4's, 5's, and 6's broken out. I think this is from the briefing book. As I said, the mortality in the WHO 6's are also small numbers, about 50 percent.

DR. BADEN: I appreciated this. Thank you for the clarification. This to me, at least, says that the WHO 4's that you enrolled are not average WHO 4's. They're WHO 4's with a high -- very sick WHO 4's.

DR. BARNETTE: Yes, that's correct.

DR. BADEN: With a 30 percent placebo mortality, that's not an average WHO 4 staging, at least in general clinical practice. Thank you.

DR. BARNETTE: That is correct.

DR. AU: Great. No further clarifying questions, Dr. Baden? If not, I'll go to Dr. --

DR. BADEN: A second one, but I can come back to it just to allow people to all share their questions. I would like to ask it right now. I can ask it quickly.

DR. AU: Yes. I think we should just plow through it.

DR. BADEN: Okay.

Then what I'll ask, again, Dr. Barnette, your slide 34, you point out the viral load at day 9, and you show that it went down 42 percent in the treated and up 412 percent in the placebo. That seems very unusual to me in that viral clearance occurs with time. So to have viral augmentation 10 days into this with all the standard of care seems unusual to me.

Do you have data of serial viral -- are we able to see data of the viral load over time or by group and absolute values to better understand what's going on here? Because again, it makes me worry that I don't understand the placebo group because they're not behaving in the usual way.

Any clarification is appreciated. Thank you.

DR. BARNETTE: Yes. This is Gary Barnette. The way we collected this was at baseline through a swab, so you understand the issues with the variability that introduces. And then we planned to assess it at day 9 or if the patient discharged

from the hospital prior to day 9, meaning last one, so we didn't collect that swab. So we really only did baseline and one study. We don't have serials. If the variability is very high, it's difficult to interpret. As I mentioned in my presentation, the p-value is 0.2712. When we go to our additional studies, specifically the WHO 3's and 4's, I think we'll collect this more rigorously, and I think that will elucidate this situation a lot.

DR. BADEN: Thank you.

DR. BARNETTE: You're welcome.

DR. AU: Dr. Lee?

DR. LEE: Thank you, Dr. Au. Janet Lee.

I have a question, actually two questions, but the first question actually Dr. Baden asked. The other one is related to requesting further clarification of the design of the study.

It's my understanding the WHO 4 with comorbidities, WHO 5, and WHO 6 would be straddling both inpatient hospital wards and the ICU. And I wanted to ask you about variability of time of enrollment that you touched upon -- I think it was

Dr. Steiner -- and 6 patients within the Vero 113 group had greater than 14 days in the hospital prior to entry of the study.

I just wanted to ask you, do you have any information related to how many were WHO 4, WHO 5, WHO 6 related to the time of enrollment just to get a better understanding of the potential imbalances of the two groups. Thank you.

DR. BARNETTE: Yes. This is Gary Barnette. Slide up, please. We had 6 patients in the treated group that were in the hospital for greater than 14 days prior to coming into the study. You're stretching my memory, but I think there were three or four WHO 4's and two were WHO 5's coming in when they started into the study.

You know, I think the argument is some people would think that those patients who've been in the hospital for a while actually would have a higher incidence of progression, or another observation would be they were progressing more slowly, of course.

What we did -- and these are the data that I

mentioned in my presentation -- we just basically said, okay, if this was [indiscernible], let's take these 6 patients out of the analysis, and you can see that the p-value is 0.0046 with an odd ratio of 2.71. And this is actually the curve that the FDA presents in their presentation, but we've blocked out the top blue line that actually obliterates those 6 patients, and you can see that the mortality benefit is maintained.

DR. LEE: Thank you.

Actually, what I was asking about was related to not only the people where the enrollment was greater than 14 days in entry, but related to also the placebo group, as well in terms of do you have information related to when actually they were enrolled in terms of entry into the study, in the ICU versus in the hospital wards?

DR. BARNETTE: This is Gary. That's an interesting question because it is difficult to answer. What we did is we classified them by WHO 4, 5, and 6, and not whether they were in the ICU or not because, as you mentioned, they did dose

straddle. And frankly, that availability as the standard practices at individual hospitals might differ whether they're in the ICU or not, but whether they need supplemental oxygen, forced oxygen, or mechanical ventilation is pretty standard to get their oxygen, their SpO_2s up high enough through that support.

So we did not analyze it by ICU versus non-ICU and that kind of thing because it has an inherent variability of operational nature rather than just a patient care nature.

DR. LEE: Thank you.

DR. AU: Thank you.

Dr. Walker?

DR. WALKER: Hi. Dr. Roblena Walker. Thank you all so much for your presentation. I just had a quick curious question, because we all know since the pandemic, study analyses have shown that people of color have experienced a very high disproportionate burden of COVID cases, as well as deaths, so there's a plethora of comorbidities and racial disparities that we can spend hours on hours

talking about.

Nonetheless, with that being said, I'm just curious, from a demographical standpoint, why was only less than about 5 percent of the patient population African Americans? Were they just not assessable or available; if you could speak to that?

DR. STEINER: Yes. This is Dr. Mitchell Steiner. We recognize that the phase 3 study did not enroll a lot of people of color, and it's not because we didn't try. As you know, this is a problem across clinical trials. I mean, we did conduct a study not only in the U.S. but Latin America and Europe, again, trying to get a diverse population, so we tried.

With that said, we're not expecting the biology to be different. I mean, microtubules are conserved across people of color and all humans, period, so we expect them to have the same benefit. But as you heard from Dr. Barnette, we do plan to conduct additional clinical studies and related indications, and we are going to have an emphasis

on recruitment of diverse populations, and we're doing that several ways, including, again, casting a net to get diverse hospitals with diverse populations involved, and there are actually third parties that you can engage that will help you specifically do that.

Now, with that said, under an EUA, for example, people of all races that meet the criteria of our product will have access to our product. And the reason that's important is that gives us an opportunity to follow them and get the additional safety information, and potentially more.

DR. WALKER: Thank you.

DR. AU: Thank you.

Dr. Evans?

DR. EVANS: This is Scott Evans, and thank you. A lot of the questions I planned to ask have been answered, but one from Dr. Baden has stimulated another thought. And I guess this is for Dr. Steiner because he presented most of this. But interpreting outcomes of the studies, or any study, depends on our understanding of

plausibility, which raises some mechanism of action questions, so I have mostly a preclinical development question related to the claims.

So it was stated in the sponsor Section 4.2.2 and slide 34, and in a few points in the presentation, that there is an antiviral effect. So I just want to understand what's actually known in that sense because as Dr. Baden pointed out, we have some unusual behavior between the two groups.

Am I correct in understanding that what was done preclinically was that Vero E6 cells were infected, and then the supernatant was collected and applied to additional cells, and then a viability assay was performed at that point, and it was from that -- yes, exactly -- that it was inferred that there was a reduction in viral replication.

The question, or what I'm getting to here, is that I'm wondering that if you have an agent -- if you have a molecule that disrupts microtubule function, what may be actually

happening is you may have an impairment of viral release, whereas if you had actually sampled the Vero E6 cells that were initially infected and done qPCR or plaque assays on life cells, that you may find there was not, in fact, an impairment of our replication, but of release.

Is that your understanding?

DR. STEINER: Yes. This is Dr. Steiner. That's exactly my understanding, and we have other lines of thought and other viruses. So that's why this assay was important to do because what's happening here is, as you know, even within coronavirus, they have a different requirement for intracellular microtubule trafficking and production versus egress and release.

So in this situation what appears to be happening with sabizabulin, and we see this in what we demonstrated in the slide that's up, is that also in pox virus, for example, when you're able to look exactly as you had mentioned, it looks like it's playing a major role in the export/egress release, and that's why this kind of assay was done

so that we can understand that part of it better. But that's exactly right.

I want to be very clear, we're not a, quote, "antiviral" in the sense that we affect something in the virus or protein that the virus has. As you mentioned, its microtubules, so it's consistent that interference with release or egress of the virus would make the most sense.

DR. EVANS: Okay. Thank you.

Just to further clarify, it is my understanding that there are no in vivo data, either preclinical or clinical, looking at systemic virus; is that correct?

DR. STEINER: No. We have a model that's an NIH model for ARDS, but in that model, it was a crude model done for only 5 days, so the information was not very clear. But the purpose of that model was to look for lung inflammation, so the endpoint was that.

So yes, we have an in vivo study, but the problem is the in vivo study didn't really tease that out because of the timing and the kind; it was

an adapted SARS-CoV-2 murine virus. But when you look in a dish like this and, again, in other viruses that we've looked at nonclinically, this looks like the mechanism.

DR. EVANS: Okay. Thank you.

DR. AU: Any additional clarifying questions for the sponsor?

DR. BADEN: Yes. This is Lindsey; when it's my turn.

DR. AU: Oh, I'm sorry. I don't think I saw you on our list.

DR. BADEN: It went off and came back, but I'm in turn with everyone else.

DR. AU: Dr. Baden, why don't you go ahead? Go ahead.

DR. BADEN: Just want to follow up on Dr. Lee's question, which was the slide 16, sort of the swimmers plot that Dr. Barnette showed. For those individuals who were hospitalized for a prolonged period of time before being treated, what was the trigger to treat them? Why at day 10 or 14 was the decision made to treat this patient now who

had been in house for so long?

A second clarifying question, which is very different, is the dose at 9 milligrams, please help me understand how you arrived at that dose and why you think that's the best dose to go forward. Thank you for clarifying these issues.

DR. BARNETTE: This is Gary Barnette. The decision to treat could have been multivariant. We could have had patients who actually progressed to WHO 4 and qualified them for the study. Also, sometimes patients are a little reticent to join a clinical trial, and then once they get to a point where they start progressing, then they come in. It's difficult to tease that out. We did not really look at this and investigate this clearly, but I think those are the two logical reasons.

Now, as far as the 9-milligram dose goes, when we initially approached the FDA back in March-April of 2020, we had run the toxicology studies. So the 9 milligram, or the equivalent to the 9 milligram, was done based on the human equivalent dose with a safety margin, a 3-fold

safety margin, to the no adverse effect level in the tox studies, and that, in particular, has shown -- the reason why we think it's an appropriate dose is because we really propose that the clinical data basically showed that it is highly effective in reducing mortality, and the safety observations are minimal.

So while we didn't do a traditional dose finding, we did justify this dose based on the HED, and we think the clinical data support this as the right dose.

DR. BADEN: Thank you. That makes sense. So if I'm to understand, the decision to enroll them and treat them was either they finally decided they wanted to -- the participant decided they wanted to participate, or more likely there was some form of progression which suggested additional treatment would make sense, if I'm understanding what likely went on. Thank you.

DR. BARNETTE: Yes, that's correct.

DR. AU: Great.

Before we move on to Dr. Seam, can I ask, if

you have your hand up and have spoke, could you lower [inaudible - audio gap] if you don't have a follow-up question. We're trying to gauge the pace of the conversation.

Dr. Seam, please go ahead.

(No response.)

DR. AU: Dr. Seam, you're on mute.

DR. SEAM: Thank you. This is Nitin Seam. I had a little trouble hearing you there, Dr. Au, for a moment. I apologize.

I wanted to follow up on, I think, something that Dr. Baden had brought up about the question about the placebo mortality and the WHO 4 being a little over 27 percent.

I just wanted to clarify. I think not in this presentation, but in reporting the interim analysis for the 150 patients, the placebo mortality was 35.2 [inaudible]. And then after the full 204, the other 54 were included, and I think that has dropped down to 29.4. I didn't see it broken down. I don't know if you all have that and I just missed it. But what was the placebo

mortality for the subsequent 54 patients after the 150 that were in the paper?

DR. BARNETTE: This is Gary Barnette. You're reading the differences exactly correct. Incidentally, after the additional 54 patients, who were predominantly WHO 4's, and with comorbidities included in the study, naturally the placebo mortality rate in that particular subset of those 54 patients were consistent with the WHO 4, which is lower than the WHO 5, lower in the placebo mortality than the WHO 5's and 6's.

DR. SEAM: Do you happen to have what that mortality was for those 54?

DR. BARNETTE: Fairly. Okay. Go back.

At day 29 in that 54 patients, the interim analysis, we had 35.2, 18 deaths out of 51 patients. Then at day 29 in the full, 2 patients in that 54 patients at day 29 passed or died, in the placebo group, so 2 out of 17 or 18.

DR. SEAM: Okay. That was 2 to 1, right?

DR. BARNETTE: Yes.

DR. SEAM: That's [indiscernible] 17?

DR. BARNETTE: Yes, 2 out of 17.

DR. SEAM: Okay. Thank you for --

(Crosstalk.)

DR. BARNETTE: -- 49, and day 60 it was more.

DR. SEAM: Yes. Thank you for clarifying.

DR. AU: Dr. Kim?

DR. KIM: Edwin Kim, University of North Carolina. My question comes back to an earlier discussion on mechanism. It seems proposed that there's antiviral as well as an anti-inflammatory effect of the medication. And I'm wondering from the sponsor whether there is a feeling of one effect to being stronger or more important than the other.

Where this question is coming from, this thinking about it, is there's sort of an ideal timing to the application of this medication, whether early on in infection if it's an antiviral effect, or later on -- as I think where a lot of this discussion is -- to prevent more the inflammatory ARDS picture. Thank you.

DR. STEINER: Yes. This is Dr. Mitchell Steiner. To answer your question, it's hard to tease that out because we had the 9-milligram human equivalent -- the 9-milligram dose, which is a concentration we can achieve in our nonclinical studies. We have pretty robust anti-inflammatory activity and pretty robust -- and again I'm going to be careful. It's antiviral because it stops the release of the virus by going after microtubules but doesn't affect the viral protein, for example, but the net of it is it's an antiviral.

So the way I would look at it is -- and Gary, Dr. Barnette, outlined this -- when you look at the WHO 4's -- and we actually had published this in IDWeek -- you see about an 80 percent reduction in mortality in that group. So what that's telling you -- and this is where you're going -- is when you look at the NIH guidelines, for example, it's all based on the pathophysiology, which is you start out with a viral load that goes up, triggers the immune response that ends up being and overexaggerated immune response, and then you

get ARDS, multiorgan failure, and death.

So the idea is you use your anti-inflammatories later and you use your antivirals earlier. Well, in this situation, as you know, remdesivir doesn't have mortality benefit, so we see a mortality benefit, whether it's because of the antiviral, or anti-inflammatory, or both. But it certainly lends a possibility that sabizabulin can be used earlier because it would be the only one of the agents that has the antiviral effect and a mortality benefit.

DR. KIM: Edwin Kim. Again, I have a follow-up to that on slide 28, the subgroup analysis of the primary endpoint, a somewhat related question.

There it seems that the ranges are wider when they're already on standard-of-care therapies, and is there some thought, again, to the timing of how this medication will be used compared to some of these standard-of-care therapies like tocilizumab or JAK inhibitors? Thank you.

DR. BARNETTE: This is Gary Barnette. What

you're seeing with the widening of the 95 percent confidence intervals, really, the number of patients in each one of those groups is probably contributing to that. The point here is that regardless of how you look at it, the absolute risk reduction is maintained.

As far as ghosting and the use of sabizabulin in conjunction with all the standards of care, as I showed in my slide, essentially, everybody in the study got a systemic corticosteroid, so I suspect that is the standard of care that can serve, really, no matter where you go. I think everybody should be on the best standard of care. Then, of course, you add sabizabulin when they qualify for the study, for dosing, meaning WHO 4 with comorbidities, et cetera, et cetera, et cetera.

As far as the others, I think that's a practice of medicine question, and I would ask Dr. Sandrock if you would opine a little bit on the use of these other standards of care.

DR. SANDROCK: Thanks, Gary. I think you

highlighted it nicely. We would like to start these early, and we always do. As the antiviral replication then progresses into an inflammatory phase, earlier is always better. So if we look at the average WHO class 4 patient who's required oxygen, multiple comorbidities -- and this is certainly a subgroup that they hopefully will have remdesivir by the time they're at that point -- and because of the required oxygen therapy, steroids will be involved, this is, at least from a clinical perspective, the ideal time where we would like to start some sabizabulin.

What we do like with the data is if we miss that window and they end up requiring more advanced therapy for their oxygen, all the way through mechanical ventilation, we feel pretty comfortable at those time points as well. So really, the sweet spot clinically is, I think when we would be considering the other anti-inflammatory, tocilizumab and baricitinib, this would be layered on top of that, roughly around that same time frame. Thank you.

DR. KIM: Thank you. And again, some of these questions are coming from thinking about what a potential future study might look like as well. No follow-up questions. Thank you.

DR. AU: Thank you.

This has been a very robust discussion. I know that we have three hands that are still up in the room. We are, though, about 30 minutes over, so I think I'm going to need to take the chair's prerogative and ask that we take a break.

After the break, we'll move directly to the FDA's presentation. I would recommend that we take a five-minute break, which would put us -- my clock says 11:37, so I would ask that we come back around 11:43. Sorry for that degree of precision, but I feel like we're getting a bit behind, and I think we need to kind of keep pace. So why don't we see each other in about five minutes? Thank you so much.

(Whereupon, at 11:37 a.m., a recess was taken.)

DR. AU: I hope everyone had a nice break.

We will now proceed with the FDA presentations, starting with Dr. Robert Busch.

FDA Presentation - Robert Busch

DR. BUSCH: Thank you, Dr. Au.

Good morning, and thank you all for taking the time to attend this advisory committee meeting today to discuss the data submitted by Veru Incorporated. My name is Robert Busch, and I'm an FDA medical officer and pulmonary critical care physician at the Atlanta VA Medical Center, and I'll be presenting the FDA's talk today, along with my colleague, Dr. Sai Dharmarajan, a senior mathematical statistician here at FDA.

The FDA's presentation today will follow the outline presented here. First, I'll present some background information on the VERU-111 EUA request on COVID-19 and on the clinical development program for sabizabulin, which the FDA presenters will call VERU-111, focusing on study V3011902, which I'll call Study 902, as the primary source of data for the authorization request, and then I'll move on to presenting a review of safety data.

After that, Dr. Dharmarajan will present the efficacy results with a focus on all-cause mortality. Then Dr. Dharmarajan and I will present the uncertainties and clinical considerations in the interpretation of results. So with that, we can get started.

VERU-111 is a new molecular entity not approved for any indication in the U.S. or worldwide. It's an oral tubulin inhibitor that binds to the colchicine binding site of microtubules and prevents cross-linking.

As a drug substance, VERU-111 is characterized as a white or whitish to yellow-brown powder. The drug product used in Study 902 was a formulated capsule, which comprised an off white, to light tan, to yellow granulated powder of the drug substance and additional excipients. We bring this issue of the color of the capsule contents up to provide context for discussion of potential unblinding later.

The proposed dose used in the primary trial was 9 milligrams by mouth or by a nasogastric tube

daily for up to 21 days or until hospital discharge. This is just a reminder of the WHO Ordinal Scale for Clinical Improvement. Subjects with WHO 5 and 6 baseline severity and a subset of WHO 4 severity were enrolled in the studies of VERU-111.

The sponsor is requested emergency use authorization of VERU-111 with the following context of use: for the treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 and who are at high risk for developing acute respiratory distress syndrome or ARDS.

The sponsor's proposed use includes at high risk of ARDS, and trials of VERU-111 represented that as shown on this slide. However, this term doesn't really have a clearly defined meaning from a regulatory or medical perspective, and it's a source of uncertainty in the EUA, which we'll discuss more later.

With that background on VERU-111's request, we can move into the overview of the clinical

program. This is the outline I'll follow as I review the program. I'll start by reviewing COVID-19 and its impact, and much of this background will be reviewed to many of you on the committee.

COVID-19 is a serious and life-threatening disease syndrome caused by the SARS-CoV-2 virus. The World Health Organization declared COVID-19 pandemic on March 11, 2020. Both the worldwide and U.S. impact of COVID-19 have been profound. Worldwide, the WHO reports over 623 million cases and 6.55 million deaths attributed to COVID-19. The CDC reports 96.9 million cases in the United States since early 2020, responsible for almost 1.1 million deaths.

As of mid October, the CDC reports over 37,000 new cases per day, over 3,000 new admissions for hospitalizations per day, and over 300 deaths per day in the United States. So the impact of this disease is still being felt every day in America and the world.

Over the course of the pandemic, new

variants of concern have appeared, leading to differences in transmissibility, virulence, and disease severity over time. Most of us understand these differences from treating patients during times like the Delta surge and the Omicron surge. SARS-CoV-2 infection can result in a wide spectrum of clinical manifestations, ranging from asymptomatic infection to critical illness, but for this discussion, we're focused on hospitalized disease and subjects with hypoxemia.

Some of these patients will progress to severe and critical hospitalized disease, with pulmonary disease characterized by pulmonary inflammation and early ARDS physiology, as well as extrapulmonary manifestations of dysregulated systemic inflammation, hypercoagulability, and even septic physiology with shock and organ failure. As subjects continue to progress, their critical COVID-19 course is generally characterized by refractory critical illness, progressive organ failure, severe ARDS, and death.

So now we can discuss available therapies

and elements of standard of care for COVID-19, first focusing on nonpharmacological elements of care, and then talking about medications.

Pulmonary supportive care for COVID-19 centers on oxygenation in most cases, while oxygenation and ventilation support often play larger roles as patients progress through ARDS. Supplemental oxygen can be supplied to patients by many different devices depending on severity. If nasal cannula is insufficient, patients may require heated, humidified high-flow nasal cannula oxygen or non-invasive positive pressure ventilation modes like CPAP or bi-level PAP.

If those measures fail, intubation and mechanical ventilation remain the standard of care, and the decision to intubate is tied to other decisions like low-tidal volume ventilation strategies, fluid management strategies, sedation, and proning. ECMO is also an option in some centers, although its efficacy is still an area of active debate. Extrapulmonary care for critical COVID-19 can be extensive and includes the measures

listed here.

Finally, importantly, there are some elements to COVID-19 care that may be less frequently discussed during reviews of trial data, including less tangible elements of care such as pandemic medical decision making, patient communication at family meetings, goals of care discussions, and decisions to withhold or withdraw life-sustaining therapies, all of which are integral to a patient's clinical course.

We can also consider pharmacologic agents available for the prevention and treatment of COVID-19, some of which form part of standard of care for the disease. One of the most important milestones in the COVID-19 pandemic has been the development and approval of safe and effective vaccines against SARS-CoV-2 that prevent infection, as well as preventing severe disease and death from COVID-19.

If we move from prevention to treatment, while now approved, remdesivir's initial May 2020 EUA in COVID-19 was based on data from 696 subjects

exposed to remdesivir plus additional controls, and the approved efficacy and safety database includes 1,592 subjects who were exposed to remdesivir with additional controls.

