FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE MEETING

(AMDAC)

Virtual Meeting

Thursday, October 7, 2021

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

Meeting Roster

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P R O C E E D I N G S

(9:00 a.m.)

Call to Order

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

My name is Lindsey Baden, and I will be chairing this meeting. I will now call the October 7, 2021 Antimicrobial Drugs Advisory Committee meeting to order. Dr. Moon Hee Choi is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

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

Dr. Baden?

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

DR. CHOI: Dr. Burgess?

CAPT BURGESS: I'm Tim Burgess. I'm an infectious diseases physician, and I direct DoD's infectious disease clinical research program at the Uniformed Services University of Health Sciences School of Medicine in Bethesda, Maryland.

DR. CHOI: Dr. Chandra?

DR. CHANDRA: Hello. I'm Richa Chandra. I am clinical development head for communicable diseases at Novartis Pharmaceuticals, and I'm a non-voting member representing the pharma industry on this advisory committee.

DR. CHOI: Dr. Green?

DR. GREEN: Hi. This is Michael Green. I'm at UPMC Children's Hospital Pittsburgh in the University of Pittsburgh School of Medicine. I'm a pediatric infectious disease physician with an

interest in transplant infectious diseases. Thank you.

DR. CHOI: Dr. Hardy?

DR. HARDY: This is David Hardy. I'm an adult infectious disease training, scientific and medical consultant. I have an academic appointment as an adjunct clinical professor at the Keck School of Medicine at USC in Los Angeles, California.

DR. CHOI: As just a reminder, if you are not speaking, please remember to mute your phone.

Dr. Hunsberger?

DR. HUNSBERGER: I'm Sally Hunsberger. I'm a biostatistician, and I work at the National Allergy and Infectious Diseases Institute.

DR. CHOI: Dr. Le?

DR. LE: Hi. I'm Dr. Jennifer Le. I am professor of pharmacy at the University of California, San Diego. My specialty is pediatric infectious diseases and clinical pharmacology.

DR. CHOI: Dr. Murphy?

DR. MURPHY: Good morning. I'm Dr. Richard Murphy. I'm an infectious diseases physician and

researcher at the White River Junction VA Medical Center in Vermont.

DR. CHOI: Dr. Perez?

DR. PEREZ: Good morning. I'm Federico Perez. I'm an infectious diseases physician at the Cleveland Veterans Affairs Medical Center in Cleveland, Ohio.

DR. CHOI: Dr. Siberry?

DR. SIBERRY: Good morning. I'm George Siberry, a pediatric infectious disease physician and medical officer in the Office of HIV/AIDS at the United States Agency for International Development, or USAID, in Washington DC. Thanks.

DR. CHOI: Dr. Walker?

DR. WALKER: Good morning. I'm Dr. Roblena Walker, chief executive officer of EMAGAHA, Inc., as well as research scientist, located in Mableton, Georgia; consumer representative.

DR. CHOI: Dr. Weina?

DR. WEINA: Hi. I'm Peter Weina. I am an adult infectious diseases physician. I'm director of the Office of Research Protections with the

Defense Health Agency in Washington, DC.

DR. CHOI: Dr. Bollard?

DR. BOLLARD: Hello. It's Catherine Bollard here. I'm the director of the Center for Cancer and Immunology Research at Children's National and the George Washington University here in Washington, DC.

DR. CHOI: Dr. Bridges?

DR. BRIDGES: Good morning. This is Nancy Bridges. I am a pediatric cardiologist and a transplant physician. I am the chief of the transplantation branch and a senior scientific officer at the National Institute of Allergy and Infectious Disease in the Division of Allergy, Immunology, and Transplantation.

DR. CHOI: Dr. Flatau?

DR. FLATAU: Hi. This is Art Flatau from Austin, Texas. I'm the patient representative and a bone marrow transplant survivor.

DR. CHOI: Dr. Gea-Banacloche?

DR. GEA-BANACLOCHE: Hello. Juan Gea-Banacloche. I am a transplant infectious

diseases physician at the NIH Clinical Center in Bethesda, Maryland.

DR. CHOI: Dr. Haidar?

DR. HAIDAR: Hi, everyone. This is Ghady Haidar. I'm a transplant infectious disease doctor and researcher at the University of Pittsburgh.

DR. CHOI: Dr. Lee?

DR. LEE: Good morning. My name is Lauren Lee. I'm an adult oncologist and bone marrow transplant physician and the medical director for the bone marrow transplant program at Brooke Army Medical Center in San Antonio, and have an interest in transplant-related infections.

DR. CHOI: Dr. Farley?