While neither approved nor authorized for this purpose, corticosteroids, and specifically dexamethasone, have been endorsed by NIH treatment guidelines and become a major component of standard of care for hospitalized subjects with COVID-19 who require supplemental oxygen due to efficacy data that suggest a reduction in mortality from trials like RECOVERY. In RECOVERY alone, 2,104 subjects were exposed to dexamethasone for the treatment of COVID-19.

Next, we have baricitinib. Baricitinib's initial EUA for COVID-19 in November 2020 was based on 515 subjects with COVID-19 exposed to baricitinib plus additional controls. Its approved COVID-19 efficacy and safety database now stands at 1,307 subjects exposed to baricitinib plus additional controls.

And finally, tocilizumab, which was

originally approved for rheumatoid arthritis in 2010 but received emergency use authorization for the treatment of COVID-19 on the basis of trial data from the RECOVERY and EMPACTA trials, among others, suggesting that tocilizumab may be effective in reducing mortality among hospitalized subjects with COVID-19 who require supplemental oxygen. 3,016 subjects exposed to tocilizumab were evaluated for the EUA issued in November of 2020.

It's important to note the dates involved here, which demonstrate that authorizations, approvals, and other practice changes for COVID-19 treatment have changed standards of care over the course of the pandemic and continue to evolve. These practice changes include the timing of the medications mentioned above, as well as anticoagulation strategy changes, changes in nonpharmacologic practices, and evaluation of multiple other ultimately ineffective medications. So comparing to trials that are even months apart, it's a complicated endeavor.

Now with that background, we can move on to

VERU-111 development. The mechanism of action of VERU-111 is understood to be through tubulin inhibition, and it binds to colchicine binding site of tubulin. The sponsor has proposed both anti-inflammatory and antiviral activity of VERU-111 in COVID-19, however, there are uncertainties in these proposed mechanisms of action.

First, some of the data presented for the anti-inflammatory mechanism of action rely on assumptions of downstream actions of VERU-111 that are similar to colchicine, but there aren't necessarily controlled experiments with VERU-111 that demonstrate each of these steps. Similarly, our Division of Virology review of the available antiviral data for VERU-111 suggested that there was no direct evidence provided to support the antiviral activity of VERU-111. This included the fact that there was no meaningful reduction in viral shedding in Study 902.

So while we know that the drug is a tubulin inhibitor and it shares its primary mechanism of action with colchicine, and we'll talk more about

colchichine later, the mechanism of the potential efficacy of VERU-111 in COVID-19 remains uncertain.

As noted, this is a new molecular entity not approved for any indication, however, VERU-111 has conducted some development in metastatic prostate cancer through two ongoing studies. Both of these studies did not contain a placebo control, were open label, and focused on metastatic prostate cancer. Further details of these studies are available in the briefing document.

The review team did not consider these cancer studies informative to our safety review, based on major differences in the disease process, in the all-male patient population and other study design differences.

In terms of COVID-19, the sponsor initially conducted a 1 to 1 randomized, double-blind, placebo-controlled, proof-of-concept trial among 39 subjects hospitalized with COVID-19, meeting enrollment criteria. The results of that trial led to the design and conduct of Study 902, an efficacy and safety trial that was initially planned to

enroll 300 subjects based on enrollment criteria we'll discuss further.

It's worth noting that communications between the division and the sponsor highlighted repeatedly that the size of the safety database was small compared to other products which had been granted EUA, and that the division proposed that at least 500 subjects treated with VERU-111 would provide a more robust characterization of both effectiveness and safety in the context of a possible clinical benefit and any potential safety concern observed.

However, during the conduct of Study 902, the sponsor proposed a sample size change from 300 down to 210 subjects, as they've noted, citing slow enrollment. This was followed by an interim analysis that suggested efficacy on the all-cause mortality endpoint, based on an analysis of the first 150 subjects. My colleague, Dr. Dharmarajan will talk about this further when he reviews the efficacy data.

This table summarizes characteristics for

both trials in COVID-19. Each trial collected data to day 60, and enrollment criteria were similar across trials. The primary endpoint differed between the two studies, but both studies included mortality endpoints. While Study 901 had a positive efficacy estimate, Study 901 at 39 subjects was too small to draw meaningful conclusions, and baseline imbalances affected the potential clinical interpretability of its data.

So as discussed in the briefing document, our focus during this meeting is primarily on Study 902, which, while still a relatively small study, randomized 204 subjects across sites in the U.S., Mexico, Argentina, Colombia, Brazil, and Bulgaria.

Now we can go into the details of Study 902. Since the sponsor's already discussed some aspects of trial design, I'll focus my discussion on points that may be important to the division's uncertainties later in the presentation. A study schematic is presented here. I'm just going to highlight a few key points.

There was no limit to how many days prospective subjects were allowed to be hospitalized or treated for COVID-19 prior to screening and enrollment. The protocol did not require any particular elements of standard of care for COVID-19 treatment, but it stated that subjects should receive local standard of care. Screening included some measurements of severity, and this occurred up to 3 days prior to formal enrollment in the day 1 baseline assessments. However, formal data collection that described a clinical course prior to screening were not available. As presented by the sponsor, subjects were then randomized and followed to day 60.

The enrollment criteria for Study 902 recruited an adult population with confirmed SARS-CoV-2 infection and low peripheral oxygen saturation, requiring supplemental oxygen at screening or documented prior to screening. This can be accomplished through ER notes or even EMT notes, for example.

The severity criteria for inclusion were

based on the WHO Ordinal Severity Scale. If a subject met criteria for WHO 5 or 6 at baseline, they can be included. However, if they met WHO 4 criteria at baseline, meaning oxygen supplementation by simple nasal cannula or simple mask, they were required to also have one or more designated comorbidities as shown in the list provided. However, as we'll discuss later, data were not collected on all these factors.

So as the summary for inclusion, this is the WHO Ordinal Scale for Severity that formed the basis for trial enrollment, and this was what the enrollment criteria allowed: subjects with WHO 5 and 6 severity, as well as a subset of subjects with WHO 4 severity who met additional criteria. The exclusion criteria were generally acceptable, and we've just listed one from the list here.

The full criteria excluded subjects enrolled in other trials, subjects with evidence of liver or renal dysfunction and subjects with WHO 7 severity at baseline. The 2 to 1 randomization in Study 902 was stratified by baseline WHO severity score to

attempt to provide for a similar baseline severity across study arms, however, randomization was not stratified by site in this multinational study.

Blinding was provided for by supplying VERU-111 drug products and placebo in matching capsules for PO administration, however, in order to administer the medication by enteral tube, such as a nasogastric tube, the protocol required the capsule to be opened and the contents to be mixed with water for administration. We'll discuss this further during the presentation when we consider potential unblinding events.

The primary endpoint for Study 902 was all-cause mortality at day 60, and of course mortality is a clinically relevant endpoint for COVID-19 and is noted in the agency's COVID-19 guidance to industry. Study 902 also evaluated the secondary endpoints listed here. Each of these endpoints incorporated mortality events through its presence in the composite endpoint or through a statistical penalty, so the mortality results directly influenced each endpoint, which is why

mortality is our focus.

Now I'll move on to describing the enrolled population. If we look at the study disposition, the initial intention to treat, or ITT, population included 134 subjects randomized to VERU-111 and 70 randomized to placebo. The safety population, comprised of subjects who received at least one dose of the study medication, was only slightly smaller, as well as the modified intention-to-treat population. The division's analyses of efficacy will focus on the ITT population and our analyses of safety will focus on the safety population.

Eighty-two percent of study participants did not complete 21 days of therapy and the mean time to discontinuation was around 9 days. The proportion of missing data in the study was relatively low, as Dr. Dharmarajan will discuss. In terms of withdrawals, 6.4 percent of subjects withdrew from the study, which was similar across arms.

So for these next few slides, I'll present a series of small but potentially clinically

meaningful imbalances in baseline factors. While these types of imbalances are somewhat expected given the small sample size, these imbalances occur in factors that might be predicted to affect a patient's COVID-19 prognosis and mortality, and in the context of the 2 to 1 randomization ratio, factors that affect the placebo mortality of a few patients would then exert more influence on the efficacy estimate.

So as we look at the demographics of the enrolled population, there was a difference in the proportion of subjects equal to or greater than 65 years of age at baseline, with a higher proportion of patients over age 65 in the placebo group. This is potentially relevant because CDC guidelines suggest that age remains the strongest risk factor for severe COVID-19 outcomes.

This next table shows some clinical characteristics. There was a small imbalance in vaccination rates at baseline, suggesting that a higher proportion of subjects in the placebo arm were hospitalized despite prior COVID-19

vaccination. All of the subjects in the Study 902 were hospitalized and required supplemental oxygen at baseline, implying that they all likely had compelling indications for dexamethasone, remdesivir, and an immunomodulator if we consider U.S. standard of care. However, the rates of these standard of care agents were considerably less than 100 percent of the study, and there were small imbalances between arms.

Since this study has a small sample size and used 2 to 1 randomizations, even when including some of these variables as prespecified covariates in the primary efficacy model, it's possible that the adjusted analyses may not have completely and correctly accounted for all of these observed imbalances. My colleague, Dr. Dharmarajan, will elaborate on this later.

So we continue to have concerns, especially about the cumulative effect of these small measured baseline imbalances, as well as potential imbalances in variables that weren't measured and how they might impact study outcomes. To put it

another way, one of the most informative measures about baseline severity is probably this, the proportion of subjects in the ICU at baseline. And acknowledging what Dr. Barnette said about differences locally, there's still an imbalance here; 38.1 percent of subjects in the VERU-111 arm were in the ICU at baseline versus 44.3 percent of subjects in the placebo arm.

Similarly, there were small imbalances in baseline comorbidities. The proportion of subjects with diabetes, hypertension, heart failure, pneumonia, acute respiratory failure, and ARDS at baseline were all numerically higher in the placebo group, while asthma and COPD were higher in the VERU-111 group.

While the enrollment criteria for WHO 4 subjects allowed for inclusion of subjects who were immunocompromised or subjects who resided primarily in a nursing home, there was no formal data collection to quantify subjects who met these criteria at baseline, or to further describe what forms of immunocompromise might have been present.

In our view, we also noticed a difference in the proportion of subjects who had received over 14 days of standard-of-care medications for COVID-19, with a higher proportion in the VERU-111 arm. This included subjects with values like 30 days, 37 days, and 55 days of corticosteroids and/or remdesivir for COVID-19 prior to randomization. Similarly, a higher proportion of subjects were hospitalized for greater than 14 days prior to randomization in the VERU-111 arm compared to placebo. This included subjects with values like 19, 28, and 30 days of hospitalization prior to study randomization.

The full scope of COVID-19 standard-of-care therapy and duration of hospitalization in Study 902 are depicted in these plots, with days of COVID-19 standard-of-care therapy on the left plot and days of hospitalization on the right. Patients treated with VERU-111 are in blue and patients in the placebo group are depicted in red. The day of randomization is labeled day 0 on the X-axis and is denoted by the black vertical line.

With these plots, we're asking you to focus primarily on the prerandomization values to the left of day 0. You can see that the VERU-111 arm contains the most extreme values for both prerandomization therapy and duration of hospitalization near the top of the plot. These ideas will come back up again when we talk about uncertainties and their effect on the interpretation of the efficacy results.

With that, I'll move on to safety. The division decided to present these safety data early in the presentation for two reasons; first, to inform the overall benefit-risk discussion regarding VERU-111 so that the committee can make informed decisions, of course; and second, to devote the rest of the presentation to the efficacy results and their uncertainty, which are the major topics for discussion today.

The primary uncertainty in the safety database is due to the extremely limited sample size, which limits our ability to adequately characterize the safety of the drug. The safety

analysis set for 902 comprised 130 subjects exposed to VERU-111 and the 69 on placebo, many of whom stopped the drug prior to day 21.

For comparison, we can refer again back to the safety database for remdesivir, baricitinib, and tocilizumab, each of which contained over 500 COVID-19 subjects exposed to each drug at the time of the initial EUA earlier in the pandemic. The division considered pooling safety data across studies, but Study 901 included only 39 subjects randomized 1 to 1, to VERU-111 versus placebo. The differences in randomization ratios and the difference in timing during the pandemic all led to our decision not to pool safety data across studies. The discussion of the analyses of the safety data from Study 901 is detailed in the briefing document, though.

For the purposes of this presentation, I'll focus on the results of Study 902 comprising 130 total subjects who received VERU-111 with a mean duration of exposure of approximately 9.1 days compared to placebo. The content and frequency of

safety evaluations for the Study 902's protocol were adequate and comparable to other trials considered safe to proceed during the COVID-19 pandemic. It included adverse event data collection to day 60, as well as additional safety data from clinical labs, and 12 lead to EKGs, for example.

As noted, the small safety database limits our ability to detect rare events, so we're going to start with common adverse events in the study. The available safety data suggested a few potential safety signals for VERU-111. When thinking further on these AEs, the limited information on this new molecular entity doesn't provide a direct mechanism linking microtubule inhibition from VERU-111 to these events, but we did observe that most of these events occurred in organ systems with populations of high turnover cells, like the immune system, GI system, bone marrow, and skin, and some were similar to colchicine, which also inhibits tubulin, so we can start with urinary tract infections.

UTIs showed one of the largest imbalances in

the study, with a higher proportion in the VERU-111 arm, and there were smaller imbalances in related terms such as urosepsis, which is not shown. Next, the overall gastrointestinal system organ class showed an imbalance towards a higher proportion of subjects in the VERU-111 with AE terms under this heading.

On digging deeper into the signal, imbalances in three areas stood out, GI hemorrhage, GI motility including diarrhea, and GI symptoms, including nausea and vomiting. GI hemorrhage showed a small imbalance, but given its importance in a critically ill population, we investigated GI hemorrhage further through an exploratory analysis using a standardized MedDRA query. This showed other potential events but still a small imbalance, but it didn't change the overall interpretation.

The other GI adverse event terms of motility issues like diarrhea and symptoms like nausea and vomiting are not surprising, given that there are documented adverse events for colchicine. Anemia was the next signal, and this showed a small

imbalance as shown on the slide. Colchicine contained some similarities here, too.

Next to last is the imbalance in epidermal and dermal conditions, including imbalances in decubitus ulcers, among others. And finally, we have venous thromboembolism adverse events with small imbalances in the AE term "deep vein thrombosis," which is shown here, as well as some other related terms, which are not shown here.

As you can see, this imbalance is small, but this topic is clinically important in the care of COVID-19, and the rates you're seeing are potentially low for COVID-19 patients and the severity of subjects enrolled in the trial. To see whether we could gain more confidence in this signal, we performed another standardized MedDRA query analysis using the SMQ, embolic and thrombotic events, venous, which captured more potential events with a similar imbalance. So again, this didn't refute the imbalances shown or the interpretation of the signal.

As I said before, characterization of

serious adverse events is limited by the small sample size. With this limitation in mind, no SAE imbalance was noted as a stand-alone potential risk, based on the available data.

We also looked to see whether safety signals from common adverse events were reciprocated in the SAEs. We did still see an imbalance in SAEs of urinary tract infections, but the serious adverse event review was inconclusive for the other signals I mentioned in the previous slide, and then one more note on death events. My colleague, Dr. Dharmarajan, will go into these events as part of the efficacy discussion, so we've deferred the review of death events as part of the safety analysis.

So to summarize, the efficacy and safety data for the sponsor's emergency use authorization request relied primarily on Study 902 a 2 to 1 randomized, double-blind, placebo-controlled efficacy and safety trial of VERU-111, in hospitalized subjects with COVID-19 on supplemental oxygen, that ultimately randomized 204 subjects and

was stopped early after an interim efficacy analysis.

In thinking about the division's focused protocol review and the key issues for discussion, first, we have the potential uncertainties related to the mechanism of action in COVID-19. As discussed, there's no direct evidence to support the claim of antiviral activity, and the proposed anti-inflammatory mechanism relies on data from colchicine. Second, there are additional potential uncertainties related to the trial design, including the clinical relevance of and the data collection for the designated population described as high risk for ARDS.

In addition, the trial did not limit the duration of prerandomization therapy for COVID-19 or prerandomization hospitalization, which we'll discuss further later. Finally, there are uncertainties related to the small sample size, which has come up again and again, which resulted in multiple small baseline imbalances in clinically relevant aspects of demographics, disease

characteristics like proportion of subjects in the ICU at baseline, standard of care therapies, and prerandomization care.

If we summarize the safety data, the most important observation to consider is that the COVID-19 specific safety database for this new molecular entity is small at 149 subjects exposed between Studies 901 and 902, and considerably smaller than most of the standard-of-care drugs available, approved, or authorized for COVID-19, such as dexamethasone, remdesivir, baricitinib, and tocilizumab. This contributes to the uncertainty in the safety of the product and limits our ability to draw conclusions on rare events or serious adverse events.

Despite this, we did see some imbalances in common adverse events, including urinary tract infections; gastrointestinal adverse events, including diarrhea and nausea and vomiting that are familiar from the safety profiles of colchicine; as well as anemia, dermatological events, and a small imbalance in venous thromboembolism events.

Of course, the overall impact of these potential safety signals on benefit-risk is dependent primarily on the level of confidence for the potential efficacy signal for mortality. So to begin the discussion on mortality, I'll turn the presentation over to my colleague, Dr. Dharmarajan, to discuss the statistical review of efficacy.

FDA Presentation - Sai Dharmarajan

DR. DHARMARAJAN: Thank you, Dr. Busch.

Good morning, everyone. I'm Sai Dharmarajan, a statistical reviewer in the Office of Biostatistics at CDER, FDA. I'll now go over the statistical review of efficacy, starting with the review of the interim analysis and study decision making, followed by a review of the main study findings and some sensitivity and subgroup analyses.

The study followed an O'Brien-Fleming group sequential design, allowing for one interim look and within the overall type 1 error controlled at 5 percent; that is a two-sided alpha of 0.05. Interim analysis was to include the first

150 randomized subjects who completed all evaluations through day 60. The sponsor initially planned the interim analysis to occur at 50 percent of the maximally sample size of 300, however, as the sponsor reduced the sample size to 210, citing slow recruitment, interim analysis was to occur when 71.4 percent of the maximum number of subjects to be enrolled had completed the trial.

The criterion for efficacy at the interim analysis was a two-sided p-value of 0.016; that is the trial would be stopped for efficacy if the two-sided p-value for the primary endpoint was lower than 0.016 at the interim stage. If the criterion was not met, the trial was to continue through the final analysis, including all 210 subjects.

The observed p-value at the interim analysis was p equals 0.0045, which is lower than the threshold p-value of 0.016, indicating the statistical boundary for efficacy was crossed; thus, the independent data monitoring committee recommended stopping the trial for efficacy. An

additional 54 subjects were already enrolled at the time of stopping and were allowed to complete the study period. Thus, while significance testing was based on the first 150 subjects at the interim analysis, information is available on 204 randomized subjects and is provided in all the analysis results that we will present.

In the following slide, we will present the interim analysis results, which formed the basis for stopping the trial, and the results from the analysis, including all 204 subjects, completed the study.

For the primary endpoint of all-cause mortality at day 60, the sponsor compared the proportion of subjects alive at day 60 in the two treatment arms using a logistic regression analysis, adjusting for treatment and in the following covariates: sex, baseline WHO Ordinal Scale score, region, and remdesivir use and dexamethasone use at baseline.

In the analysis, missing outcome data in 4 subjects in the VERU-111 arm and 2 subjects in

the placebo was handled using multiple imputation, with the imputation model including the same covariates and, additionally, treatment discontinuation status and hospital discharge status.

The sponsor reported the odds ratio and 95 percent confidence intervals for treatment comparison. Here, we also present the risk difference and 95 percent confidence intervals. At interim, 76.5 percent of the subjects treated in the VERU-111 and 53.8 percent of the subjects in the placebo arm remained alive at day 60. The odds ratio for odds of staying alive at day 60 was 3.20 in favor of treatment, and the risk difference indicated a 23.1 percent change in the risk of mortality.

Among all 204 randomized subjects, 78.4 percent of the subjects treated in the VERU-111 and 58.6 percent of the subjects in the placebo arm remained alive at day 60. The odds ratio for odds of staying alive was 2.77 in favor of treatment, and the analysis indicated a

19 percent greater chance of remaining alive in the treatment group.

To assess the robustness of the primary analysis findings, the sponsor conducted a sensitivity analysis that considered the full range of possible response rates in subjects with missing data, the response being defined as being alive at day 60.

Specifically in this analysis, imputations were performed independently between the two treatment groups such that in the most extreme and favorable case for VERU-111, the imputed response rate in subjects with missing data in the VERU-111 arm was zero percent and the placebo arm was 100 percent, and the most extreme favorable case for VERU-111, the imputed response rate in the subjects missing data in the VERU-111 arm was 100 percent and the placebo arm was zero percent.

Timely analysis conclusions remained robust even to missing data assumptions, with the treatment comparison in the most extreme unfavorable case being similar to that seen in the

primary analysis with an odds ratio of 2.16 and the risk difference of 17.7 percent.

To provide an understanding of the overall trajectory of the treatment effect, in this slide we present the comparison of mortality in the two treatment arms at day 29 and other time points. At day 29, 110, or 82.1 percent, of the subjects remained alive in the VERU-111 arm and 48, or 68.6 percent, of the subjects remained alive in the placebo arm.

Treatment comparisons using the same logistic regression model as done in the primary analysis revealed that the proportion of subjects alive was higher in the VERU-111 arm, with an odds ratio of 2.15 for odds of being alive at day 29 and the risk difference of 11.9 percent favoring treatment.

We note that the treatment effect in terms of difference in mortality was lower at day 29 and earlier time points than at day 60. This is also seen here in the Kaplan-Meier plot of survival curves, which seemed to diverge further after

day 29.

As noted previously, baseline imbalances were observed in the timing of enrollment into the study with respect to clinical course and duration of standard-of-care therapy. The potential effect of these imbalances on study findings were explored using sensitivity analyses that adjusted for the baseline factors of additional covariates and the primary analysis of the primary endpoint, and subgroup analysis defined by the timing of enrollment into the study with respect to clinical course and duration of standard-of-care therapy. In the following slides, we'll present the results of these analyses and discuss the findings and the limitations for interpretation.

First, we look at the results of sensitivity analysis, including an adjustment for baseline imbalances in days hospitalized and days of standard-of-care therapy prior to randomization in the primary logistic regression analysis model. The results from the primary analysis are also included in the first row of the table for

comparison.

After adjusting for days hospitalized prior to randomization, the estimated treatment effect in terms of odds ratio, for the odds of staying alive at day 60, was 2.58, which was slightly lower than that reported in the primary analysis. And likewise, adjusting for days of standard-of-care therapy prior to randomization also produced a slightly lower odds ratio of 2.65. However, adjusting for these imbalances did not seem to affect the estimate of the risk difference summary measure.

Here, we present the results of the primary analysis by subgroups defined by days hospitalized and days of standard-of-care therapy prior to randomization. This analysis explored if the treatment effect remained consistent across subjects with different amounts of days in hospital and days of standard-of-care therapy prior to randomization.

The results indicate that the numerical trend for efficacy was maintained in subgroups of

patients who are hospitalized less than 5 days and less than 10 days prior to randomization, and also in patients with less than 5 days and less than 10 days of standard-of-care therapy prior to randomization. The estimated odds ratio for the odds of remaining alive at day 60 ranged from 2.38 to 4.18 in these subgroups, and the estimated risk difference ranged from 15.8 to 20.2 percent. We noted the cutoffs of less than 5 and less than 10 were arbitrarily chosen. We also note that the findings were consistent for other cutoff values explored.

We thought that the addition of covariates to control for baseline imbalances in days of hospitalization and days of standard-of-care therapy prior to randomization had minimal impact on the primary analysis results, and that subgroup analysis results were consistent with the primary analysis results. However, it is important to note that these post hoc analyses are simplistic explorations using available data and may not have correctly captured the relationship between these

imbalance factors and the outcome.

Further, exploration of the effect of the interaction of these imbalance factors was not possible due to limitations of the sample size. As such, these exploratory analysis do not completely eliminate the concern that these baseline imbalances across treatment groups may have impacted the study findings. A larger study where such imbalances are less likely to occur after randomization would be needed to confirm the lack of influence of baseline imbalances on study findings.

As presented by the sponsor, a positive trend for efficacy was seen in secondary endpoints of alive and free of respiratory failure at day 29, days in ICU, days in hospital, and days on mechanical ventilation, and clinical improvement on the WHO Ordinal Scale. It is important to note that the calculation of each of these secondary endpoints are influenced by the mortality results since each secondary endpoint contains a component of mortality or provides a numerical penalty for

mortality events. Thus, while supportive, these results were influenced by results in mortality.

We also note that the imbalances in timing of enrollment, specifically in terms of days hospitalized and days of standard-of-care therapy prior to randomization, may influence the clinical interpretation of some secondary endpoints such as days in hospital. My colleague, Dr. Busch, will discuss more about this issue, later.

In summary, Study 902 met the statistical criterion for stopping at the interim analysis stage for efficacy. Data from all 204 subjects completing the study indicates a treatment benefit for all-cause mortality at day 60. Primary analysis results remained robust to missing data assumptions. Exploratory analysis seemed to indicate a minimal impact of baseline imbalances in timing of enrollment with respect to clinical course and duration of standard-of-care therapy on study findings, although, as mentioned above, these analyses do not completely eliminate the concern caused by these imbalances.

Finally, a positive numerical trend for efficacy was also consistent across subgroups defined by age, baseline WHO Ordinal Scale score, region, remdesivir use and dexamethasone use at baseline.

Now my colleague, Dr. Busch, and I will talk about uncertainties in the efficacy data and some clinical considerations.

Our review has identified a number of uncertainties with the data, which we raised in the context of this small trial in critically ill patients. These uncertainties or issues are listed in this slide. In the following slides, we'll discuss each of these issues in detail, and I'll start with the first one on high placebo group mortality rate.

Based on the planned severity level of patients to be enrolled, the sponsor utilized a reasonable assumption that the placebo mortality rate would lie between 15 percent and 30 percent, consistent with other studies with comparable severity. However, the day 60 mortality rate in

the placebo group in Study 902 was 39.7 percent.

At the interim analysis stage, the day 60 mortality rate in the 52 subjects in the placebo group who completed the study was 45.1 percent, and among subjects within North America, it was 63.6 percent. While it is challenging to make direct comparisons to other randomized-controlled trials, we show here that prior and concurrent studies conducted in populations with similar baseline severity have reported lower day 60 mortality rates for the placebo arm.

For example, the placebo group mortality rate was 15 percent in the COV-BARRIER study. This included subjects with baseline disease severities corresponding to the 8-point WHO Ordinal Scale scores 3, 4, and 5. A placebo group mortality rate at day 60 was 25 percent in the REMDACTA study and 11 percent in another study of sarulimab, both of which included subjects with baseline disease severities corresponding to WHO Ordinal Scale scores of 4, 5, 6, and 7. All three of these trials were concluded before the start of Study

902.

In a more recent trial, the ACTIV-1 IM, conducted from October 2020 to December 2021, and including subjects with predominantly baseline disease severities responding to WHO Ordinal Scale scores of 4, 5, 6, the day 60 mortality rate in the placebo group was reported to be 16.5 percent. In another trial, ACTIV-3b, which is conducted in an overlapping time frame with Study 902 in the U.S. and in some Brazilian sites, and included subjects with a baseline WHO Ordinal Scale score of 5 and 6, the day 90 mortality rate in the placebo arm was 35 percent.

Given these data from recent trials and other trials which were conducted earlier in the pandemic when treatment options were limited and in the presence of variants soon to be associated with a higher mortality rate, the mortality rate observed in Study 902 appears to be higher than what would be expected in the study population during the time frame in which the study was conducted, calling into question the

interpretability of results and the patient population studied.

This slide just lists the references for the information displayed in the table we just saw, showing that in the day 60 mortality rate, the placebo group in Study 902 was higher than expected, based on data from prior and concurrent studies.

While discussing the high placebo mortality rates here, we have focused on day 60 mortality, as this is what is used for the primary endpoint, the results of which were used to justify stopping early for efficacy. We also note that a few studies had a similar day 29 mortality rate in the placebo group, but we also note that these studies were conducted earlier in the pandemic with potential differences in standard-of-care therapies and viral variants.

It is also worth noting that the treatment difference at day 29 was much lower than that observed at day 60, with an odds ratio of 2.15 and with 95 percent confidence intervals going from

1.02 to 4.56, and a risk difference of 11.9 percent with 95 percent confidence intervals going from negative 0.3 to 24.2 percent. This indicates that much of the differentiation between treatment arms occurred after day 29.

With that, I'll now turn it back over to Dr. Busch for a discussion of other uncertainties and clinical considerations.

FDA Presentation - Robert Busch

DR. BUSCH: Thank you, Dr. Dharmarajan.

Earlier, we mentioned potential unblinding as an uncertainty in the program. While VERU-111 and placebo products for Study 902 were supplied in matching capsules, the contents were not identical. For those who couldn't take oral medications, the protocol noted that the capsule should be broken open and the contents mixed with water for administration through an enteral tube. Because the placebo and VERU-111 products were visually different, there was the potential for unblinding. In response to an information request, the sponsor sent us these pictures.

So this is what the care providers saw when they opened the capsules. In these pictures, the VERU-111 product used in Study 902 is on the left, while the placebo product is in the middle. As we noted previously, the drug product was an off-white, to light tan, to yellow granular powder, and this information was available in the investigators brochure, and here are pictures of the products once they are mixed with water.

So this is what care providers would see in the syringe before injecting into the enteral tube, for example. There were differences in appearance, especially color, as well as differences in the dissolution properties of the capsule contents. Once again, the VERU-111 drug product from Study 902 is on the left, while the placebo product is in the middle.

So the potential for unblinding existed, at least in subjects who couldn't take medications by mouth. When we asked further about this potential unblinding, the sponsor reported that 23.9 percent of subjects in the VERU-111 arm received at least

one dose of study drug via nasogastric tube, compared to 32.9 percent of subjects in the placebo arm. However, they also acknowledged that the data collected only addressed administration by nasogastric tube, meaning that data were not collected to quantify other forms of enteral tubes like orogastric or percutaneous gastrostomy, or even what happened with subjects with impaired swallowing who couldn't take the capsule intact, so the scope of the potential unblinding in Study 902 was uncertain.

So then, does it matter that unblinding may have occurred? Mortality is often thought of as an objective endpoint for clinical trials, and we acknowledge that whether a clinical event of death occurred is not influenced by knowledge of treatment assignment. This means that a mortality event is not vulnerable to ascertainment bias.

However, the mortality endpoint can be influenced by the knowledge of treatment assignment through the conscious or subconscious differential use of treatments, or other aspects of care between

arms, which could lead to influence on the rate or timing of death events, and this is known as performance bias. Prior studies suggest that inadequately blinded trials overestimate efficacy, including trials that measure mortality, potentially due to the influence of performance bias, and these data were reviewed in the briefing document.

An additional issue in Study 902 is that the potential unblinding is confound by severity, so the subjects who have clinical decline, and especially intubation and mechanical ventilation, are also the subjects most likely to require an enteral tube, whether NG, OG, PEG, or other. This combination of knowing that sicker subjects had a higher likelihood of unblinding, and not being able to know how many subjects might have been unblinded in total, makes exploring this topic further very difficult for two reasons.

First, because sensitivity analyses about this group of subjects ultimately can't get past the fact that they had a higher severity and a

higher likelihood of death, regardless of potential unblinding; and second, since only data on NG tubes were collected, we don't know the full scope of potential unblinding in Study 902, so the completeness of any sensitivity analysis is also an issue here. This potential unblinding is relevant, though, because it has the potential to influence care during the trial, including goals of care decision making, which I'll discuss more later.

There were several features of Study 902 that may have made it more vulnerable to performance bias. The care of subjects with critical COVID-19 involves frequent, clinically relevant interventions, many of which require medical decision making about the benefit-risk of the intervention in the context of the subjects' perceived overall prognosis.

In addition, it's worth noting that the only data available to investigators regarding the efficacy of VERU-111 at this point were data from the 39 subjects in Study 901. The investigators brochure stated that the mortality results from

Study 901 represents an 82 percent relative reduction in mortality in the VERU-111 population, which could have influenced treatment expectations.

Finally, the urgency of these interventions may have been influenced by the overall care patterns of the pandemic. Unfortunately, the limited data collection in the study, while not necessarily different from many other trials during the pandemic, does not allow us to explore these uncertainties further. Even if we conducted a sensitivity analysis, we can't be sure how many subjects had enteral tubes, and an efficacy result in a potentially unblinded population could be due to the drug or it could be interpreted to show influence of performance bias, and we don't have additional data that would help us to disentangle this.

So while we cannot definitively say that unblinding occurred, differences in the appearance of the study drug product raise this possibility. These uncertainties are intensified by the small sample size and the 2 to 1 randomization ratio of

Study 902, where any effect on the mortality of even a few subjects in the placebo group may have exaggerated effect on the overall results.

If we move to standard of care, the use of local standard of care for COVID-19 introduces uncertainty in the interpretation of the mortality data for U.S. healthcare systems because in some cases, it appeared to differ substantially from accepted elements of U.S. standard of care.

Given the population, each subject had compelling indications for remdesivir, dexamethasone, as well as an immunomodulator in a U.S. healthcare center. However, when we look at the data, little remdesivir use occurred outside of the United States in Study 902, and even this approximately 28 percent of subjects showed an imbalance across arms.

Similarly immunomodulator use was less than 10 percent in Study 902. Baseline corticosteroid use hovered around 80 percent in Study 902, but that number doesn't take into account both the small baseline imbalance or the durations of

therapy provided.

This plot focuses on the top results from each study arm for COVID-19. It's a subset or like a zoom-in of the graph I showed earlier that maintains the randomization ratio, so it's actually slightly mislabeled in the briefing document since it isn't simply the top 15 values; it's the top 10 values from the VERU-111, shown in blue, and the top 5 from the placebo arm, shown in red, to maintain randomization. The top 15 values are actually populated by 12 values in the VERU-111 arm and three in the placebo arm.

But regardless, you can again see that there was a higher proportion of subjects with more than 14 days of prerandomization therapy in the VERU-111 arm, and that some subjects received corticosteroids for over 30 days prior to randomization. If we include the post-randomization duration, there were subjects who received corticosteroids for over 50 days. There's uncertainty in how these different practice patterns might influence the efficacy results and

in whether these data are informative in the context of U.S. practice patterns.

Next, as mentioned previously, there were baseline imbalances in measured elements of standard-of-care therapies between arms, including remdesivir, corticosteroid use at baseline, and proportion of subjects in the ICU at baseline. In addition, while we have some data on medications, data collection on nonpharmacologic elements of standard of care in Study 902 at baseline was limited, as well as before and after randomization.

Because of this, it's difficult to assess the full scope of potential differences in standard of care, and it's also difficult to explore the potential influence of performance bias on post-randomization care in the setting of potential unblinding events. Again, these concerns are compounded in the setting of a small trial.

Next, we can talk about the timing of enrollment in relation to the subjects' COVID-19 clinical course. This graph shows the top 15 values for the duration of prerandomization in

hospitalization in Study 902, another zoom-in from a previous plot, and the top 15 values for this data point just happened to mirror the 2 to 1 randomization ratio.

The days hospitalized is shown in blue for the VERU-111 arm and red for the placebo arm. As you can see, there is an imbalance between treatment arms for subjects who are in the hospital greater than 14 days prior to randomization. But what we can't really know is, for example, what the clinical course was for that person who had been in the hospital for 30 days prior to randomization. Was that person slowly getting worse prior to randomization or had they already turned a corner and were getting better? It's difficult to know, other than to say that they met inclusion criteria at that one cutpoint.

This creates uncertainty in the results for these subjects with long prerandomization hospitalizations because it's difficult to put results from someone who's been hospitalized for 30 days in context with the expected use for

VERU-111 if it were authorized.

Presumably, subjects who might receive VERU-111 would be subjects who were relatively early in their COVID-19 clinical course, similar to the use of remdesivir, dexamethasone, and immunomodulators. But these subjects who were in the hospital longer might have differed in clinically relevant ways compared to subjects admitted and on oxygen within the last 5 days, for example. Their prognosis or their goals of care might have been better known, or they might even have already turned the corner and were improving.

As I noted earlier, the data on severity and clinical course prior to screening and baseline assessments are very limited in this study. However, despite that, there are some data that suggests that some subjects were on a clinical trajectory of improvement prior to randomization.

For example, the data suggests that 2 subjects were extubated between screening and randomization prior to any study drug. In addition, one subject required high-flow nasal

cannula on day 1 of the study, meaning WHO 5, and was discharged from the hospital on day 2; so these subjects were probably already getting better but were enrolled and randomized.

It's unclear how the mortality data for these subjects might influence the overall results in a small study like this since their prognosis may have been clear even without study drug. Moreover, these few examples may not provide us with the full scope of this uncertainty. These examples came from analyses of the available data points of screening and baseline values, but the few prerandomization data points may not tell the whole story, especially for subjects who were already hospitalized for 2 to 4 weeks.

So now we return to goals of care. I'm going to focus on the wording of "goals of care" to include both the patient and family's contribution and the care team's contribution to decision making like do not intubate and do not attempt resuscitation, the general focus of care, as well as other decisions to withhold or withdraw

life-sustaining therapies.

The first point here is that Study 902 did not collect data on goals of care. This is not unusual in critical care trials. We included data in the briefing documents suggesting that only about 35 percent of critical care trials collect any data on goals of care, despite this being a major part of ICU care. However, even though data were not collected, we do have evidence from the study narratives that suggest these conversations did occur. Examples include one narrative that stated, "intubation had been refused," and another that stated, "The patient received no treatment for the event of cardiorespiratory arrest."

These two examples likely led to imminent death events, but it's more difficult to capture in the narrative other events like a shift to comfort, focused care, terminal extubation, or a clinical decision that renal replacement therapy would not change a subject's prognosis, or similar things.

Because we can't quantify or qualify goals of care in Study 902, their effect on the observed

mortality is impossible to determine definitively. However, we cannot ignore the effect of goals of care decision making since evidence suggests that this type of decision making precedes death in most critically ill subjects in randomized trials.

Data from the ETHICUS trial suggested that goals of care conversations precede 75 percent of deaths in European ICUs, and other data reinforced this idea in other regions. In addition, there are data that suggest that goals of care decision making may be an independent predictor of death, even after controlling for severity and other factors, implying that a decision to withdraw or withhold life-sustaining therapy has the potential to directly affect a trial subject's mortality endpoint, and not simply be another marker of extreme severity or that a subject is on a clinical trajectory of worsening.

Complicating these considerations is the evidence suggesting that goals of care decision making is highly variable, with variability attributed to region, site, and even individual

positions within a site. And there's more variability based on factors like the provider and family's religious and personal beliefs, and the local paradigm of patient/family-centered care versus patriarchal care. So even if we had data on all reasonable markers of severity, we couldn't just use severity as a proxy to judge how these decisions affected the mortality endpoint.

Finally, complicating this further, studies suggest that goals of care decision making occurred more frequently during the COVID-19 pandemic and that patients, providers, and families may have chosen to limit life-sustaining therapies more frequently during the pandemic.

So we have uncertainty in the effects of goals of care decision making on the mortality endpoint of this small study, but we don't have a way to analyze whether variability and goals of care decision making between sites, regions, or even within sites may have influenced mortality rates differentially. And in this context of goals of care decision making under high stress pandemic

conditions, we also have to again consider whether potential unblinding might have consciously or subconsciously influenced goals of care decisions.

As noted previously, the only data available to investigators for VERU-111's efficacy in COVID-19 endorsed a major effect on mortality. If a provider knew a subject was receiving placebo and on a clear clinical trajectory of decline, it's hard to believe that the potential to collect additional trial data would outweigh the responsibility to clarify goals of care decision making and avoid unnecessary suffering.

Contrast this scenario with a scenario where the same subject is known to receive an investigational product which recorded a previous mortality benefit, and we must consider whether the communication and decision making might be consciously or subconsciously influenced.

Finally, all these considerations, once again, are heightened by the fact that this was a small trial with a 2 to 1 randomization ratio, where few death events in the placebo arm might

have had an exaggerated effect on mortality results, and where potentially in the best case scenario, the lack of 4 events in the placebo arm could have made the results not statistically significant.

It's important to note here that when we point out these uncertainties in goals of care influencing the interpretation of the trial's endpoint, the division does not in any way imply that goes of care decision making in Study 902 was ethically or medically inappropriate for the subjects.

Decisions to enter into goals of care conversations and decisions to withhold or withdraw life-sustaining therapy are based on many factors, including clinical severity, patient autonomy, and avoidance of unnecessary suffering, and these may not always align with concerns related to interpreting trial data and endpoints.

Switching gears, we can try to put these results in context with the efficacy of other tubulin inhibitors in COVID-19, mainly colchicine.

While caution should be exercised when comparing results across clinical trials and across drug products within a class, we provide these data for consideration given colchicine's similar accepted mechanism of action. The totality of available data from randomized-controlled clinical trials do not support the efficacy of colchicine on clinically relevant endpoints in COVID-19.

Importantly for this discussion, there was one small trial that enrolled 105 subjects early in the pandemic, which suggested a potential mortality benefit for colchicine. However, subsequent larger clinical trials, including RECOVERY, did not reciprocate these findings, and a Cochrane meta-analysis performed in 2021, that included data from over 11,000 hospitalized participants, suggested a mortality risk ratio of 1 at day 28 for colchicine. The authors concluded that colchicine results showed little to no difference in all-cause mortality up to 28 days. A later even larger meta-analysis reinforced these findings, so we can't borrow support from colchicine.

And finally, one uncertainty that was noted before, the proposed patient population for use, specifically, the uncertainty is whether the proposed definition of high risk of ARDS is adequately represented in Study 902 and whether it adequately defines a clinically meaningful patient population, as we've noted multiple times, is a small study. Only 20 subjects out of 204 were intubated at baseline, so there is uncertainty in how much confidence we can ascribe to the results in the WHO 6 subgroup.

We also have to remember that only subjects with WHO 4 were required to have one of the listed high risks of ARDS comorbidities to enroll. Out of 204 subjects, 116 were WHO 5 or 6 at baseline, leaving just 88 subjects to fully provide evidence on the efficacy of VERU-111, representing each of these comorbidities in combination with WHO 4 severity, and there were fewer than 30 in the placebo group.

We presented comorbidities for the entire enrolled population in our prior tables, but of

course the number of subjects for each comorbidity in the WHO 4 population is even lower, so it's uncertain how much confidence to ascribe to the efficacy results in each individual comorbidity in this WHO 4 group, and we have to reiterate that data on the number of subjects who were immunocompromised, and how they qualified for that designation were not collected.

This is important because having a drug with a context of use specifically targeted at immunocompromised subjects would represent a major change in standard of care since it would be the only drug labeled specifically for that population. But we don't know how many subjects may have been immunocompromised in Study 902.

So we presented multiple potential uncertainties in our review of the efficacy data from Study 902, and as described by Dr. Karimi-Shah previously, many of these issues might not influence the overall interpretation of a very large trial, but they do lead to uncertainty in the small trial with a 2 to 1 randomization ratio,

small baseline imbalances, limited data collection, and concerns for potential unblinding effects. And while we performed some exploratory sensitivity analysis, as did the sponsor, these are not able to fully resolve all these uncertainties.

So in summary, the placebo mortality rate in Study 902, especially at U.S. and North American sites and in the WHO 4 group, stands out at this point in the pandemic. The potential unblinding events from opening study drug capsules may have led to performance bias. There were small but clinically relevant imbalances in Study 902 in baseline standard-of-care medications for COVID-19. Also, the rates and durations of standard-of-care therapies suggest that standard of care in Study 902 may not be representative of U.S. standard-of-care practices.

Some subjects were already on a clinical trajectory of improvement prior to randomization in Study 902, complicating the interpretation of their efficacy data for the proposed context of use. Goals of care decision making is a frequent

occurrence in critically ill patients, and potential unblinding and prior available efficacy data in this study may have led to subconscious influence on goals of care decision making.

In the face of these uncertainties related to Study 902 specifically, we also have to acknowledge that available data for the tubulin inhibitor colchicine suggests a lack of efficacy of colchicine on mortality. And in terms of applicability to clinical medicine in the patients we see, we have uncertainty in whether the designated study population is clinically meaningful as defined, and whether the study provides adequate confidence in each component of that population.

Finally, the lack of data collection on enteral tubes, nonpharmacologic aspects of care, details of clinical trajectory, and goals of care decision making limit our ability to further explore the potential influence of these topics on mortality results.

With all that, the question we're asking the

committee to discuss is whether the available benefit-risk evidence supports the contention that VERU-111 may be effective to treat COVID-19 in the face of these uncertainties presented. Balancing these uncertainties is the unexpected but statistically significant and potentially clinically meaningful difference in all-cause mortality observed in Study 902. This observed difference stands out in the context of the ongoing COVID-19 pandemic, as multiple presenters have noted. With over 300 deaths per day in the U.S. alone and the unmet need for additional therapies, especially those that decrease mortality, balancing our considerations, we welcome your input on these topics.