DR. FARLEY: Good morning. John Farley, director of the Office of Infectious Diseases at the Center for Drug Evaluation and Research at FDA.

DR. CHOI: Dr. Birnkrant?

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

DR. CHOI: Dr. Belew?

DR. BELEW: Good morning; Yodit Belew. I am the associate director for therapeutic review in the Division of Antivirals, Office of Infectious Disease, CDER, FDA.

DR. CHOI: Dr. Singer?

DR. SINGER: Good morning. This is Mary Singer, medical team leader, Division of Antivirals.

DR. CHOI: Dr. Pikis?

(No response.)

DR. CHOI: Dr. Pikis, perhaps you might be muted.

(No response.)

DR. CHOI: Dr. Pikis?

DR. PIKIS: Hi. I'm Andreas Pikis. I'm a medical officer with the Division of Antivirals at FDA.

DR. CHOI: Dr. Komatsu?

DR. KOMATSU: Good morning. My name is Takashi Komatsu, and I am the clinical virology reviewer at the Division of Antivirals.

DR. CHOI: Thank you.

Dr. Baden, if you can check the message on the chat, please.

DR. BADEN: Yes.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from

discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Moon Hee Choi will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

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

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

meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

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

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C., Section 208, their employers. These

interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of new drug application, NDA 215596, for maribavir oral tablets, submitted by Takeda Pharmaceuticals USA, Incorporated, for the treatment of adults with post-transplant cytomegalovirus infection and/or disease, including infections resistant and/or refractory to ganciclovir, valganciclovir, cidofovir, or foscarnet. This is a particular matters meeting during which specific matters related to Takeda's NDA be discussed.

Based on the agenda of today's meeting and all financial interests reported by the committee members and temporary voting members, no financial 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. Richa Chandra is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Chandra's role at this meeting is to represent industry in general and not any particular company. Dr. Chandra is employed by Novartis Pharmaceuticals.

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

DR. BADEN: We will proceed with the FDA introductory remarks from Dr. Deborah Birnkrant.

Dr. Birnkrant, please?

DR. BIRNKRANT: Thank you; waiting for the first slide. Are they up?

DR. BADEN: We see a slide NDA 215596 across the title.

DR. BIRNKRANT: Okay. It just showed up on my computer, so we're ready to go.

DR. BADEN: Thank you, Dr. Birnkrant. Please go ahead.

FDA Opening Remarks – Debra Birnkrant

DR. BIRNKRANT: Absolutely.

Well, good morning again. I would like to welcome everyone to the Antimicrobial Drugs Advisory Committee meeting. I would like to thank today's committee for making the time to review and discuss Takeda's NDA for maribavir tablets for treatment of resistant or refractory CMV infection and disease in transplant patients. I would also like to thank our review team for their efforts in preparing for today's meeting, as well as the applicant.

As background, briefly, CMV is a member of

the beta herpesvirus group. After primary infection, life-long latency is established. CMV is one of the most frequent opportunistic pathogens in transplant recipients, so it is a rare disease based on the number of transplants in the United States.

The incidence of CMV infection and disease depends on a number of factors, including transplant type, donor and recipient serostatus, and level of immunosuppression. Clinical manifestations of CMV infections in transplant patients range from asymptomatic to tissue-invasive disease, such as pneumonitis, colitis, hepatitis, and allograft infection. Clinical manifestations may also include other indirect effects, such as rejection and a higher mortality rate post-transplant. To prevent CMV disease, most patients receive either prophylaxis or pre-emptive therapy.

There are limited options for treating or preventing CMV disease, as you are aware. Note the following five drugs have limited indications for either treatment of CMV retinitis or prevention of

CMV, and they include letermovir, indicated for CMV prophylaxis in stem cell transplants; ganciclovir and valganciclovir, indicated in prevention of CMV and transplant recipients and solid organ transplant recipients, respectively, and for the treatment of CMV retinitis; and foscarnet and cidofovir, indicated for treatment of CMV retinitis. There are no approved therapeutics for treatment of CMV infection or disease in transplant patients.

Adding to the limited therapeutic options are significant toxicities seen with the antiviral products that are used. For example, ganciclovir and valganciclovir cause myelosuppression; foscarnet causes renal toxicity, severe electrolyte abnormalities, and many other adverse reactions; and cidofovir is also known to induce severe renal toxicity.

More specifically, some patients, like the ones enrolled in Trial 303 that you will hear about today, will develop CMV infection that is refractory to available therapies with or without

documented genotypic resistance. Resistance most commonly occurs after prolonged antiviral treatment in the setting of immunosuppressive therapy post-transplant. These infections are associated with worse clinical outcomes.