As we discussed in the briefing document, the division is also considering what additional information will be necessary to clarify the uncertainties that we've brought up regardless of whether or not the drug is authorized. A few options exist for this, including requiring additional trials as a condition of a potentially

EUA. If this were the case, regulations require that the new study be in the same population of the EUA. Because of this, for the purposes of the committee discussion, we're going to ask you to focus on subjects with WHO 5 and 6 severity, and WHO 4 severity with additional selected comorbidities.

Both the division and the sponsor have already discussed preliminary elements of trial design, and as stated in the briefing document, use of a randomized, double-blind, placebo-controlled superiority design may be the most feasible and practical. However, understanding committee's opinions on this is also part of our goals, but there are other considerations, including how best to address the uncertainties brought up in the division's review. Some of these considerations are noted here on this slide. In the committee's discussion, we ask that you consider providing additional input on these elements.

This concludes this morning's FDA presentation. At this point, I'll turn the meeting

back over to the committee chair to allow for clarifying questions for the FDA, and Dr. Karimi-Shah will return later to provide the charge to the committee. Thank you so much for your attention.

Clarifying Questions to the FDA

DR. AU: Thank you for that presentation.

We will now take clarifying questions for the FDA. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your questions 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 end the end of your follow-up question with, "That is all for my questions," so that we can move on to the next panel member. Thank you.

Let's go ahead and start with Dr. May.

DR. MAY: Yes. Susanne May. I have a couple of clarifying questions.

Number one, I didn't see it in the document, but the last presenter, you mentioned 4 deaths in the placebo group. If 4 deaths in the placebo group would not have occurred, that then the results would not have been statistically significant; is that correct?

DR. KARIMI-SHAH: Hi. This is Banu Karimi-Shah. Can you hear me?

DR. MAY: Yes.

DR. KARIMI-SHAH: Hi, Dr. May. I'm going to ask Dr. Dharmarajan to address your question.

DR. MAY: Okay.

DR. DHARMARAJAN: Hey. This is Dr. Sai Dharmarajan, statistical reviewer at CDER, FDA.

In the morning session, Dr. Chertow asked this question on how many deaths in the placebo group would be required to change the statistical significance of the primary endpoint results. In our analysis, the FDA found that if the placebo

group had four fewer deaths, the primary logistic regression analysis model would have yielded a p-value greater than the nominal significance level of 0.05 for the treatment effect; that is the treatment effect estimate would no longer be nominally significant at the 0.05 level, and this is with data, including all 204 randomized subjects who completed the study, and this is, again, in the primary logistic regression analysis model, which adjusted for other covariates as well about the treatment.

DR. MAY: Great. Thank you. That was as I understood, then.

The other question that I have is, the height of mortality rate in the placebo group, could that for this study be based on a lower percent vaccinated compared to the other studies that were shown and compared to? Then, actually for this particular study, I believe the percent vaccinated is slightly in the direction against the treatment group. So those are two related questions.

DR. KARIMI-SHAH: Thanks, Dr. May. This is Banu Karimi-Shah. I'm going to ask Dr. Busch to address your question.

Dr. Busch?

DR. BUSCH: Sure. Thank you for this question. The first part was, is the vaccination rate different from other trials? I think that's difficult to answer without being somewhat speculative just because, again, the difference in timing of the trials and differences in sites, internationally especially, leads to differences in rates of vaccination, and even the types of vaccinations.

I believe what we've presented were the FDA approved vaccinations, but of course internationally, people may have had -- well, internationally, people may have had other vaccinations that were not approved here in the U.S., so I'm somewhat limited in what I can give you on that, and I apologize for that.

The second question was, there was imbalance. Yes. The placebo group did have a

higher FDA-approved vaccination rate, however, there are two ways to sort of interpret. You can interpret that as they are better protected, or you can interpret that, since they're hospitalized, they're hospitalized despite a higher rate of vaccination. So again, that's a little bit up for interpretation.

Does that answer the question sufficiently?

DR. MAY: Yes, that answers all of my questions. Thank you.

DR. BUSCH: Thanks.

DR. AU: Great.

Dr. Chertow?

CAPT CHERTOW: Okay. This is Dan Chertow, and I just want to say thank you to the presenters for the excellent presentation, and I had two questions, the first of which Dr. May asked and Dr. Dharmarajan answered, which is to ask if the FDA had done that, quote/unquote "tipping-point analysis" to inform us as a committee how many patients we're talking about that would need to have lived in the placebo group to make a

difference in the primary outcome?

Obviously, that's relevant because the case has been reasonably made that there are differences in the two groups, the drug versus study placebo group as it relates to baseline characteristics, as it relates to treatment standard of care, and as it potentially relates to this issue of performance bias as a function of potential unblinding due to the capsule and such.

So I think that's helpful to know that perhaps if any of those issues added up to an outcome of four differences in the placebo group, there would be a difference.

My second question, which was not yet asked, has to do with whether or not the sponsor provided FDA any evidence supporting biologic plausibility of drug efficacy along the pathway, supporting an impact on host response or inflammatory response, either as it relates to changes in cell populations or cellular mediators and inflammation, and/or soluble mediators of inflammation.

I mean, we talked about viral load as one

proposed mechanism, but were there additional data supporting biologic plausibility affecting host inflammatory response? Thank you.

DR. KARIMI-SHAH: Thanks, Dr. Chertow. I'm going to ask Dr. Yunzhao Ren, our clinical pharmacologist, to answer your question.

DR. REN: Hi. This is Yunzhao Ren, the clinical pharmacologist from FDA.

Can you hear me?

DR. AU: Yes, we can hear you.

CAPT CHERTOW: Yes.

DR. REN: Okay.

We actually raised the same question to Veru during the review and, unfortunately, they did not collect any cytokine data in their clinical studies. So it's like the in vivo inflammation or anti-inflammatory evidence is completely missing for this program. The sponsor conducted some in vitro anti-inflammatory effect. I'll defer this evaluation to our nonclinical team.

DR. KARIMI-SHAH: This is Dr. Karimi-Shah again. I'm going to ask Dr. Salicru, our

pharmacologist/toxicologist colleague, to add anything further.

DR. SALICRU: Hi. This is Eleni Salicru, the nonclinical reviewer, and from the nonclinical perspective, we evaluated the anti-inflammatory claim of the drug, and other than the septic shock model data that the sponsor presented, looking at cytokine release, they didn't present any data looking at particular cell populations to that effect.

CAPT CHERTOW: Thank you. My question has been adequately answered. Thank you so much for your responses.

DR. AU: Thank you.

Dr. Lee, I saw that you had your hand up and put it down. Did we answer your question?

DR. LEE: Yes. Dr. May asked the same question that I had, and Dr. Chertow as well. Thank you.

DR. AU: That's what happened. Thank you so much.

Dr. Shaw?

DR. SHAW: Yes. Thank you. This is Pamela Shaw. This is a question for the presenting statistician of the FDA, and this is with respect to your slide 80, which I think was slide 95 in the PDF overall. I just had a clarifying question. These might be results that were just being also presented by the sponsor, but since I saw it twice, I think I need to ask this question because I'm a little confused as to what's being presented.

This is the primary endpoint results, and it's starring the number of people that were missing, both at the interim analysis, and then at the final analysis of 204. I guess I was just trying to understand in terms of how the missingness was treated because the denominator sort of adds up to the total. So somehow something was imputed in the numbers that were presented, and I just wanted to understand what was being imputed in the simple percents, and then the analysis that was presented in this table; if that makes sense.

I'm just a little confused by the place where it says four were missing for the Vero arm

and few in the placebo, and yet all 204 are being listed in terms of the survival status in the ITT in that table. It just seemed a little confusing there.

DR. KARIMI-SHAH: Yes. Hi. This is Dr. Karimi-Shah, FDA. We're trying to get that slide up for you, Dr. Shaw.

Slide 80, please, if we could get that up, and then I will call turn your question over to Dr. Dharmarajan.

Hey. This is Sai Dharmarajan. I think we can wait to the slide to come up.

Yes. The numbers, they do add up to 100 percent, including the missing -- the imputations were for the the treatment comparison estimates, so specifically for the odds ratio and 95 percent confidence interval, and this difference in the 95 percent confidence interval. For these analyses, to get these data estimates, the missing outcomes where imputed; so, yes.

DR. SHAW: So you just took a snapshot, single [indiscernible] just for the sake of the

table.

DR. DHARMARAJAN: It was multiply imputed --

DR. OKAY.

DR. DHARMARAJAN: -- with the covariates that were adjusted for in the primary analysis, and also the treatment discontinuation status. These are the grades for the imputation model.

DR. SHAW: Alright. Thank you. That answered my question.

DR. AU: Thank you very much.

This is David Au. I see a number of hands going up, but it's also 1:05 on the East Coast. What I think I will do is I think we're going to have an opportunity to make up a little bit of time after the open public hearing portion, so I'm going to ask that anyone who has a question to please remember that question, and we'll come back to it. Right now I have Dr. Baden, Dr. Kim, and Dr. Gillen on my list for that time period.

What I'd like to do is let's give ourselves a half an hour for a lunch period. So why don't we

come back at 1:35, if that's ok with everyone, and that will give us a little bit of time to kind of refresh and the like. And then we'll go to the open public hearing session, and then we can address these other clarifying questions, including Dr. Shapiro, if your question is unanswered from early in the day.

Thank you. Let's adjourn for about 30 minutes. Thank you very much.

(Whereupon, at 1:07 p.m., a lunch recess was taken.)

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

(1:35 p.m.)

Open Public Hearing

DR. AU: I hope everyone had an opportunity to have a nice little break. I think we're going to go ahead and get started again. We will now begin the open public hearing session.

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

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

in connection with your participation in the meeting.

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

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

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

Speaker number 1, your audio is now connected. Will speaker number 1 begin and introduce yourself? Please state your name and any organization that you are representing for the record. Thank you.

DR. CALLENDER: Hello. Thank you for this opportunity to speak today on behalf of the National Center for Health Research. My name is Ealena Callender. I'm a physician with a master's in public health, and I'm a senior fellow at our nonprofit think tank.

Our center conducts, analyzes, and scrutinizes research on a range of health issues, with a particular focus on which prevention strategies and treatments are most effective for which patients and consumers. We do not accept funding from companies that make products that are the subject of our work, so we have no conflicts of interest.

Every day, hundreds of men and women die due to COVID-19. In the third year of this worldwide pandemic, we are still searching for safe,

reliable, and effective treatments for severely ill patients. Initial data for Veru's drug, sabizabulin, or VERU-111, is promising, but the study leaves unanswered questions about safety and efficacy. The question for you is whether better evidence is needed before the emergency use authorization is granted.

Veru's multicenter, placebo-controlled phase 3 clinical trial found a significant reduction in mortality for patients in the treatment group. The decrease in mortality is impressive, 20 percent for sabizabulin versus 45 percent for placebo, but the strength of this data remains unclear due to the relatively small size of the study.

The analysis included only 94 patients in the treatment group and 51 in the placebo group. The placebo group seems to have an abnormally high mortality rate. They were older, had a higher WHO severity score, and are more likely to have diabetes, hypertension, and heart failure. All of these could have caused the higher mortality rate

compared to those in the treatment group.

Did the placebo group experience higher mortality because it had more risk factors for severe disease or because they did not receive the treatment? This is impossible to determine due to the characteristics of this particular study.

In general, small study size can be problematic. Such studies have a significant potential for certain types of bias. They may also produce false positive results or an overestimate of the magnitude of an association. Also, with so few patients, it's impossible to determine if there are relatively rare but serious side effects.

Medical products can be considered for EUA if they may be effective to prevent, diagnose, or treat serious or life-threatening diseases caused by COVID-19. In addition, FDA requires that the benefits outweigh the potential risks of the treatment and that there is no adequate approved and available alternative for diagnosing, preventing, or treating the disease or condition.

The evidence presented today is obviously

stronger than the evidence for some previous COVID treatments that were authorized under the Emergency Use Authorization, so we are in a different situation today because we have several different safe and effective vaccines to help prevent severe illness, hospitalization, and death from COVID-19. Moreover, there are treatments available to help manage severe illness in these patients.

The drugs in use today have been studied and used on thousands of patients thus far. While there may be some uncertainty about their risks or benefits for specific types of patient's, they have been studied on a much larger scale than this one small study.

When we have multiple options to offer patients for both prevention and treatment, should FDA authorize the use of a treatment based on a comparison with the placebo group that is at a higher risk of mortality in so many important ways? Would a reasonable compromise require the company to start enrolling patients in a study of a better matched placebo group prior to making the EUA

decision? Unfortunately, it would be very difficult to conduct a confirmatory study once the drug is on the market.

For that reason, we urge this committee to recommend the FDA require better data before granting emergency use authorization for this drug. Thank you again for the opportunity to speak today.

Clarifying Questions (continued)

DR. AU: Thank you very much for the comments.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now take the remaining clarifying questions. Please raise your hand icon to indicate that you have a question, and remember to please put your hand down after you've asked your question. 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. As a gentle reminder, it would be helpful to acknowledge the end of your question with a thank you, and end the end of your follow-up question with, "That is all for my questions," so that we can move on to the next panel member

Why don't we start with Dr. Baden?

DR. BADEN: Yes. Thank you. And I did want to thank both the applicant and the agency for terrific presentations on a tremendous amount of data, and for making it interpretable so we can wrestle with the issues at hand.

My question to the agency in follow-up to their discussion has to do with, what do you make of two things; one, the virologic data that were presented; and number two, the dosing regimen that is proposed? How do you think about those two parameters in terms of our confidence that we understand the virologic data and that we have the dosing regimen correct? Thank you.

DR. KARIMI-SHAH: Thank you, Dr. Baden. This is Dr. Karimi-Shah from the FDA. Your question is in two parts, one for the virologic data and one for the dosing regimen.

For the virologic data, I'm going to turn it over to my colleague, Dr. Takashi Komatsu.

DR. KOMATSU: Hi. This is Takashi Komatsu. I'm the virology reviewer from the Division of Antivirals. Thank you for the question.

With respect to the viral shedding data, as was already discussed earlier in this morning's presentation, it was very difficult for us to really make any definitive conclusions, partially because of the huge variability that was already noted this morning; just a handful of patients can pretty much swing the overall mean values. In fact, if we look at the median value, the window between these two treatment points closes much more rapidly. Secondly, as was also noted in this morning's discussions, the serial data were not collected or presented, so again, you really can't make any definitive conclusions based off of the

viral shedding data.

As the sponsor noted this morning, I think the future studies that they were proposing, as they were suggesting, I think data collected from those studies will probably shed more insight in terms of viral shedding data. So to conclude, we really can't make any definitive conclusions based off of the viral shedding data that was collected from this study. Thank you.

DR. BADEN: If I may ask a follow-up to the virologic question? Thank you for those comments.

One, don't we normally look at virologic data on a log scale, which may change how we see it? And number two, the persistence of virus 9 days later, a period of illness, enrollment, treatment 9 days later, the persistence of virus at a meaningful level, is that surprising to you?

DR. KOMATSU: Thank you for those questions. Yes, we do look at it in log terms typically, and we have looked at the data presented in that format. When we look at it that way, the window basically closes much more between these arms.

It's really a handful of patients with very high values, especially in the placebo arm, that's really throwing those values off.

Now, if you look at the median value, actually by being none, most of these patients actually were no longer shedding virus. So if you look at the median values, these data look much more similar to the data that you are more used to seeing. Thank you.

DR. BADEN: Very helpful. Thank you. Sorry for interrupting.

DR. REN: Hi. This is Yunzhao Ren, the clinical pharmacology team leader from FDA again. I can speak on behalf of the dosing regimen selection or exploration in this program.

We all know that the 9-milligram BID regimen studied in phase 3 Study 902 was informed from the phase 2 Study 901, and dose selection in Study 901 is informed by the nonclinical study in the previous prostate cancer clinical program. We considered the phase 2 Study 901 more like a proof-of-concept study, which the sponsor only

studied one dose. Because there was some trend to showing potential efficacy, we do allow sponsor to bring just one dose into their phase 3 study

In terms of the selection of dosing regimen, based on what the sponsor submitted, VERU-111, it is a reversible tubulin inhibitor, and the half-life in humans is quite short; it's only about 5 hours. So therefore, we consider the BID regimen is suitable for treating -- the micro tubulin, based on the mechanism of action.

I'm not sure if that asked -- all these questions.

DR. BADEN: Thank you very much. The response is very helpful.

DR. REN: Thank you.

DR. AU: Great.

Dr. Kim, you had your hand up before we went on lunch and for the open public period. Did you have a follow-up question or clarifying question?

DR. KIM: Yes. Edwin Kim. I'm grappling with trying to understand the mortality rate that we've been discussing throughout the day of being

higher than maybe expected, and I guess I'm trying to find which slide it was. But I'm not sure if this is for -- I guess it's mostly for the FDA.

It seems that the posted comparator studies with their mortality rates, only one of the studies is conducted over the same time period, the ACTIV-2, and that one, they seem to suggest a higher mortality rate. It does make me wonder, the people that are actually going into the hospital, the people that are actually volunteering to consent for a clinical trial, I would anticipate they were different now or later in the pandemic than the ones early on, where we took sort of all-comers, and people might have been more willing and interested in signing up for trial. And I'm curious if the agency would have any comment towards that, if that is a proper way to think about it or not. Thank you.

DR. BUSCH: Hi. This is Rob Busch from the agency. Certainly that's an interesting perspective. Of course, some parts of it would be a little bit speculative. I'm not sure that we

were able to collect those types of data or get some sense of that from other trials either. But when we're talking about the mortality across those different studies, you're certainly right to say that, again, there are differences there that make the comparisons challenging, and we tried to couch ours in those terms.

But again, some of the things you mentioned, the differences in the trial, when Dr. Baden asked a question about the WHO 4 earlier, I believe Dr. Barnette admitted that this group is not just WHO 4, but WHO 4 plus comorbidities. And we agree with that, but it's also not too much of a stretch to say that many of the subjects hospitalized, at least in the U.S., and progressing to WHO 4 disease will have these comorbidities like diabetes and hypertension anyway. So I don't think that would have changed over the course of the pandemic.

So when we look at the 4's here, again, it's not a 1 to 1 comparison, and we want to acknowledge that, but to just say that the enrolled sample of WHO 4 subjects should have a worse prognosis than

the vanilla WHO 4 group, I'm not sure that we can agree with that because the referenced WHO 4 mortality rate doesn't really account for the presence of any of these comorbidities.

But over the course of the study, again, we're trying to use this to show broad trends, and we agree with you that the direct comparisons are challenging, to say the least. I hope that answers your question. It's a difficult question and a good one.

DR. KIM: Yes. That's very helpful. Thank you. No follow-up questions.

DR. AU: Great.

Dr. Gillen?

DR. GILLEN: Great. Thank you. This is Daniel Gillen. I'd echo everyone in thanking the sponsor and the FDA for great presentations. I have two questions, actually, but the first is for Dr. Dharmarajan on the FDA analysis. I apologize. They're on the slide, the two tables inside the FDA's briefing document. But on table 9, you did a sensitivity analysis, and I think there's a

sensitivity analyses presented, I will say, by both the FDA and the sponsor and are quite complete, but leaving no stone unturned, I have one question about what was presented in table 9 there.

When you looked for the sensitivity analysis adjusting for comorbidities, you considered any versus none, and I think you'll lose much of the signal in the comorbidity imbalances that occurred inside of the study. What I'm referring to, is if you look at table 6 where you have the breakdown of characteristics for the patients that's in the briefing document from the FDA, the biggest imbalances are coming from asthma and COPD, which is going to be for chronic lung disease, the only CRF captured events that's considered there., then also with respect to cancer, where that was not one of the comorbidities included for the WHO 4 individuals, but it didn't have immunocompromised individuals, so this may play into that to some degree.

So the question, now that I've set that up, is did we look at an analysis -- again, just making

sure on completeness sake -- where we considered these specific imbalances in these particular comorbidities that were part of the inclusion criteria, particularly on the WHO 4 population?

DR. DHARMARAJAN: Hey. This is Sai Dharmarajan from the FDA. To answer your question, Dr. Gillen, they did lose information by adjusting for the comorbidities as any versus none. But on the flip side, you weren't able to adjust, I guess, for individual comorbidities because of the limited sample size. So I guess the question then becomes, which comorbidities should we prioritize and which we should leave out of the adjustment? So for that reason, we weren't able to do that kind of analysis where we were comfortable adjusting for each of the individual comorbidities.

That's my statistical take on it. I'll call on my clinical colleague, Dr. Busch, to add anything if he has to.

DR. GILLEN: While we're waiting for Dr. Busch, what I would say is we're clearly in a data-driven scenario anyways, where we're looking

at sensitivity analyses on these things. So rather than ranking those comorbidities, I would argue your potential ranking can come from where your largest imbalances were occurring, and determining as you group those, those particular comorbidities that were of the biggest imbalance, what impact that might have had on the overall primary analysis.

DR. BUSCH: This is Dr. Busch. It's an interesting question you bring up. I'm not sure I can address that second part from a methods perspective, however, we had some concerns about the things, specifically again, data-driven and what's available from a clinical perspective, and especially things that would influence towards this result that we see; and, full disclosure, that was perhaps more important to look at for us.

One thing that has come up as well is that we were a little bit less focused on asthma and COPD, not only because there were few subjects in the trial with those comorbidities, but also because, at least at ATS -- sorry, American

Thoracic Society -- there was some data presented this year that suggested that asthma was perhaps less of a risk factor for COVID-19 outcomes than previously thought, so that may have also influenced our thinking about what to include.

Then of course, I think Dr. Dharmarajan mentioned that there just weren't enough people to throw as many things as we wanted to in a model and account for everything at once and, of course, that's just probably a function of the sample size. Then I don't believe we did an analysis of ICU at baseline, for example, and things like that, so there were a lot of situations where we were limited both by the time we had for the review, as well as the data available to us. I hope that's a reasonable answer.

DR. GILLEN: It is. I guess I would just point out that you've got 55 people pulled in one of those three categories that I just discussed, and we're talking about a main effect adjustment here, not an interaction, but I'll go ahead and leave it at that. I do think it's something that

should be considered.

If I can ask my my second question, and this could be addressed by the FDA and the sponsor, but it stems off of a quote that was triggered to me by Dr. Barnette during his presentation, and it's been relevant to potential biases from the unblinding that could come forward in terms of decisions on on how to treat a patient if unblinding were to have occurred.

When Dr. Barnette was presenting slide CO-32, his statement that I wrote down was, "There was no difference in change of standard of care," and this was, again, with respect to the FDA's questioning of potential biases.

I'm very curious to know how one assessed whether there was no change of standard of care, and if the FDA had to take on this; if they were able to, A, empirically assess whether there was any particular change in standard of care between individuals, and their thoughts on that statement.

DR. KARIMI-SHAH: Thank you for that question. This is Banu Karimi-Shah, FDA. We can

start with that, and I'll turn the podium over to Dr. Busch.

DR. BUSCH: Sure. So that's another great question. As I tried to highlight in the presentation, many of our sensitivity analyses were limited by what data was collected. And again, this is not impugning the sponsor in any way because this is not different from many other critical care trials, or COVID-19 trials that weren't necessarily critical care, conducted during the pandemic.

But for example, things like ventilator settings, proning, neuromuscular blockade, fluid strategies -- and you could probably do anticoagulation, although doses weren't always apparent -- all these things that may have really influenced how you treat the entirety of a patient who's critically ill, those data were not available.

So we have some medication data, mostly the name and the timing, the dates, but it's kind of difficult to say what was done appropriately. And

then you also have to take into account the fact that this was local standard of care, so again the idea that somebody got well over 50 days of dexamethasone or corticosteroids makes it difficult to examine how we would very clearly and thoughtfully interpret those elements of standard of care, whereas many of the nonpharmacologic elements of care, and even, again, goals of care, which are part of standard of care, those data just weren't there.

So I agree with Dr. Barnette, and all of us tried to do the sensitivity analyses that we could. Some of those were limited by the data collection; some of those, like the NG tube thing, were limited just by the idea that data were collected, but it wasn't the entire scope of the potential issue, but we did the best we could with what we had. I hope that's a reasonable answer again. If there's any follow-up, I'm happy to address it.

DR. GILLEN: No, I think it is, but if I can interpret your statement, making a blanket statement about there's no difference in change of

standard of care is a bit of a strong statement, given the observed data that we have, which is my take on it as well, and why I wrote it down.

Do I fairly interpret your response?

DR. BUSCH: Yes, I think that's fair. We would be hesitant to make a broad statement of everything is fine, yes.

DR. GILLEN: Thank you.

DR. AU: Thank you.

Dr. Shapiro?

DR. SHAPIRO: I think they addressed it. Thanks.

DR. AU: Okay. Great.

This is David Au. I had one last question, which again goes a little bit back to the question of blinding/unblinding.

When the FDA showed the pictures of the compound in comparison to placebo, can I ask, do we know -- and this is either for the FDA or the sponsor -- who administered the drug or the placebo, and were they trained on the differences between the differences in color?

DR. KARIMI-SHAH: Hi. This is Banu Karimi-Shah, FDA. We can start with this, Dr. Au, and I will turn the podium over to Dr. Busch, and then we can see if the sponsor has anything to add.

DR. BUSCH: Hi. This is Rob Busch again. If we can bring up slide 98 from the FDA presentation just to show the pictures again?

Based on the protocol, as far as I know, there wasn't any training of personnel about differences in the product. I don't know that that was a part of the training. It was like a single statement about they can open them up and mix them with water.

In terms of who administered the study drug, we talked about this, and the sponsor talked to us about this during the IR, and I think the general consensus, although again there wasn't necessarily a data point for this, was that, generally, we would expect that ICU nurses -- especially in these situations, again, because it's sort of linked to severity -- or floor nurses would be administering this product. So we had a discussion about how

that might impact the general care team, depending on the situation, and the country, and the practice there. Certainly in the ICU where I work at, anything that comes up to an ICU nurse is talked about.

So I think it would be challenging to say that this type of thing would not be filtered up the line, but in terms of the direct answer, again, and other places across the world, I'm not sure that the care pattern would be the same, or the multidisciplinary team would be the same. So it's difficult to answer the question without just speculation in terms of what the impact would be of the person giving the drug and potentially seeing this.

I guess I'll pass it over to the sponsor to address potentially whether people were trained to look for this in some way.

DR. BARNETTE: Hello. This is Gary Barnette. No, people were not trained on the colors of the materials, and we do know that in our study -- and I think the FDA confirmed in the site

inspections -- that there was no evidence of unblinding.

I would ask Dr. Sandrock to opine on whether these would be discussed and what the impact of this might have on treatment in his clinical site.

DR. SANDROCK: Yes. Thanks, Gary.

Generally, even though nurses do, and particularly ICU nurses, spend a lot of time talking about cases, this wouldn't be something very commonly discussed unless there was a lot of variability. So if one dose was clear, one dose was colored yellow or brown, they might come back and sort of discuss the variability, but if they received a placebo or a study drug consistently, I think there probably, in my experience, wouldn't be a whole lot of discussion other than, "Hey, they're enrolled in a trial, this is the experimental drug, we don't know if they're getting placebo or the agent, and we're really not going to spend a lot of time discussing it." And most of the time, the nurses don't talk about those things, particularly in the ICU. We're usually just too busy to really

spend time on that level of detail between study drug or [indiscernible]. In my experience, I haven't seen it much here.

DR. AU: Great. Thank you. I don't have any additional comments.

Dr. Seam?

DR. SEAM: Yes. Thank you. This is Nitin Seam. One question, I think it was Dr. Busch who alluded to this earlier, thinking about the prior drugs that have been approved via EUA, baricitinib and the IL-6 inhibitors. We've been talking a lot about sample size here.

Do you know offhand what were the end of the studies that have been used at that time to approve those via EUA?

DR. KARIMI-SHAH: Thanks, Dr. Seam.

DR. BUSCH: Hi. This is --

DR. KARIMI-SHAH: Dr. Karimi-Shah here.

Oh, sorry. Go ahead, Dr. Busch.

DR. BUSCH: Sorry. I was just waiting -- your microphone is turned on from Adobe Connect.

This is Rob Busch. We do. I tried to present some of that, but perhaps it didn't come across very well. Remdesivir started with -- and I guess this is slide 20 and 21 from our presentation. Remdesivir's initial May 2020 EUA in COVID-19 had data from 696 subjects exposed to remdesivir, plus the additional controls. And then the approved efficacy and safety database that's labeled -- not all trials, but just the labeled trials for the approval -- included 1,592 subjects exposed to remdesivir, and then additional controls.

If we move to baricitinib, dexamethasone had 3,000-ish subjects in RECOVERY, but is not authorized to approved for that purpose. So then baricitinib's initial COVID-19 in November 2020 had 515 subjects with COVID-19 exposed to baricitinib, plus additional controls. Also it had a history of use for other purposes in rheumatology as an approved drug. Then its approved COVID-19 efficacy and safety database, as labeled, not including the rheumatologic, but just the approved COVID-19

efficacy and safety database that's labeled, stands at 1,307 subjects exposed to baricitinib, plus additional controls.

Then the final one right now is tocilizumab, barring other occurrences recently. Tocilizumab was, again, already approved since 2010 for rheumatoid arthritis, but its EUA in November of 2020 included a lot of data, RECOVERY, and EMPACTA, and other trials. And actually there were 3,016 subjects exposed to tocilizumab that were evaluated, plus additional controls, for the EUA that was ultimately issued in November of 2020.

DR. SEAM: Just to follow up very briefly -- thank you for that and sharing the slide. But those are the numbers at the time of the EUA; is that right?

DR. BUSCH: Correct. It's 600 something for remdesivir, and 500 something for baricitinib, and 3,000 for tocilizumab.

DR. SEAM: Thank you so much, Dr. Busch. That's all the questions I have.

DR. BUSCH: Thank you.

DR. AU: Thank you.

Dr. Chertow?

CAPT CHERTOW: Thank you. This is Dan Chertow. My question relates to equipoise and feasibility of repeating a study that matches and perhaps enhances the design of the existing study that we're discussing today, and let me be specific if I can.

Let's say that the committee made a determination that the drug met criteria for EUA approval that the known or potential benefits outweigh known or potential risks, but that there was a stipulation that an additional trial needed to be done within the defined time frame for continuing EUA approval, and then perhaps ultimately for final approval for FDA. Let's say that was the position of the committee.

When you have studies of this nature that suggest such a difference in outcome, obviously, there's a discussion to be had around equipoise. I think an argument can be made, given the uncertainties that have been presented, that

equipoise is perhaps achievable. But even if that were the case, are there examples where data such as this has existed, where EUA approval is permitted on a time-limited basis, and a study of similar design has been requested, and that it has shown that implementing that study is actually feasible, given the challenges of having a drug now available, and then ultimately implementing the study?

Can you say anything about historical examples that might match this and make comments about feasibility of an additional study?

DR. KARIMI-SHAH: Hi. This is Dr. Karimi-Shah, FDA. We're going to start with this. I'm going to turn the podium over to Dr. Busch, and then we have a few additional FDA folks who may want to chime in as well.

DR. BUSCH: Dr. Chertow, there are a lot of good questions in what you asked, so let me try and break them down bit by bit.

The first one is whether there is equipoise, so first, we acknowledge that in the face of a

mortality difference, that is always a challenge. Discussions internally within the FDA and talking with the sponsor as well, with these uncertainties that we have and some of the issues we brought up, I think you noted that perhaps there is enough equipoise to do it.

Then probably the bulk of the question was more to do with, if you have an efficacy result, and then especially mortality, what's the feasibility of doing it in other examples? So there's probably not a direct match because as Dr. Wei I think pointed out, he said the words, I think, "I have never seen such a risk difference," and of course, I think that's where we are, too. Of course it's a question of how you interpret that skepticism versus saying this is amazing, so how do we get to that next point?

In terms of precedent, we do have baricitinib, so it's slightly different, but baricitinib had trials underway -- or had their second trial underway at the time of the issue of the original EUA. I think it was the KHAA trial or

something, was underway, and those results were pending, but it wasn't the exact same scenario where it would be done after the results were already public. So that had already started, at least enrollment. I think they were a little further along.

Tocilizumab didn't do any new trials after the EUA, as far as we're sort of talking internally. Then in terms of equipoise and things like that, we are asking the committee to ask about this, of course, to sort of opine.

So there's not really a precise match, and one of the questions that we're asking you, of course, is directly what you're asking; is it a situation where we feel like that would be feasible or workable, and what will that mean? It's not clear whether that should weigh in on the decision of may be effective, but it's certainly a concern that's very valid.

I'll push it back to Dr. Karimi-Shah and anyone else from the FDA side to add to that, but I hope that at least addressed the concern because we

agree with the general point.

CAPT CHERTOW: Yes. I guess I'll see if others from FDA would like to comment. My response to your comments, which I appreciate -- thank you for them -- would be that, clearly, it is the role of the committee to have these conversations around equipoise and feasibility.

My question, is there precedent to help guide us, a relevant precedent to help guide us, where there actually are examples where you see, at least in a small trial, which I will say, quote/unquote, "has flaws," where there's such a mortality difference, where you've been able to then go on and actually accomplish an additional similar trial as a requirement for the EUA approval? That's really my question. Are there other examples where that's been accomplished? And perhaps, again, maybe that's germane to our fundamental question or not, but it does have some bearing.

DR. KARIMI-SHAH: Hi. This is Banu Karimi-Shah, FDA. And, yes, Dr. Chertow, you're

exactly right. I think each of our EUA applications has its own set of different challenges, and while we have issued conditions of authorization for other drugs that have been authorized, this is really a new area, and we don't have a relevant precedent here; so again, part of what we're asking the committee to weigh in on. Thank you.

CAPT CHERTOW: I appreciate the response. Thank you for your response.

DR. AU: Thank you.

To continue this robust discussion, Dr. Baden?

DR. BADEN: Yes. Just building on Dr. Chertow's comment, and thinking about it from another side, but it's an issue we've all been struggling with.

Given the purported mechanism, and that this may be relevant to how virus cellular interaction occurs, and therefore abrogating the negative effects of viral infections, and extending the thought experiment to other respiratory

viruses -- as the applicant suggested, maybe this should work for flu or RSV -- if a trial were done in flu or RSV, a similar kind of criteria, and were negative, how would that then inform this type of authorization if this authorization went forward?

I'm just sort of asking a thought experiment to both the applicant and the agency, is if a well-done superiority trial in flu, as proposed, turned out to be negative, how would the applicants view it in terms of the mechanism and the findings in this study? How would the agency view that kind of result? Thank you for entertaining my thought experiment.

DR. KARIMI-SHAH: Thank you, Dr. Baden. This is Banu Karimi-Shah, FDA. Let me first start off with the nuances here of requiring another trial.

In the face of an emergency use authorization and a trial that would be done as a condition of authorization, we would require that trial to be done in the same patient population in whom the drug was authorized. So in this case, we

are asking you, if authorized, who the appropriate patient population would be, but for the sake of discussion, if it were the population whom the sponsor's defined and studied, that trial would have to take place in those patients.

Now, if we were talking about a more general trial in other viruses, this would be more supportive of a potential marketing approval or a new drug application for the future, but not so much as a condition of authorization because, again, that would be a trial that would be done in a different patient population, so I think that's important to draw out those differences there.

DR. BADEN: No. Thank you. That's very helpful; so if the applicant said that they were in discussion about such a trial. I was trying to think through how that would inform us, but I hear you, that that would stand on its own merit. Thank you.

DR. AU: Dr. Seam?

DR. SEAM: I'm sorry. I had not put my hand down from the prior question. I have no questions.

DR. AU: Okay. Great.

Let me ask the committee if there are any questions before we move on, or any other clarifying questions?

(No response.)

DR. AU: Seeing none -- thank you, Dr. Karimi-Shah -- the committee will now turn its attention to the task at hand, the careful consideration of the data before the committee, as well as public comments.

We will now proceed with the questions to the committee and panel discussions. I would like to remind the public observers that while this meeting is open for public observation, public attendees may not participate --

DR. STEVENSON: Excuse me. This is Takyiah speaking. I'm so sorry to interrupt.

Dr. Au, could you please go to part 14 in the script?

DR. AU: I apologize. I skipped that. I will do that.

DR. STEVENSON: No problem. Thank you.

DR. AU: So retract all that. I apologize.

We will now proceed with the FDA charge to the committee from Dr. Karimi-Shah. Thank you.

Charge to the Committee - Banu Karimi-Shah

DR. KARIMI-SHAH: Thank you, Dr. Au, and no problem.

This is Banu Karimi-Shah again. First, before I get started, I just want to extend a huge thanks to the committee members for your thoughtful and robust discussion already today. I know there will be more as we go through these discussion and voting questions. So I will now turn to close the presentation portion of this Pulmonary-Allergy Drugs Advisory Committee meeting with the formal charge to the committee.

I'd like to take the next few minutes to provide a brief reminder of the proposed use of VERU-111, an overview of the benefit-risk considerations, and the regulatory framework upon which our decision making is based. I will then close with the discussion and voting questions.

The proposed use of VERU-111 is reviewed on

this slide. It's for the treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19, with positive results of direct SARS-CoV-2 viral testing, who are hospitalized, who are at high risk for developing ARDS, and for whom alternative COVID-19 treatment options authorized by FDA are not accessible or not clinically appropriate.

As part of the discussion, we will specifically ask the committee to discuss the proposed use with respect to the patient population in whom VERU-111 should be used if authorized.

I will now summarize the benefit-risk considerations. The FDA review team acknowledges that Study 902 met its prespecified primary endpoint of all-cause mortality at day 60. You will recall this slide from Dr. Dharmarajan's statistical presentation, which summarized the primary endpoint results and showed that at interim, 76.5 percent of subjects treated in the Veru arm and 53.8 percent of the subjects in the placebo arm remained alive at day 60. The odds

ratio for odds of staying alive was 3.2 in favor of treatment, and the risk difference indicated a 23.1 percent change in the risk of mortality.

Among all 204 randomized subjects, 78.4 percent of subjects treated in the Veru arm and 58.6 percent of the subjects in the placebo arm remained alive at day 60. The odds ratio for the odds of staying alive was 2.77 in favor of treatment, and the analysis indicated a 19 percent greater chance of remaining alive in the treatment group.

In the face of an ongoing pandemic, a survival benefit is difficult to discount, and certainly all-cause mortality is an important and clinically meaningful endpoint. As Dr. Wei mentioned as part of the sponsor's presentation, these results were somewhat remarkable, and something that he had not previously seen. When we saw these results, we experienced this feeling as well. As we delved deeper, our review revealed several uncertainties as reviewed by Drs. Busch and Dharmarajan in their presentation.

You have heard this mentioned many times today. While many of these issues are not unique to this critical care trial and may not influence the overall interpretation of results in a very large trial, all of these issues together in a small trial, which is more vulnerable to imbalances, raise questions about the results.

Further, these issues raise concern that even when using an objective endpoint such as mortality, observed results can be subject to biases in a small trial of short duration in critically ill patients. I summarize these uncertainties here.

The high placebo mortality rate in Study 902, especially at U.S. and North American sites, stands out at this point in the pandemic. The potential unblinding events from opening study drug capsules may have led to performance bias. There were small imbalances in clinically relevant baseline standard-of-care medications for COVID-19, as well as durations of standard-of-care therapies prior to randomization that suggest that standard

of care in Study 902 may not be representative of U.S. standard-of-care practices. In addition, the lack of additional data on other elements of standard of care limits our ability to further investigate their impact on the efficacy result.

With respect to timing of enrollment, some subjects were already on a clinical trajectory of improvement prior to randomization in Study 902, complicating the interpretation of their efficacy data for the proposed context of use. We do not have the information to assess the effect of goals of care decision making in this small trial, especially important due to the potential for unblinding and prior available efficacy data that may have led to subconscious influence on goals of care decision making.

Given the small sample size and unclear mechanism of action in COVID-19, we have also looked at available data for a drug with a similar mechanism of action, colchicine, a tubulin inhibitor. These data suggest a lack of efficacy for colchicine on mortality. And finally, we have

uncertainty in whether the designated study population is clinically meaningful as stated, and whether the study provides adequate confidence in each component of that population.

It is important to note that based on our review and conducted sensitivity analyses, none of these uncertainties or imbalances alone invalidate the mortality benefit observing Study 902. However, as Dr. Dharmarajan pointed out in his presentation, these analyses were simplistic explorations of the impact of adding additional baseline factors into a logistic regression analysis model and may not have accurately captured the relationship between the imbalanced factors and the outcome.

Further exploration of the effect and imbalances in individual comorbidities and interaction of imbalanced factors was not possible due to the limitations of the sample size and lack of additional data collection around many of these elements.

Again, while not having this type of

information is not atypical for critical care trials, these factors could be impactful in a study of this small size, randomized 2 to 1, in which the outcome of a few placebo patients could change the result, and our exploratory analyses do not entirely eliminate the concern that certain baseline imbalances across treatment groups may have impacted the study result. We ask the advisory committee to consider these uncertainties together and how they may affect the interpretation of the robustness of the mortality results.

With respect to the evaluation of risk, the evaluation of the potential risks in the VERU-111 development program is limited by the atypically small safety database, comprising a total of 149 subjects who received VERU-111 for the proposed use in COVID-19. Additionally, VERU-111 is a new molecular entity not approved for any other indication, and therefore, our ability to leverage other safety information from relevant previous human experience is limited.

We acknowledge that in the face of a

potential mortality benefit, there are few safety signals that would contribute to an unfavorable benefit-risk assessment. We have provided an overview of our analysis of this limited safety data, but the biggest issue for the safety evaluation in this program is its small size and resulting limitations, identifying significant safety signals. It will be important for the committee to weigh the level of uncertainty in safety that is acceptable in a program with a potential mortality benefit.

I will use the next few slides to once again review the regulatory framework which FDA uses to assess applications for emergency use authorization. Our authority is a result of the declaration enabling FDA to issue EUAs as a part of the U.S. government response to the COVID-19 public health emergency.

For those of you who have participated as panel members in RACs in the past, you will note that this is a different framework than what we use for approval. The FDA may issue an EUA if, based

on the totality of scientific evidence available, it is reasonable to believe that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition that can be caused by SARS-CoV-2, and that the known and potential benefits of the product outweigh the known and potential risks of the product; also, there is no adequate approved and available alternative to the product for diagnosing, preventing, or treating the disease or condition.

Further, the FDA may require appropriate conditions with respect to collection and analysis of information concerning the safety and effectiveness of the product with respect to the use of such product during the period when the authorization is in effect and a reasonable time following such period.

This is an important point to note because even in the face of issuing an authorization, FDA may require additional trials in the population in whom the authorization is issued in order to gather

more efficacy and safety data for the proposed use. We will ask you to discuss considerations for additional trials to be conducted, if authorized, as a condition of authorization, given the uncertainties noted. I have summarized these on the next slide.

As a condition of authorization, regulations require that the new study be in the same population as that in which the product is authorized. While the appropriate population is something we will ask you to discuss, per the sponsor's proposal, this would be in subjects with WHO 5 and 6 severity or WHO 4 severity with additional selected comorbidities.

Both the division and the sponsor have already discussed preliminary elements of trial design, and as stated in the briefing document, use of a randomized double-blind, placebo-controlled superiority design may be the most feasible and practical, however, we seek the committee's input on this proposal.

The proposed study should also consider

additional elements to account for the uncertainties raised, and we will ask the committee members to provide input on these additional study elements, including trial size and interim decision making, placebo control, active control, or combinations of both, and then considerations of the uncertainties raised by the FDA in Study 902 as enumerated here. We will also ask the committee to opine on elements of standard of care for COVID-19, both pharmacological and nonpharmacological, that should be taken into account in such a study.

Before I summarize the discussion and voting questions for the committee, I want to reiterate the following EUA consideration. FDA's authorization of a medical product under EUA is not the same as the agency's approval or licensure of a product. The may be effective standard for EUAs provides for a lower level of evidence in the substantial evidence of effectiveness standard that FDA uses for product approval. Further, a product may be considered for an EUA if it's determined that the known and potential benefits outweigh the

known and potential risks, based on the totality of scientific evidence.

For an emergency use authorization, the agency authorizes a healthcare provider fact sheet and a patient fact sheet, which are similar to prescribing information in the patient labeling or medication guide for approved products. And as part of its authorization, FDA will establish, to the extent practicable, conditions in the EUA that it finds necessary to protect the public health, and periodically, FDA will review the circumstances and appropriateness of the EUA.

With these EUA considerations and statutory requirements in mind, we can now move to the questions

Question 1 is a discussion question. We ask the committee, discuss the strengths of the all-cause mortality data, specifically considering the uncertainties raised by the agency in Study 902, including the high observed placebo mortality rate; potential for unblinding; differences in standard of care before and during

the trial; differences in timing of enrollment; potential differences in goals of care decision making; and defining the studied population.

Question 2 is also a discussion question. We ask the committee to discuss your level of concern regarding the limited size of the safety database for this new molecular entity.

Question 3 is a voting question. We ask, do the known and potential benefits of VERU-111, when used for the treatment of adult patients hospitalized with COVID-19 at high risk of ARDS, outweigh the known and potential risks of VERU-111?

In part A, if you vote yes, we ask you to discuss the appropriate patient population in which VERU-111 should be authorized. In part B, if you vote no, we ask you to discuss what additional data would be necessary to assess the benefits versus the risks of treatment.

Finally, question 4 is a discussion question. We ask, if authorized, the agency believes that additional data are necessary to understand the benefit-risk assessment as a

condition of authorization. Please discuss the proposed design aspects of a study to provide this additional data.

Thank you once again for your time and your attention. I will now turn the podium back to the chair to begin the discussion.

Questions to the Committee and Discussion

DR. AU: Thank you, Dr. Karimi-Shah.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now proceed with the questions to the committee and panel discussions. I would like to remind the 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 will pause for any questions or comments concerning its wording, then we will open the question to discussion. We will start with question 1.

Discuss the strength of the all-cause

mortality data, specifically considering the uncertainties raised by the agency in Study 902, including the high observed placebo mortality rate; potential for unblinding; differences in standard of care before and during the trial; differences in timing of enrollment; potential differences in goals of care decision making; and defining the studied population.

Are there any questions about the wording of the discussion question?

(No response.)

DR. AU: Seeing none, if there are no questions or comments concerning the wording of the question, we will now open the question to discussion. I would ask the panel members to use the raise-hand for recognition. They're starting to come up, so thank you.

Dr. Chertow, I'll give you the floor.

(No response.)

DR. AU: Dr. Chertow, you're on mute if you're speaking.

CAPT CHERTOW: Got it. This is Dan Chertow.

Thank you for the opportunity to speak on this question, and for the clear presentation of the question.

My take on this I think should have come across in the prior questions that I raised, and my take is as follows; that clearly there's a profound mortality difference between drug and placebo in the study, but ultimately, given the questions around differences in groups and potential unblinding, et cetera, that may have had an impact on the outcome. The fact that just three individuals in the placebo group would have changed a statistically significant outcome, it seems to me that the data is suggestive, but it is not definitive. So I think the strength of the data, at best, would be considered moderate, and I'll leave my comments at that. Thank you.

DR. AU: Thank you.

Dr. Gillen?

DR. GILLEN: Daniel Gillen. Thank you.

Yes, I'm fairly consistent with Dr. Chertow. I would say that on face value, when we look at the

observed data that are here, the point estimate is clearly impressive with respect to the 60-day mortality. I think that it's clear that the data has been analyzed in multiple ways to assess sensitivity.

I don't think that the issue is going to come from being able to adjust out differences at baseline from these groups and the small imbalances in this type of trial. I think the question really comes down to a lack of precision overall in long-term follow-up, and that's where the question begins to arise, like the question as to why this study was stopped prematurely relative to the pre-planned sample size, to be quite honest, but that's neither here nor there at this point.

With respect to the placebo mortality rate, while it's higher in this population, I think that there are potential reasons for that. I believe it was Dr. Kim who had brought up a very feasible type of explanation in the sense that this is a fast-moving disease, different comorbidities, and different treatments that folks are dealing with

over time. And while the sponsor said it's over a short time period, it's quite a dynamic system that we're dealing with. So it could very well be that that baseline measure of mortality is really rapidly changing, given the patient pool that we're dealing with and coming into trials.

So I'm less concerned that this is maybe not representative of where we are today. I think it's open for debate, and I don't think there's evidence one way or the other. But I do believe that some issues with the blinding could invoke questions in my mind about this, and I do think that given the small trial size, that there could be easy shifts in these things, depending upon what the baseline severity of disease might have been or any potential differences could have come through in the patient population.

So because of that, my enthusiasm is certainly tempered, though, again, on face value, the point estimate itself is impressive here, but it does not rise to the level of what is mostly considered to be the standards that we would look

for on something like this. Thank you.

DR. AU: Thank you.

Dr. Shaw?

DR. SHAW: Yes. This is Pamela Shaw. I'd just like to add a little bit to what's been said. I agree with all the thoughts that have been expressed so far regarding this charge, this first question.

This is a very difficult decision. I'm trying to think about the EUA and the level of evidence, specifically with respect to mortality, and I think that justifies this EUA at this stage. I think a lot about this emergency use authorization is in the U.S. population in the setting of U.S. standard of care, and the Trial 902 had 67 individuals from the U.S. being exposed to U.S. standard of care, and only 23 of those were on the placebo.

So we're looking at this authorization, this use, in a population for which we've seen 23 people informing this 56.5 percent mortality rate in the U.S. placebo population. I've done some work in

the U.S. in the COVID trials and with the COVID EHR, and I'm trying to wrap my head around this background rate because I think it is kind of concerning to think about who that represents and what is the target population.

I'm not sure we can say that we enrolled the target population, so that makes it in the sense that they seem much sicker with that high of a mortality rate. I think we saw early on in the pandemic, when a lot of people were on the ventilator, and on pressors, and people not -- there was a high mortality rate early on in those WHO 7's, and in a few months that changed, even in that very sick population. But then a year later, I don't know, it seems the 56.5 percent is a little bit concerning in a clinical trial population who tends to have a better standard of care than a general population.

So I guess my concern is the small numbers may have enrolled a population a little different than the target, which makes it a challenge to figure out who, if there's an authorization at this

point. I guess my question is, is it really clear -- and I'm sort of turning the question back to the FDA. Do we know who we would authorize this in? That's the thing I find -- it would be this group of people, in the U.S., that have this really high rate. I find that's a challenge, and it maybe is the small numbers making us feel a little uncomfortable with -- I think no one's disputing this, but no matter how you turn the data around, you're seeing roughly a 20 percent risk difference, but how much of that can be attributed to the mechanism of action of this drug, or can be attributed to the expected mortality rates that we should have seen that could have allowed for such a large difference? It has to be a high mortality rate in a background in order to see such a large difference.

So just a lot of questions being raised by these results, at least in my mind. So in terms of going back to the question -- and I'll finish -- I think it is an impressive number, the 20 percent risk difference, but I find it probably a product

with the small numbers, so then that's a concern when I think about there's a lot of precedence for having an authorized use when there's just a small exposure to this drug, really.

I guess sort of like what Dr. Gillen said, I'm trying to understand what motivates an authorization at this point, given there's only been 200 people on this previous trial, and maybe 30 more before that. If we can't even enroll a full 300, it's just sort of wrapping my head around how could we get data that could help us feel better about this EUA in any kind of short fashion when a lot of people could get exposed to the drug in the meantime?

So those are just some of my concerns, and if I displayed any ignorances in my concerns, I'm happy to be educated during this discussion period. Thank you very much.

DR. AU: Thank you.

Dr. Kim?

DR. KIM: Edwin Kim, University of North Carolina. I'm really just going to echo what I

think all the previous speakers have mentioned. I think the data is very impressive, and no matter how they seem to slice and dice it, the benefits seemed to withstand all of those different analyses. I think not having a clear understanding of the mechanism and the one comparator of colchicine not showing a clear benefit is worrisome to an extent, as well, of course, all these uncertainties that have been brought up.

My sense is all of these uncertainties and all would bring down maybe the magnitude of the benefit, but I don't know that I've heard enough that makes me worried they would not be a benefit. So that will kind of play into the next discussion, I think, when we compare these benefits to the risks. Thank you

DR. AU: Thank you.

Dr. Baden?

DR. BADEN: Yes. Thank you.

I think that the mortality endpoint is an endpoint that we all care the most about and should be cleanest in its assessment. The challenges, as

already raised, is it's unclear who, although I would say who is people at a 30 to 50 percent mortality risk, and I'm not sure the WHO scale adequately captures that as used in this study.

The what, I'm also not sure is fully worked out in terms of the dosimetry, but we have a dose given that had the effect seen, so that is a good place to start. The when is also not so clear because some folks were sick for a long time and some for a short time, and it's unclear triggers for treatment and some definitions are also unclear, but we know what they did, and that would then be the framing.

There are the threats to validity that have been raised, but we're still left with this mortality benefit even in the face of these threats to validity that nip at the sides and the heels, but I'm not sure vitiate the result. As with anything early in development, there are more questions than answers, but the endpoint of interest is such a powerful one. Over.

DR. AU: Thank you.

Ms. Schwartzott?

MS. SCHWARTZOTT: Hi. I am the patient representative. I've currently had COVID for about 12 days, so excuse my voice and coughing if I do. I've also had COVID at least 5 times in the past. Early on in 2020, it was a really, really bad case, but I survived it out of the hospital, and had it several times after, which damaged my lungs.

So a year ago, about a year and a half ago, I was hospitalized with what turned out to be rhinovirus and not COVID, but they said that the damage from COVID is what caused my lungs to react so badly. I was one of those World Health Organization's 5 or sick. I didn't quite get fully to 6 because I refused the vent, but they said I needed it.

So I have the unusual understanding for our debate because I represent what the patient wants. The problem is that is not always what really should happen. I would have done anything to breathe. So it's up to the FDA and us to look at both sides to protect the patient, who will likely

want the drug at any cost. And while the drug sounds extremely promising and the all-cause mortality data is very promising, what are the real results?

I'm questioning the true efficacy results. Did the pre-standard of care cause the patient to live or was it the VERU-111? It might be a mix of care, as it was with me. I improved, and I lived during that mix of care, obviously, without severe, since I didn't have COVID anyway. But on the other hand, if these results are true, it is possible that we could have an additional medication that improves outcomes and saves patients, and that's really important.

I am leaning towards suggesting another study because it puts the drug out there under strict conditions while collecting data for potential future use. I simply don't feel we have enough data, but feel that this has enough promise to deserve a future study.

Really quick, in regard to the potential unblinding, that doesn't bother me quite as much.

The nurse might and should have noticed that the color difference was there, but they still would not know which was the drug and which was the placebo.

The goals of care, that really varies from doctor to doctor and nurse to nurse. I was in a really big New York City hospital, and the ER doc that initially treated me wanted me on the vent. We're not in the same mind-set as my specialist who treated me in the ICU, and fought for me and my wishes, and he was right. So you could be in the best hospital in the world or you could be in a small hospital; that is going to change no matter what, and it will on future studies, if there are any.

I just think there are too many variables for the small group that was studied. If this would be back in 2020, I would have voted yes immediately, but now we have other options and vaccines, so I question do we need to rush this into the emergency situation or should we do another study? Those are just my thoughts as

patient representative.

DR. AU: Thank you for those comments.

Dr. Seam?

DR. SEAM: Sorry, Dr. Au. Did you call me, Dr. Nitin Seam?

DR. AU: Yes.

DR. SEAM: Ms. Schwartzott's comments really resonate with me. We all think about saving lives with COVID and take that very seriously, the most important thing [indiscernible]. I echo a lot of her thoughts. I struggle in terms of the strength of the evidence, with the low end of its 2 to 1 randomization, and then the early stopping really makes that control group end very small, and that small change can then cause that control group's mortality to be out of whack, as we discussed.

I don't know what are the potential differences, but there are many differences, potential differences, that the FDA pointed out, a few patients being made DNR, difference in ventilator strategies that could certainly make a difference and possibly explain why the control

group mortality is so high.

I do think it is an outlier when you contextualize it with the timing of the second half of '21, early '22, and the SOHO-COVID study just came out in JAMA, looking at high flow versus non-rebreather, and they have a mortality in both groups [indiscernible], similar hypoxemia [indiscernible] cohort, so I am concerned about that.

I think the other question that hasn't been raised in this discussion is, where would it fit with the rest of our armamentarium? A small minority of patients have received the other therapies that we do give for this sort of patient, like baricitinib and so forth, so we really have to think about that. You worry you're giving something else, and there's potential for harm if you're not giving something else that's already been approved via the EUA process that has a larger end. I'll stop there. Thank you.

DR. AU: Thank you.

Dr. May?

DR. MAY: Susanne May. Just a correction, I believe a minor one or a small one. I believe the first two speakers, Dr. Chertow, had mentioned that three individuals would change the results. I think it was four, which is not much different than three, but nevertheless, even if there were 4 individuals in the placebo group who would not have died, the effect estimate would still be very impressive. It would not be necessarily statistically significant, but still very impressive; I believe still almost 20 percent.

I am struck by the effect size. Some of the concerns that were raised, particularly by the FDA, they would have been known before this study was started. Even with the reduction in sample size from 300 to now just over 200, even with the 300, there wouldn't have been more than 200 individuals exposed to the treatment, which is still quite a bit lower than other treatments that received this approval, emergency approval.

I'm also wondering what we would need to see for this kind of study that we couldn't have

anticipated upfront, with regard to some of the concerns, that would make us approve this. There doesn't seem to be a huge red flag with regard to any of the safety outcomes. And yes, the numbers are relatively small, but that didn't seem to be a huge flag. There also doesn't seem to be a huge flag with regard to imbalances. Yes, in totality, they could have changed the results, but they would have had to be all, or almost all, working at the same time to really reverse a benefit.

So maybe it's not only discussion, but if there is another question to the FDA here, it is, when this study was started, some of the concerns that are still raised now could have been anticipated before it was started, and what would the agency have wanted to see differently for this study to not bring this to the advisory committee but be convinced and go ahead with the emergency use authorization? And that's my comment and question.

DR. AU: Thank you, Dr. May.

Is there someone at FDA who can address

Dr. May's question?

DR. KARIMI-SHAH: Yes. Hi, Dr. Au. This is Dr. Karimi-Shah, FDA. I'm going to ask Dr. Busch to address Dr. May's question.

DR. AU: Thank you.

DR. BUSCH: Hi. This is Rob Busch. Sorry. I'm just trying to unmute everything and get everything set.

So we did mention -- find my slide -- during the presentation that communications between the division and the sponsor highlighted repeatedly that the size of the safety database was small compared to other products which had been granted the EUA, and that the division proposed that at least 500 subjects treated with VERU-111 would provide a more robust characterization of both effectiveness and safety.

I think that during the pandemic, there are certain things that we have power to regulate and certain things that we do not. If a sponsor proposes a study where the sample size is not ideal for our purposes, that may not be a reason to stop

the trial. We can give advice, but we can't force that issue. I think that we had an expectation that there might be another trial.

In addition, I think it's important to note that we also cautioned against the 2 to 1 randomization ratio. Again, we may have expected a bigger study to begin with, and we didn't necessarily expect the sample size to go down further.

In all this context, again, we are somewhat limited in the power of what we can do, and we didn't want to shut down research during the pandemic if it seemed notable. We have to acknowledge, though, too, the reason this is at an advisory committee with so few subjects is because of the point estimate. I don't think there was a way for us to predict -- again, as the sponsor presenter said, "I've never seen a risk difference --" again, we keep coming back to that.

We might have expected that we would have another trial. We might have expected that we would have more people in the trial along the way

before the sample size changed. But we did make clear to the sponsor, a few times, we would expect 500 subjects. So that's a reasonable discussion of where our expectations stood in the context of a pandemic.

DR. AU: Thank you.

Dr. May, does that address your question?

DR. MAY: Yes. Thank you. That was very helpful. Thank you very much.

DR. AU: Yes.

Dr. Baden, is your hand up?

DR. BADEN: I re-raised it because I think I wasn't as clear on some of my thoughts, and Dr. May helped jiggle them, so thank you.

As we think about the threats to validity, which is part of what we're getting at, the reason we have a placebo group is to tell us how the population being studied behaves, and this population being studied, whatever classification we have at baseline, is a 30 to 50 percent mortality population. That's what it is, whether or not we have adequate ways to describe it at

baseline when we enroll them.

Then the threats to validity if randomization works may be the play of chance or may be because of differential handling of the participants, and that's what some of these issues are about unblinding. If we believe that unblinding leading to the goals of care and the application of standard of care was so differential that it would change the mortality outcome, then that changes our ability to interpret the efficacy.

If on the other hand we're not as convinced that that's a threat to validity because the doctors caring for the patient will always be aggressive in caring for the patient, as discussed today, there are ways that things can infuse themselves into that discussion. But even though I'm concerned about the time to enrollment and concerned about the high placebo rate, randomization should have mitigated those concerns. So it's really differential unblinding leading to differential management post-randomization that would be the threat to validity on the mortality

outcome that I think is the issue in terms of study conduct; and that the placebo group is telling us the population that they were studying, whether or not it's like other populations -- it may not be -- but this is the population they were studying.

Then the other issue that's ruminating in terms of larger numbers, which of course we all want, I'm trying to put myself on the DSMB. If this were a 500-person study, or a 1,000-person study, or a 5,000-person study, at what point -- if you're on the DSMB and you see a mortality difference like this, would you allow the study to continue?

So I just want to be careful that we think carefully about what actually is operationalizable in the field, given the data that were seen in real time and we're seeing now; because even though I want more data desperately, I also can understand how a safety committee would be appropriately concerned about letting a study go on where there's a big mortality difference, and then how would that

be looked at by us and others.

Since we're in a discussion mode, I'm sharing more ruminations than dogmatic or definitive insights. They told us the population they studied, and are the factors that would lead to differential post-randomization care a threat to validity for the endpoint seen or not, because that is ultimately whether or not we believe the findings. Thank you.

DR. AU: Thank you.

Dr. Seam, your hand is up. Can I ask if you just didn't put it down from the previous or you have another point? Oh, it just went down. I'll assume that is you didn't have any additional points.

Dr. Carlson?

DR. CARLSON: Thank you.

I think it's been a great discussion, and I think there is still a lot of benefit potentially for this drug. I am following up on a comment that Dr. Baden made about all liking more data, and I'd just like a little clarification from the FDA

whether those data would be required pre-authorization or can it be obtained post.

Then the second comment was that I believe the sponsor had raised their hand and had a point to clarify, but hadn't yet been called on. That's my commentary.

DR. AU: Thank you.

We'll start with the FDA, and I did not see the sponsor's hand, so I apologize about that.

FDA?

DR. KARIMI-SHAH: Yes. Hi. This is Banu Karimi-Shah, FDA. Thank you for your question.

Part of the discussion and part of the question today is if more data is required, when to require it? As you heard in our presentation, it can be a condition of authorization. So if you all feel that there's enough here to authorize with a condition, then the data can be obtained post-authorization. However, if a decision ultimately comes down not to authorize, then the further data would be acquired either before another authorization request were to come in or

potentially a marketing application.

So if we don't authorize the current request, we don't require any further data from the sponsor, but if we were to authorize, then the data could be required. The study could be required as a condition of authorization.

Is that responsive to your question?

DR. CARLSON: Yes. Thank you.

DR. AU: Great.

I'm sorry. Let me ask, I think the sponsor had their hand up. Did they have a comment?

DR. BARNETTE: Yes, thank you, Dr. Au. This is Gary Barnette from the sponsor.

The question has been asked multiple times today, what number of patients needs to switched? Basically, deaths need to be switched from placebo treatment for this to lose statistical significance. And in the break, we did run some analyses. I had our independent group, Dr. Wei, run some analyses on this, and there's multiple ways to do this specific analysis. But I would ask Dr. Wei to share his analysis the way he did it,

and I think the number is a lot higher than four.

Dr. Wei?

DR. WEI: Thank you, Gary.

This is L.J. Wei. Allow me just to share very quickly what I did during the lunch hour. I appreciate our FDA colleague presenting the tipping-point analysis, and the gentleman claimed that we need 4 people moving from placebo, 4 deaths to treatment arm. That would bring down the significance level or bring up, if you want to say.

I did a very simple calculation. For my calculation, I needed 6 patients probably, not only four. But remember, if we move with 6 deaths from placebo to treatment arm, that means you artificially make the number of deaths to 12, not six. So I'd like to emphasize six is not really a correct number we should have cited. In fact, you actually make this difference enlarged to 12. So that's my point.

Another point, if you'll allow me, Chairman, thinking about the RECOVER trial, which demonstrates dexamethasone is a factor, that trial

is a 2 to 1 ratio; two means placebo patients, one is the treatment arm. And with a open label, they didn't have a prespecified sample size at all, and during the trial, after the trial is over, they found out there were a very sick patient, so that's a benefit for the patient, but the death rate difference is only 11 percent.

I just want to mention the drug trial, RECOVER, so-called by UK people, was not really ideal even compared to this current [indiscernible] trial. Thank you very much.

DR. AU: Thank you.

Dr. Lee?

DR. LEE: I just wanted to rebut on that because regarding the dexamethasone trial, it's a much larger trial, and there was biological plausibility.

The other thing is I don't think we are arguing about the point estimates being impressive. I think it's really the question about robustness of the data affected by lingering uncertainties, mainly related to the small sample size. I just

want to bring that up because I think these trials are very difficult to do -- I recognize that completely -- but we are charged to make a recommendation to the FDA related to emergency use authorization of a drug we don't really understand, and then a very small sample size and some lingering uncertainties. So that's my comment there.

DR. WEI: Sorry, ma'am. If I may, for the RECOVERY trial, we only had 300 patients in the traded arm; not very large.

DR. AU: I'm sorry. I'm going to interrupt the sponsor. Please wait to be called on. Actually, I'm going to curtail this conversation because this is really not about other trials. I really don't feel like this is about the question at hand, so I'm going to curtail that part of the conversation.

I saw Dr. Shapiro's hand go up.

Dr. Shapiro?

DR. SHAPIRO: I'll drop it. It was about that as well, just that the dexamethasone was a

totally different time of the pandemic, a different thing, but we'll curtail that conversation.

DR. AU: Thank you.

DR. KARIMI-SHAH: Dr. Au, this is Dr. Karimi-Shah. I'm sorry. Could the FDA have an opportunity to respond to the new analyses that was presented?

DR. AU: Yes, absolutely.

DR. KARIMI-SHAH: Thank you so much. I had raised my hand, but I know I'm sort of low down on the list of the hand-raisers here.

Could I please ask Dr. Dharmarajan if he would respond to the analysis?

DR. DHARMARAJAN: Yes. Thank you. This is Said Dharmarajan from the FDA.

I will just briefly explain how we got to the number 4. What we did was the primary analysis was a logistic regression analysis model which controlled for treatment and four other baseline covariates. So in this analysis module, we looked at the subjects who had the most influence on the treatment effect estimate, and we saw that if we

changed the four subjects that had the most influence -- and these four subjects had an outcome of death, so if you change the death status to being alive, then the analyses you did are not nominally significant results at the 0.05 level.

So that is how we arrived at the number 4, and again, pointing out that this was a conditional treatment effect estimate and adjusting for the covariates. So we ran the analysis and we checked which were the most influential patients, and saw how many of them would be required; in other words, what would be the minimum amount of patients required to kind of get the results.

DR. AU: Thank you.

I'm going to move to Dr. Gillen.

DR. GILLEN: [Inaudible] -- opined, but I just had a quick clarification, given what the FDA just said.

By definition of influence, then, what you did was look at the delta-betas, I presume, on the treatment effect. Was that your definition of the 4 people that had the highest influence? I just

want to contextualize how you did what you did.

DR. DHARMARAJAN: Yes. This is Sai Dharmarajan again from the FDA. And yes, you're absolutely right. You're exactly right. It's delta-betas.

DR. GILLEN: Okay. Thank you.

DR. AU: Dr. Karimi-Shah, I see your hand is up. Is that from the previous or do you have another comment you'd like to make?

DR. KARIMI-SHAH: Thanks, Dr. Au, and thank you for calling on me again. Banu Karimi-Shah. I just wanted to reiterate Dr. Lee's point that RECOVERY enrolled thousands of subjects, and we have a lot of prior information on dexamethasone. That point was made by Dr. Lee, but thank you.

DR. AU: Great.

Dr. Gillen, your hand is still up. Do you have another point you'd like to make?

(No response.)

DR. AU: Okay. I'll take that as a no.

If there are no other comments -- oh, Ms. Schwartzott?

MS. SCHWARTZOTT: Okay. Listening to all these comments and this discussion, my thinking is evolving. The doctors that enrolled these patients originally, hopefully took the risk because there was a clear need when other treatments were not working.

It bothers me that halting this treatment that is so promising takes away an option, but I'm still concerned about the lack of data. It also bothers me that there's a placebo group, even though I understand why it's there. But if I'm that upset about the placebo group, that means that I have faith in the drug. So I feel strongly that we continue with this data collection to determine the less controlled use in the past -- or in the future.

Now, here's the debate. If you require data collection under emergency use, should you be doing that or voting no and requiring a new trial? My question is, if the future data shows safety and efficacy concerns after enrollment and treatment of future patients in the emergency use, maybe this is

the most efficient way to go. What would that look like if those -- would it immediately be pulled? Would we come back for more discussion? Which is the more efficient, faster approach for more data collection?

I hope that's not too much --

DR. AU: No, I think that's a really important point. I think that part of the conversation will continue to evolve as we go to the different questions.

Do you have any other points? Otherwise, I want to shift to Dr. May.

MS. SCHWARTZOTT: That's a no.

DR. AU: Okay. Great.

Dr. May?

DR. MAY: Yes. Susanne May. I just wanted to clarify again the differences in analysis that were done by the FDA, as well as by the sponsor with regard to those individuals.

The way that I understood it with the question that Dr. Gillen asked as well on the DS [ph] betas, this is not requiring 8 individuals,

as Dr. Wei was saying for his analysis. It is just truly 4 individuals that were picked to be the ones that had the most influence on the analysis.

So I do truly believe that it is just the four if they are picked as having the biggest influence, and it does not require more than four to change the results to be not statistically significant, and that was also my comment.

DR. AU: Great.

Let me see if I can summarize this discussion. I found the discussion incredibly robust. I think, in general, there was mostly consensus, and I would, actually, no dissent but some variations on interpretation.

What I heard from the group -- and at the end, please correct me or add to anything that I may have missed -- was the trial results, if you look at the point estimates on face, are impressive; that the effect is clinically meaningful and large, and perhaps different than other competing potential products out there.

The underlying concerns are really around

the stability of the estimates and the fact that the overall number is really among the smallest that we would have seen among the other types of trials out there. That's in the context of this still going on pandemic and how its continued to evolve over time, but part of the questions come back to issues of internal validity and whether or not small differences in underlying control arms would really affect the internal validity of the study.

We've recognized, as the discussion has been, that the overall number of patients that would need to shift are not that large. Even if you used the largest number that was presented, it would still represent about 10 percent of the population. So overall, the number needed to change the outcome of the trial is relatively small, and it speaks to the underlying instability in the estimate.

There are also issues around more rare types of risks may not be realized in a population that was of this size, so it comes back to conversation

about what is truth and some uncertainty about whether or not we truly understand what truth is in this context. There was a number of discussions about what a future study might look like and how that data might be collected, either prior or after an EUA, and it seems to me that both of those possibilities are on the table.

I think those are the major points that I heard. If there are any others that anyone thinks I failed to mention, I'm happy to entertain those now.

(No response.)

DR. AU: Fine. I think we can go on to question number 2. Question 2 is, discuss your level of concern regarding the limited size of the safety database for this new molecular entity.

If there are no questions or comments concerning the wording of the question, we will now open the question to discussion. Are there any questions or concerns about the wording?

(No response.)

DR. AU: Great. Let's go on to the

discussion.

I'll just open as we're waiting for people to raise their hands. This is David Au. I feel like we've actually had a fair discussion of this topic already, but I think it would be useful to kind of recapitulate some of them for the record.

Dr. Chertow, we'll start with you.

CAPT CHERTOW: Okay. This is Dan Chertow. Thank you for the question. I really appreciate the conversation and the clarifications about my three versus four comment, and then the subsequent discussion around it. I thought it was very helpful.

As it relates to this question, I reflect on our charge and the statute that the FDA uses to make these EUA determinations. The wording of that states, "known and potential benefits and known and potential risks." So I think that most folks in this group -- and I don't want to speak for folks, but I don't think anybody in the group would say that the benefits are, quote/unquote, "known beyond a doubt." There has been doubt that was raised,

but I think most folks would agree that there are data to support potential benefit of the drug.

Then if you take the flip side of it and say, "Well, what about known or potential risks?" I think, based upon the data that was presented, understanding that the group that has been studied, with this new entity, is a small group, whether you include the population from the prostate cancer, or not -- studies -- that if you look at the wording of the charge, known and potential risks, things that fall into the known category, that seems so far, understanding limited size seems to be an empty. I don't think anything falls in the known category.

There are a few things that were raised that would fall into the potential category, although those risks, when compared to the potential life-saving benefit, seemed, on average, small. So I realize we're making our decisions -- of course, the comments, the discussion are quite helpful -- but I go back to what is the language that's guiding us. And I would be interested to

know if anybody in the group interprets the language differently, and/or guidance from the FDA saying, "Dr. Chertow, you're interpreting the language incorrectly." That's it. Over.

DR. AU: Thank you.

Let me call on the FDA for a moment to follow up that on your interpretation because I think that would be helpful to the group.

DR. KARIMI-SHAH: Hi. This is Dr. Karimi-Shah, FDA. I can respond to Dr. Chertow's question.

Again, from the wording in the charge, yes, it's based on the totality of scientific evidence, first of all, if the known and potential benefits of the product to treat this condition outweigh the known and potential risks, so you have that wording correct. And again, there is leeway in the wording for this very reason because the standard for emergency use authorization is a different standard than the approval standard.

So again, this is something that we are asking for your interpretation of because it is not

straightforward but, again, you do have the wording correct in terms of how you're thinking about the issue.

DR. AU: Thank you very much.

Dr. Gillen?

DR. GILLEN: Thank you. Daniel Gillen.

I'll put this in context of the way I think about most safety problems, and that is with safety, were concerned with rare events, and it's generally not the thing that we have observed; it's the things that we're worried about not having yet observed.

It is true, for me anyway, that mortality is certainly probably the biggest safety endpoint, and we've already discussed that ad nauseam with respect to the study and talked about the benefits based upon the observed data. But I think that when we think about why a trial size of 500 might be recommended, well, when you think about having 300 patients treated, you can think about the upper bound of a 95 percent confidence interval if you haven't seen a rare safety event occur yet, and

that's going to be approximately 3 over N, so that gives you about a 1 percent upper bound.

To this point, if we just take the 902 data -- and I know we can also include some of the 901 data; I would be a little hesitant of including the prostate cancer data -- we're at about 2.1 percent upper bound if I include the 901 data along with the 902 data, and that's not exactly reassuring on rare safety signals in a brand new molecule.

So again, all of this goes into the context of the original sample size wasn't huge, it was 300, but dropping it down to 210 removes 30 percent of the sample size, 30 percent of the treated patients that you're going to see. So when we think about the role of sample size, particularly with respect to safety, we want to think about the precision of those extremely rare events.

So I guess it's coming across now that I do have a concern about the level of that limited safety sample size data that we have. Again, a lot of it is offset by the fact that the mortality

signal that we've seen to this point is strong, but there are still rare events that could be occurring that we may not be observing in this patient population. Thank you.

DR. AU: Thank you.

Let's see. Dr. Baden?

DR. BADEN: Lindsey Baden.

This question I think is easy to answer. Level of concern regarding limited size of the safety database for a new molecular entity, extremely high. Level of concern is through the roof, very high. I'm not even worried about rare events. I'm worried about common events. However, I look at this in relation to the outcome of greatest concern mortality. So in the context of high mortality, the amount of safety data for other kinds of events I'm less concerned about.

If the mortality benefit were substantially lower, then this becomes a much greater concern. So at least as I think about it, I think about it in relation to the totality of the data in terms of what kind of safety am I worried about that would

outweigh the kinds of benefit that are being proposed. So level of concern, very high, even for common events; on the other hand, what set of events would outweigh mortality? Over.

DR. AU: Thank you.

Dr. Evans, you had your hand up briefly. Did you have a point that you'd like to make?

DR. EVANS: Well, I actually briefly had it up because I was just trying to get some things in the record as you'd requested, and that seems to have been accomplished. I'm sorry. First of all, this is Scott Evans.

I am somewhere between Dr. Gillen and Dr. Baden on this current topic because, as stated, not only is it a new molecule, it's one where the mechanism action is not clear to me. I know that there's a demonstrated effect on microtubule function and how it actually functions to exert an antiviral effect, and there are inferences about impact on inflammasome activation. But I am certainly not clear on the mechanism of action, which I think further drives up my concern about

the level of scrutiny we have to give to potential safety events because we just don't know what we're looking for.

I think that's what Dr. Gillen was alluding to earlier, but I do think that's an important concern. And I think it's informative that FDA had previously recommended 500 or more patients at least to start off with. So I'll stop there. Thanks.

DR. AU: Thank you.

Dr. Shaw?

DR. SHAW: Yes. This is Pamela Shaw. I just wanted to state some of my concerns for the record regarding the safety database. I share some of the concerns that have been expressed. It is a small number of individuals that have been exposed. We don't really understand the safety, and we're looking at the potential benefit or efficacy, and we're nervous about it because of the small 2 to 1 randomized trial that was stopped early, or with fewer people than originally planned.

My concern about the EUA, if we think that

this mortality benefit is robust, the 20 percent risk difference, you really only need another trial of 200 people to see that with 80 percent or more power. So I'm trying to understand the rush in terms of the risk-benefit of the EUA now, which is somehow we don't think we can enroll 200 people in a short period of time to get more information both on safety or efficacy. And I'm not saying 200 is the right number, but I'm trying to think, if we do the EUA, what conditional safety information can we get if we're on the one hand saying we need EUA because we can't do another small trial, given the original request of at least 500 people?

So I guess I'm not seeing the argument for why this is different than before. I heard from the FDA that the only reason we're here is because of the effect size, because ordinarily for an EUA, I think I heard you wouldn't be doing it with just less than 100 people in the U.S.. We wouldn't be doing it with so little evidence with our new molecular entity, but it's this risk difference.

So for me, I'm just not convinced that it's

enough to push us against what's been usual safety accumulation before unleashing this to a broader use. Those are some of my thoughts on a general level of discomfort that there hasn't been enough data accrued to motivate an EUA with such a small amount of safety data; not enough evidence on efficacy or safety at this point. I find it concerning. Thank you.

DR. AU: Thank you so much.

Dr. Kim?

DR. KIM: Edwin Kim, University of North Carolina. Normally, I think, yes, the limited size of the safety database with a new molecular entity would have me quite concerned, but here, I think what I've tried to balance out in my head is it's going to be the idea that this is intended for a 21-day course while hospitalized, as opposed to long-term use of some other medication like colchicine.

This is in patients that are at high risk for ARDS, as well as mortality, as we've spoken about previously, so I think those are a couple of

the factors that have me, I guess, more tolerant, I guess, is maybe the best word I would use of this limited size.

Additional data accumulated, whether in a study or in real life, is going to be critical here to truly understand that, but I think a limited dosing -- if I'm understanding correctly, 21 days and that's it, in a hospital setting, in a patient that is otherwise at high-risk -- has me, again, a little bit more willing to tolerate a level of risk. Thank you.

DR. AU: Thank you.

Dr. Gillen, do you have follow-up?

DR. GILLEN: Yes. Daniel Gillen. Thank you, and I just wanted to clarify something with respect to Dr. Baden's comments regarding what I was saying. I don't disagree with Dr. Baden, and I appreciate the fact that -- and as I mentioned, mortality is the number one safety outcome that I would be thinking of.

If I were taking the mortality rates that we saw in the placebo arm at face value, that those

were a fact, then it would lower my concern about the rare events. The issue that I struggle with here is that it's highly variable relative to what we've seen across multiple studies -- you saw this in the FDA's document -- and we don't know where that mortality rate is going off into the future because of such a fast-changing environment that we're dealing with.

So if we're talking about approval of a drug that's going to be used down the road, I do think, for multiple individuals as we come through with different concomitant medications and other settings, we do need to worry about the rare event that might come up in a brand new molecule for which we have a limited understanding of the mechanism of action.

So that's my take on this, and why I stated what I stated about the rare events, and how many subjects we would need to roll out of 1 percent and then rate [indiscernible]. Thank you.

DR. AU: Thank you.

I actually rose my hand, so I'll lower it

now. I just wanted to actually kind of add on to what Dr. Kim had said and in context of Dr. Shaw as well, which is this is an ongoing pandemic with still a number of people, 3 to 400 people, dying a day. So I think the issue that we're balancing is a competing risk issue. What is the potential benefit for that individual patient who's in the hospital versus the risk of the other people who would be exposed to drug who are also in the hospital?

So I just wanted to contextualize the decision. I agree with what everyone has said thus far, which is that the safety data set is very limited, and is inadequate to be able to really make any definitive comments about. But I just wanted to point in terms of risk balance from a patient perspective, I wonder where patients would also fall on understanding a potential for benefit against a potential for risk. That's all I wanted to add. Thank you.

Dr. May?

DR. MAY: Susanne May. Regarding safety,

one other concern that can come up is that people get the drug that may not need it at all, and I was wondering, and I noticed that in the New England Journal of Medicine paper that shows the study characteristics of patients, they included at least one individual in each of the groups that had an oxygen saturation level of 100 percent. Unless that's a mistake, I thought that was part of the exclusion criteria, that it would have to be less than or equal to 94.

So I'm wondering whether there were a number of individuals in this study that did not meet inclusion criteria or met exclusion criteria that received the drug, and how that would influence our view of safety and the limited safety data, and potentially having individuals that received the drug but actually didn't need it.

DR. AU: Thank you. Do you want that comment to go to -- do you want that query addressed by the sponsor or by FDA, or both?

DR. MAY: I think it could probably be the sponsor with regard to meeting exclusion or

inclusion criteria, but the FDA might have that data as well.

DR. BARNETTE: Mr. Chairman, this is Gary Barnette. Is it ok if I address that?

DR. AU: Please do.

DR. BARNETTE: Thank you.

Again, this is Gary Barnette. What you're seeing in the New England Journal of Medicine paper is not the inclusion/exclusion criterion number; it's actually the number on day 1. So those patients were already on supplemental oxygen. Every patient coming into the study, and I think Dr. Busch mentioned, we collected the data in their charts or in their emergency room visit, what their O2 levels were before they came into the study, and as long as they were less than 94. We didn't dechallenge them from oxygen and then measure their O2 levels to see if they were eligible; we used their hospital levels coming in.

DR. AU: Thank you for that answer.

DR. MAY: Very helpful, yes. Thanks.

DR. AU: Dr. Seam, I'm going to give you the

privilege of being the last person to comment. Thank you.

DR. SEAM: Thank you. I'll be brief. I think the only other thing I'd say in terms of this safety database, as we discussed before, this would be given to the same patients who would also be receiving things like baricitinib, tocilizumab, and other things, and a minority of patients received that, so we're not sure about that interaction.

DR. AU: Great. Thank you.

Let me see if I can summarize some of the comments from the committee, and please, as I mentioned last time, let me know if I've really missed any important concepts here.

Overall, I think, again, there was general consensus from the committee that there was really a lack of a significant safety database in the sense that the number of patients that were enrolled in the actual trial were smaller than the number that would have been in the original trial, in that there are additional concerns around the fact that this is really a new substance that

doesn't have a clear mechanism of action, so we're not exactly clear what the safety signals may present.

There was some comment around what is the urgency around an emergency use authorization in the context of ongoing availability of treatment, and whether or not it would be beneficial to have a more significant safety database in that context. I think that needs to be offset, as was brought up, by the issues of a known mortality or demonstrated mortality benefit if you take the trial data on face. But I think, in general, as I noted earlier, I think there's a consensus that there is insufficient amount of information in the safety data to be confident about a lot of rare events, or even common events, and then also around drug-drug interactions and the like.

Let me send this back to the committee and see if there any points that people made that I've missed.

I see Ms. Schwartzott.

MS. SCHWARTZOTT: I asked some questions

about the timeline and the control of the emergency use criteria. I'm wondering how strict the emergency use criteria can be. Can the enrollment criteria be limited to severe cases like the World Health Organization's 5 and 6 levels when other treatments have not worked, and the patient is deteriorating? How strict can we go on that?

Also, how often are those data collections viewed by the FDA? How much control is there; and then what the timeline would be for emergency use if we chose to go that route instead of requiring another full trial? It seems to me that it would be a more efficient use to have control over the emergency use, and move it forward that way, than to start all over again with a trial that would likely take a lot longer. That's just my thoughts and question.

DR. AU: Thank you.

Can the FDA comment on some of those for us, please?

DR. KARIMI-SHAH: Hi. This is Dr. Karimi-Shah from FDA.

Thank you for your question, Ms. Schwartzott. I think it had multiple parts to it. The first part of it, I think what you are asking was if we could restrict the further data that's required to a more severe population than what the authorization is issued in? Was that your question?

MS. SCHWARTZOTT: Yes. I'm concerned, just as other doctors were, that maybe it was being used for patients like in category 4. I question if that was really necessary.

DR. KARIMI-SHAH: If I understand your question, I think that, again, that's one of the questions that we're asking the committee, is the appropriate population, and if this were to be authorized, who that population would be.

As per the statutory requirements for a condition of authorization, the trial to be conducted would be in the patient population in whom it was authorized because that would really be the only way in which we could gather data for the authorized population.

So if the committee feels that there's only enough data for, let's say, the WHO 5 and 6 category, and that's in whom it should be authorized, then the condition of authorization would then be in those patients. It kind of goes to reason that if you're thinking that the condition of authorization trial should only be in a certain population, that it probably shouldn't be authorized in the broader population to begin with.

In terms of the timeline, what I can say is we always review the data as expeditiously as possible as it comes in, and it's really based on the information available to us. We try to make a determination that the criteria for issuance are met. So before we issue that condition of authorization, we would negotiate those timelines on any condition with the sponsor. So there's some flexibility there, but there's also an element of expeditiousness and efficiency.

MS. SCHWARTZOTT: Thank you.

DR. AU: Thank you. I think that was an important question.

I don't think I necessarily need to summarize again, but I do think we're at a opportunity to have a short break. I know it's 3:52 Eastern Time right now.

Can I give everyone five minutes just to rest and stretch a little bit, and then we'll come back to question number 3, which is a voting question, and then question number 4, which is a discussion question again. So why don't we come back in five minutes or at 57 after the hour? Thank you.

(Whereupon, at 3:52 p.m., a recess was taken.)

DR. AU: Welcome back, everyone. We will now move on to the next question, which is a voting question. Takyiah Stevenson will provide the instructions for the voting.

DR. STEVENSON: Question 3 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record, and all questions and

discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Thereafter, the chairperson will go down the roster and each voting

member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to, however you should also address any subparts of the voting question, if any.

Are there any questions about the voting process before we begin?

(No response.)

DR. AU: Great.

I will read question 3. Do the known and potential benefits of VERU-111, when used for the treatment of adult patients hospitalized with COVID-19 at high risk of ARDS, outweigh the known and potential risks of VERU-111? If yes, discuss the appropriate patient populations in which VERU-111 should be authorized. If no, discuss what additional data would be necessary to assess the benefit versus risks of treatment.

Are there any questions or issues about the wording of the voting question?

(No response.)

DR. AU: If there are no questions or

comments concerning the wording of the question, we will now begin the voting on question 3.

DR. STEVENSON: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. STEVENSON: Voting has closed and is now complete. Once the vote results display, I will read the vote results into the record.

(Pause.)

DR. STEVENSON: The vote results are displayed. I will read the vote totals 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.

There are 5 yeses, 8 noes, and zero abstentions.

DR. AU: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote, if you wish.

We'll start with Dr. Chertow.

CAPT CHERTOW: Daniel Chertow, and I voted yes, and the rationale was based upon the language for our charge. It was my impression that there were neither clearly known benefits nor clearly known harm or risk, but that the potential benefits, based upon the data that are available, outweighed the potential risks, based upon the data that are available in the context of this patient population that is hospitalized for severe and critical illness under monitoring for a drug that's going to be administered for a short interim. Over.

DR. AU: Thank you.

Dr. Gillen?

DR. GILLEN: Yes. Daniel Gillen. I voted no. The reason why, given the data that we have currently, I believe that we have a limited -- both

efficacy and safety -- data set with a new molecule, where we don't have a full understanding of the mechanism of action. I don't know if we're ever guaranteed to know that completely, but certainly we're far from it at this point.

I have to say, whether or not I should have considered this, I think that, at this point, taking these data and putting this out under an EUA would likely harm our ability to answer this question truly in the long run, which I wish would have been done before, actually, with a reasonable sample size. So that fear of actually being able to fully understand the risk-benefit profile in patients partly led to my decision. Thank you.

DR. AU: Thank you.

David Au. I voted yes for the exact same rationale as Dr. Chertow.

Dr. Kim?

DR. KIM: Edwin Kim, University of North Carolina. I voted yes. As previously mentioned, I think the benefit of protecting against mortality, although maybe the magnitude is not as big because

of some of these uncertainties, I think there is likely a benefit to be had, and the risks of a short course, 21-day, in-hospital treatment I think are going to be manageable. So the benefits do outweigh the risks, in my opinion. Thank you.

DR. AU: Thank you.

Dr. Lee?

DR. LEE: Janet Lee. I voted no, and it was mainly because of the concerns related to robustness affected by the lingering uncertainties and the small sample size. In reference to the second portion of the question that's asked, if no, I would have liked additional sample size, and perhaps going forward, maybe a superiority design proposal as recommended by the FDA would increase my confidence level. Over.

DR. AU: Thank you.

Ms. Schwartzott?

MS. SCHWARTZOTT: I voted yes, kind of along the same lines as Dr. Chertow and Dr. Kim. I felt that the benefit of avoiding death was greater than the risk of the adverse event, considering that it

is in a hospital setting, but I do feel there should be future control by the FDA. Thank you.

DR. AU: Thank you.

Dr. Baden?

DR. BADEN: I agree with all of the previous voters, both yes and no, in that I think we're all on the edge of how --

DR. AU: I'm sorry, Dr. Baden. Could I have you state your name before --

DR. BADEN: Oh. Lindsey Baden, Brigham and Women's, Boston. I agree with the prior voters who voted both yes and no because we're all on the edge of how do we weigh the efficacy signal and the absence of a safety signal with the absence of safety data. And as already stated, in this population of severely ill individuals and -- I kept stating before -- 30 percent mortality, I'm not sure what led to the WHO 4. It's the WHO 5's and 6's, hospitalized, failed maximal standard of care, who, as discussed, hundreds are dying a day across the country, let alone elsewhere, how can we generate data while leveraging the EUA statute to

provide additional therapies? And I think we can do both.

I think if focused on the population that was studied, then as Dr. Chertow said, the wording of the statute is the known -- what we anticipate the benefits and the risks to be on balance, it's favorable, as I don't like mortality.

So I voted yes. I think there are ways to focus the authorization to the population that's more likely to benefit and ways to generate data that can continue to inform us about safety and efficacy, and that we can do both. But I would like this to be available to those of us taking care of patients the next day, to week, to month, who have no other options and are facing a sad mortality rate. Over.

DR. AU: Thank you.

Can I ask you one follow-up, which is what is the appropriate population for which VERU-111 would be authorized, or should be authorized, do you think?

DR. BADEN: Yes. In my view, hospitalized,

WHO 5 and 6, failing standard of care, the maximum standard-of-care therapy. I think that's as best as I can sift through the data available because there's a lot of opacity of exactly who was studied and what was done, but that would be the population, from what I'm aware of at this point, that I would favor.

DR. AU: Thank you.

Dr. Seam?

DR. SEAM: Nitin Seam. I voted no. I think, again, as Dr. Baden said, I think a lot of agreed, most of us agreed, about a lot of the [indiscernible]. I think for me, fundamentally, I worry about the efficacy question. The mortality with such a low end is quite high for what we're seeing right now, the standards of current care met for this population.

I echo with Dr. Baden. I think the group we want to study is high-flow nasal cannula, non-invasive ventilation, or mechanically ventilated patients, but those patients, particularly a group receiving steroids, as well as

baricitinib, toci, and so forth. So I'd like to see a larger trial with a proper placebo group, a 1 to 1 trial with a larger endpoint.

DR. AU: Thank you. Could you comment on whether you think any additional data would be necessary or just the volume of patients would be necessary in terms of being able to assess the benefit versus risk of treatment?

DR. SEAM: Yes. Well, I think it's an interesting question. I think, for me, the WHO 4 with a mortality of 27 and some percent is quite high. Again, I think the sponsor's mentioned they had people who had multiple comorbid criteria. I'm really not sure about all those being, quote/unquote, "at risk for ARDS," and I'm not sure about the other studies that include WHO 4, how many of those had. So I would say groups 5 and 6 would be the group I think should be studied as well.

Again, with 5 and 6, if possible in a future study, really understanding the elements of critical care, or standardizing the process, or is

everyone receiving low tidal ventilation, is there a threshold for prone positioning, and all the standards that we use, and the typical processes that we're managing in our ICUs for COVID.

DR. AU: Thank you very much.

Dr. Shaw?

DR. SHAW: Yes. Pamela Shaw. I voted no. I think why, as to question B, is I don't think I'm able to judge the potential benefit with the data so far. Particularly in the target population, you would be exposed to the emergency use authorization, which too few people in the United States subject to the standard of care -- that we would kind of understand in the United States -- have been exposed to this drug so far.

So for me, I really think I do need to see an additional trial to get that number exposed closer to the 500 or so; that is what the FDA was generally comfortable with. In addition, if that was just a smaller trial, even repeating the trial that was done, we'd be able to really have good power to see if that effect size was at all robust

or repeatable, and potentially in this better defined population. I think that would be tremendously helpful from both understanding the potential benefit and the potential risk.

Also, I think the uncertain mechanism of action and the better blinding is adding to this inability to judge the efficacy, so some information on viral load trajectories would also be helpful in that additional data.

DR. AU: Thank you.

Dr. Walker?

DR. WALKER: Hi. Dr. Roblena Walker. I agree with Dr. Shaw and the other committee members who have expressed no. I think the limitation of efficacy data, as well as the safety data, is what made my determination to vote no, and moving forward, I think additional baseline data would need to be incorporated into another study.

In addition to that, looking at the sample size, along with the demographics of the sample size, was a concern of mine, too, and a closer assessment of the biological chemistry of the drug

among additional comorbidities I think would also be useful. Thank you.

DR. AU: Thank you very much.

Dr. Evans?

DR. EVANS: This is Scott Evans from Houston, and I voted no. I found this to be a challenging vote because I certainly agree that there is an impressive point estimate for the effect. But as has been said by a few colleagues already, it's hard to know whether to believe that effect because of the potential anomalies observed in the placebo mortality; some peculiarities of the viral burden patterns; and potential imbalance factors between the groups in the setting of a small size, where only a small number of outcomes would need to be changed to influence results.

We have, as has been also mentioned, poor [indiscernible] in the mechanism of action, and related to that, I have concerns that the current data are not necessarily representative of the proposed context of use. And actually taking that a step further, listening to my colleagues, I'm not

even sure what the right context of use is, because what I've heard said by other members of this committee is this might be something we could throw at people who were failing everything else we could do. And if the mechanism of action is as proposed, that is likely too late to intervene. If we understand mechanism correctly, the patient might benefit much more at an early stage, perhaps the patient who is newly diagnosed and rapidly failing, not someone who's been sitting on the wards 14 or 30 days, and certainly not one who's already received maximal therapy.

That's what I would look for in follow-on data, would be a better clarification of who are the populations that are responsive, and certainly broaden the number of patients in the trial. Thank you.

DR. AU: Thank you very much.

Dr. Shapiro?

DR. SHAPIRO: Yes. Dave Shapiro. I voted no. I think the multiple concerns raised over efficacy and safety due to the small sample size,

combined with the place where we are right now with the evolution of the virus itself, and the immunity, and the current therapy, there are hundreds dying a day. If they're dying of ARDS and lower lung disease, it should be pretty easily achievable to get a larger study and prove it.

DR. AU: Very good

Dr. May?

DR. MAY: Susanne May. I voted no, and just adding on to Dr. Shapiro's comments, one of the other main things that didn't convince me to approve this is the lack of robustness of the results, even though they're impressive, for a new molecular entity that has no direct evidence to support the antiviral activity. I would think that it does require a second study that should have a substantial number of patients in the U.S. Those were my comments.

DR. AU: Thank you, Dr. May.

Let me see if I can summarize. We have a vote of 5 to 8, which is obviously a split decision. On the other hand, I don't actually

think we actually have that much dissidence in terms of the rationale. I think it was just a matter of where people fell on the judgment side.

Overall, I think the ways that the yeses kind of weighed were they took a little more stock in the potential of benefit versus the potential of harm, while still acknowledging that there were a number of important limitations to the data, and that those data included the instability of the estimates and confidence that we had within the trial results, mostly around sample size, issues around mechanism, as well as some issues representative of the U.S. population and treatments for standard of care.

I think that all kind of speaks a little bit to what we would want to see in terms of an appropriate case in population. I don't think we're here to kind of design a study, but the consensus I think I heard was really more around WHO 5 and 6, with some consideration around 3, and how should this drug be used in the context of failure of other therapies?

I do think that also raised the issue that in terms of data collection or in study design, there needed to be better standardization of current treatment therapies, current therapies that are available to patients, either the collection or standardization in the enrollment process.

Finally, among several people, there was a discounting of a need for emergency use authorization just because the way the pandemic has shifted over time, that therapies and mortality are smaller than they were or less than they were before. But even in that context, because of the number of ongoing deaths, it seemed like there was the ability to recruit a new study sample in this for a new trial. I appreciate the committee's vote and summary of that.

We will now move on to question 4, which is a discussion question. I'll read it now.

If authorized, the agency believes that additional data are necessary to understand the benefit-risk assessment as a condition of authorization. Please discuss the proposed design

aspects of the study to provide this additional data.

If there are no questions or comments concerning the wording of the question, we will now open the question to discussion.

(No response.)

DR. AU: I don't hear any questions or concerns, so let's go ahead and open the question for discussion. Could people use the raise hand function again?

Dr. Lee?

DR. LEE: Can you hear me?

DR. AU: Yes, I can hear you.

DR. LEE: I just wanted to ask about the study population because you had suggested that some folks had thought subjects with WHO 5 and 6 severity -- but then there was some discussion about WHO 4 severity because maybe WHO 5 and 6 populations, it was a little bit too late. And I just wanted a little bit of discussion surrounding that component. That might be helpful.

DR. AU: Thank you for bringing that up,

Dr. Lee.

I do think that's a reasonable point in the context of the trial results that included WHO 4 patients. At least the data presented by the sponsor, it didn't look like there was significant heterogeneity of treatments based on WHO stage at least.

I see that there are a number of hands up. Is there anyone who would like to comment on Dr. Lee's concern?

DR. BADEN: I mean, I'm happy to try and comment. I may not be able to -- this is Lindsey Baden in Boston.

I'm happy to try and comment, Dr. Lee, but it's also just how I've been thinking about this problem, like everyone else. I'm not sure the WHO staging properly captured the enrollment here, or at least it's not fitting for me in terms of the overall literature and how it's used.

The issue of WHO group 4, and with comorbidity, I think that there can be study designs that can allow us to collect information

and realize that we may not properly understand the mortality in a given population within safety analysis that's been used in a variety of studies, whereas as events occur, the DSMB can look at it.

I'm uncomfortable with requiring a sample size that allows a very high mortality in a group. At some point, if the mortality is higher than we expect and there's a difference between the groups, the role of the DSMB and the IRB is to make sure that we don't excessively expose risk to the volunteers, and that's all volunteers, not just volunteers in a given group.

So I worry that the WHO framing doesn't give us the granularity that any of us want, so that a study in my mind can be designed that uses that kind of criteria but has a way to follow, monitor, and a DSMB review as each death occurs. And if it's as high as it was in the study that we've been discussing, then it shouldn't take very long for a threshold to be met, but that threshold may not be met with 500 enrolled. That threshold may be met with a much smaller number open to all the

criticism that we've been -- discussion that we've been having, but I think it would allow more data.

That could be the same thing with WHO 5 and 6. One could imagine, if not authorized, a study that has a safety event rate monitoring that can minimize mortality. If authorized, and authorized for a certain group, then one could imagine the group not in the authorization, for argument's sake, WHO 4 with comorbidity. They could be randomized to placebo or active and have the safety monitoring that could allow the kind of insight that we all want.

So I don't know if that completely addresses it. I'm just not sure that the WHO 4, 5, 6 has the granularity that any of us want. There's a WHO 10. There are a variety of different staging systems, so this is not homogeneous. It's quite a complex area, in my view, staging the risk at time zero of presentation, using this ordinal scale and having the kind of predictability that we wanted. Study designs can take that into consideration, mitigating the inadequacies of the WHO scale.

Over.

DR. AU: Thank you.

Let me ask the committee if there's any other discussion points on this. I appreciate the comment, Dr. Baden.

DR. SEAM: Dr. Au, it's Nitin Seam. Just going back to Dr. Lee's original point, I think that's something we do struggle with. Is it the antiviral effect versus an anti-inflammatory effect? If we accept the paradigm that early on antivirals like this will be more beneficial, and then reducing inflammation as you go up the ordinal scale.

I think that's the challenge, and I don't think we have enough information. And certainly correct me if I'm wrong, but I believe the FDA virology review didn't really feel like they had a good handle on that in terms of plausibility mechanism-wise, so I think that's a struggle there.

Just in terms of in 2022, you would expect, if you're looking at a group with a higher mortality -- I think Dr. Baden's points are very

fair, but those will typically be the patients with ARDS with lower P to F ratios, so those would typically be those patients on the ordinal scale 5 or 6. But that's a different point than, again, what Dr. Lee was talking about; are we thinking about the antiviral versus anti-inflammatory effect. I'll stop there.

DR. AU: Let me follow up with the committee on this, and then we'll see if anyone else has a comment on Dr. Lee's point, and then we can move on from there.

One of the issues that came up in this discussion and speaks to this issue is the timing, and how should FDA -- does anyone have a comment or thought about how the FDA should consider time since infection; time since symptom initiation; time since hospitalization, in terms of enrollment criteria? Because we saw with the NATIVE trial that there was quite a bit of variability that led to some other questions around whether or not patients were actually improving prior to initiation of treatment.

So does anyone have a recommendation around those points?

(No response.)

DR. AU: We don't have to. We can leave that for the FDA to negotiate with the sponsor, but it does speak to mechanism of why this compound might be beneficial.

DR. EVANS: This is Scott Evans. Your comments are in line with what I was saying in response to question number 3, which is, in my impression, this agent may be most likely to be effective in the first days of symptoms, so perhaps suggesting initiation by day 2 or day 3 of hospitalization makes more mechanistic sense to me than trialing it many days into the progression of disease.

DR. AU: I don't think we're here to design the trial on behalf of FDA or the sponsor, but just to give them consideration.

Are there any more comments regarding Dr. Lee's, otherwise we'll go to Dr. Baden.

DR. SHAW: This is Pamela Shaw. I did have

a comment.

DR. AU: Sorry.

DR. SHAW: Okay. Thanks.

I just wanted to comment specifically about the target population and even timing. One thing that often complicates these COVID-19 studies is that many people were already hospitalized. They were not hospitalized because of the COVID-19 diagnosis, but cancer or immunocompromised.

So I wasn't sure if this may help in terms of understanding all the background therapy, whether or not in the next trial, at least stratifying on this, and whether or not someone's being hospitalized for COVID-19 or whether they were folks who were already hospitalized, that could be a variable that a modest size trial would be important to think about. That's all.

DR. AU: Thank you.

Let's move on to Dr. Baden. You had a separate point, I believe, so the floor is yours.

DR. BADEN: No. I think we've been having the discussion, and I've sort of shared my

reflections. I think that the data to date are in the severely ill with COVID and because of COVID. So I think the mitigation that this tool may have is in that context. And the question is, how do we generate more data to convince us all that we're on the right path? We've been discussing the issues, I've been reflecting, so I have little to add to the discussion, to this point. Thank you.

DR. AU: Great.

Dr. Seam?

DR. SEAM: I'm sorry. I have nothing to add.

DR. AU: Okay. Great.

DR. KARIMI-SHAH: Dr. Au?

DR. AU: Yes?

DR. KARIMI-SHAH: This is Dr. Karimi-Shah, and we really do appreciate all of the considerations that the committee is giving. And you're absolutely right, we'll have to take all of these things back in the consideration of the design of another trial, but we really do welcome any specific input, trial design, how to deal with

these uncertainties, and we appreciate any specific considerations that the committee could provide as we take this back into further consideration. So I just wanted to clarify that. Thank you.

DR. AU: Thank you. I appreciate that.

Dr. Chertow?

CAPT CHERTOW: Hi. Dan Chertow. Just one comment about a proposal for a future design is to include biomarkers not just around the virus, but also around the host immune response, and ideally around the host group immune response that is along the mechanistic pathway by which this drug is hypothesized to have a benefit.

This is challenging because it requires capturing certain sample types, whether it's blood, or PBMCs, or otherwise, and characterizing them in a careful way to begin to unravel the types of questions that people are asking around what is the right dose; what is the right time of administration relative to when the illness starts; what's the right duration of administration; and what's the right population?

The truth is that one can try to glean that from doing statistics on large studies and different populations, but ultimately biologies revealed in the samples, and correlating those findings with the meaningful clinical endpoints, I think is our path forward to beginning to understand that.

So I would strongly encourage the sponsor to do that, and think about it carefully, and FDA to encourage this evaluation longitudinally of biomarkers; not just relevant to viral load, but to the proposed host response. Over.

DR. AU: Thank you.

Dr. Shaw?

DR. SHAW: I'm sorry. My hand should not be raised if you're talking to Pamela. Sorry about that.

DR. AU: No worries. No worries.

Ms. Schwartzott?

MS. SCHWARTZOTT: This is Jennifer Schwartzott. I think that there's a need to be variable with the requirements for the study,

whether it be enrollment, the time of enrollment in it, the level of the patient, or any of these categories, because this disease is so variable.

When I went into the hospital, I was already at level 5, really straddling level 6 because they wanted to vent me. But I had been walking around fine the day before, and the day before that; zero issues whatsoever. So this can happen really, really fast. All my other times with COVID, it was the same thing.

So different people go in with different comorbidities, but they also have different levels quickly or that last for a long time, where it could change, so it should be up to the particular physician to make those determinations.

Let's see. I just feel that the FDA should also monitor the overuse, though, to make sure that it is not being put through just to study the drug, which I would hope they wouldn't do. It should be based on the patient. Thank you very much.

DR. AU: Thank you.

Dr. Lee?

DR. LEE: Oh, I thought Dr. Shapiro was ahead of me.

DR. SHAPIRO: Go ahead, Janet.

DR. LEE: I just wanted to follow up on this short comment because I was thinking along the lines of what Dr. Shaw had said, and just practically speaking, I think the subjects with WHO 5 and 6 severity would be easier to identify. These are the people probably at high risk for ARDS. I think the WHO 4 severity might be a little bit tougher even with the additional selected comorbidities, and I think one of the colleagues had mentioned one of the criteria might be just hospitalized for COVID-19 because many people come in with incidental COVID-19.

So I don't know if that would be something that's helpful to the FDA, but at least the WHO 5 are the ones with the high-flow, non-invasive ventilation; and 6, these are the people who are really at risk for ARDS, and then maybe the ones who may be failing the current therapies available. That's just my comment there. Thank you.

DR. AU: Thank you.

Dr. Shapiro?

DR. SHAPIRO: I would just say that as you design the new study to really think about what's killing people now and in the next few months to come with the current variants and this state. For example, yes, we could tip patients into ARDS. That's great. You probably want to get them a little bit earlier. It doesn't have a direct predilection like it might have at the beginning of the study. And other patients are just getting their underlying disease tipped over by COVID -- cardiac disease and other -- and it could have an effect on those, even independent of ARDS. I don't want to complicate things, but I would take a careful look at the current modes of people dying today.

DR. AU: Great. Thank you.

Any other discussions? I think this has been a useful discussion for FDA.

(No response.)

DR. AU: If no other points, let me see if I

can summarize a little bit. This is going to be a little more challenging for me.

Well, I think I heard a number of discussions, but I think one of the points is that we need to triangulate and converge on understanding why this compound may work, and the idea there was a number of points around uncertainty about mechanism of action. Because there was this concern about mechanism of action, it went to questions around the dosing, the timing, the administration, and the population.

When considering the study design and the future execution of studies, maybe something that actually has more mechanistic orientation that includes biomarkers and indicators of the host immune response to help in understanding the outcomes data to make sure that the data is consistent, which has been one of the common themes throughout this discussion; do we have internal validity and do all the data converge on the same answer?

There were also discussions around to ensure

that there is proper heterogeneity of treatment effects, and particularly around particular demographic populations in that the virus and its effect on mortality has continued to change over time, and that using criteria that may have provided some degree of homogeneity or estimated population effects may not necessarily be valid today; so thinking about whether or not the WHO classification, which is an ordinal scale -- whether or not that's really the correct way to think about the enrollment population, as well as thinking about why these patients may be dying today as opposed to why they died two years ago. I think those are all incredibly insightful and valuable suggestions back to the agency.

Let me pause and again ask the committee if there was something that you think that I missed in that summary.

DR. BADEN: Dr. Au, Dr. Baden here. May I comment?

DR. AU: Absolutely.

DR. BADEN: Terrific job, complicated

concept. I really want to amplify the concept that mechanism of action is critically important. Antiviral effects versus anti-inflammatory effects, it is very tricky to try to do a study that addresses both. So I would commend the applicant and the agency in thinking very carefully about one study fits all mechanisms because they probably do have different kinetics and manifest differently in different populations.

At least given what's been presented today, I am unconvinced there are any data on antiviral effect, but it would be very important, as you think of clinical studies, to separate those and make sure the questions asked really leverage the mechanistic pathway just as discussed. Thank you.

DR. AU: Thank you. I appreciate that.

Any other comments?

(No response.)

DR. AU: Hearing none, I think before we adjourn, are there any last comments from the FDA?

DR. KARIMI-SHAH: Yes. Thank you so much, Dr. Au. This is Banu Karimi-Shah, FDA.

Wow. Thank you so much. I'd like to really take this opportunity on behalf of my team here at FDA to thank the committee members for their efforts, both in the really robust discussion today and the work that you all have clearly put in to prepare for this advisory committee meeting.

The preparation is no small task, given the amount of information we give you to digest, and we realize this. A special thank you for those of you who have been here for two days in a row with us, including our chair, Dr. Au. We appreciate the time you take out of your busy lives to help us discuss these matters that are important to the public health.

So as we go forward, we have a lot to think about with all of your input, and we'll certainly take into consideration all of the things that you have discussed as we complete our review and make our determination regarding the authorization.

I'd also just like to take this opportunity to thank the sponsor, who has been really responsive to all of our inquiries throughout the

review of this EUA and has been very professional to work with. Then finally, I'd like to thank my team, who has worked efficiently and thoughtfully to bring this forward for public discussion, which you can see the work that goes into this.

So thank you again, and with that, I'll turn it back to Dr. Au to close the meeting.

Adjournment

DR. AU: Thank you so much.

I will echo what you said. I could hear the passion in the sponsor's presentation, and I've heard it repeated many times that they've been working hand-in-hand with the FDA, which is definitely appreciated.

I want to thank everyone for the degree of preparation. These are long meetings and somewhat challenging environments in this virtual world of ours. But I do feel like what we do here is for the public good, so I think we should all feel great about the conversation. It was robust and in-depth, and it was greatly appreciated by many.

So I just wanted to thank everyone, and I'll

go ahead and adjourn the meeting. Thank you so much.

(Whereupon, at 4:51 p.m., the meeting was adjourned.)