So for these patients, in particular, there is clearly an unmet medical need for safe and effective anti-CMV drugs because no drugs are approved for treatment of resistant or refractory CMV disease in the post-transplant setting. Underscoring the medical need is the fact that the drugs that were used in the investigator-assigned therapy arm in Trial 303 and in practice are used off-label.

What will and what won't we be discussing today? As we are only considering a limited population of refractory patients with and without genotypic resistance, a lot of time will not be spent on review of prophylaxis trials, nor will trials supporting a broader population, namely the population in 302, be discussed. Rather, we will focus on Trials 202 and 303 in support of the

indication under discussion today.

The applicant's proposed indication that appeared in the Federal Register notice for this meeting appears on this slide, however, a narrower indication will be discussed today -- that is refractory with or without genotypic resistance -- because trial results from Trial 302 are not available.

I will note that to support the revised indication, we will present primary and secondary analyses, as well as support of sensitivity, analyses and subgroup analyses. Additional analyses were conducted to address potential biases in the open-label design of the phase 3 clinical trial in refractory patients with and without genotypic resistance, where maribavir was compared to investigator-assigned therapy based on resistance testing.

The trial also cannot be blinded due to the bitter taste associated with maribavir that would lead to unmasking and the intravenous delivery of some of the products, and the need to dose reduce

in the setting of toxicity in the IAT arm thwarted the open-label design.

Prior to the voting questions, we will ask the committee to address discussion question number 1 and consider the following: that the indication is for a limited population with an unmet medical need; consider the trial design issues related to an open-label design; the primary efficacy results along with results from the sensitivity and subgroup analyses; as well as the safety of maribavir.

Voting question 2 is focused on patients who are refractory with genotypic resistance. Voting question 3 focuses on the population who is refractory to treatment without documented resistance.

Note there's a trend of benefit of maribavir over IAT that was seen in this population, and although the findings were not statistically significant, it is important to highlight that the number of patients in this subgroup was relatively small and the clinical trial was not powered for

this assessment.

I would also like to call your attention to the FDA's guidance document on CMV and transplantation, Developing Drugs to Treat or Prevent Disease. In the section under Trials for Treating CMV Infections Resistant or Refractory to Treatment with Available Drugs, it states that to include both groups of patients, that is resistant and refractory to treatment, the sponsor should demonstrate statistical significance in the overall population. Efficacy in the subgroups of resistant and refractory to CMV antiviral drugs should be consistent with the overall treatment effect.

Now we can turn to the agenda. Briefly following my remarks, I'll turn it back to the designated federal official, and then the applicant will present their findings, which will be followed by clarifying questions. This will be followed by the FDA presentation by Dr. Andreas Pikis and Dr. Takashi Komatsu, with time for clarifying questions. There will be an open public hearing at 1 p.m., which will be followed by the charge to the

committee, discussion, and voting questions.

Thank you very much. I'd like to turn it back to Moon Hee Choi.

DR. BADEN: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the 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 interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

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

issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Takeda's presentation. I will turn it over to Dr. Cronin from Takeda, who will guide the presentation.

Dr. Cronin?

Applicant Presentation – Michael Cronin

DR. CRONIN: Thank you and good morning. To the chair, members of the panel, the FDA, and members of the public who are watching today, I'm Michael Cronin, director of Global Regulatory Affairs at Takeda. We're pleased to be here with you today to discuss maribavir.

Maribavir is a novel antiviral for the treatment of resistant/refractory, post-transplant, cytomegalovirus infection that represents a therapeutic advance over available therapy. Maribavir is orally bioavailable with a novel mechanism of action that is differentiated from the shared mechanism of action of existing CMV antivirals. This enables maribavir to treat CMV

infections that are refractory with or without genotypic resistance to prior therapy.

Thus, maribavir fulfills a high unmet medical need due to its demonstrated efficacy in post-transplant CMV infection and its favorable safety and tolerability profile, which provides a safety advantage over existing CMV antivirals.

Known as a rare disease overall, post-transplant CMV is a common and serious threat for patients who received a second chance at life with a transplant. Approximately one-third of these transplant recipients will develop CMV infection, and if left untreated, CMV infection can progress -- [inaudible – audio lost].

(Pause.)

DR. CRONIN: Are we back? And if so, I'll resume I believe with slide CO-4.

DR. BADEN: Yes. Dr. Cronin, I can hear you now. We lost you at the second bullet on this slide.

DR. CRONIN: Excellent. Thank you so much.

So as I mentioned, if left untreated, CMV

infection can progress to severe and even life-threatening, tissue-invasive disease. Importantly, CMV, if left untreated, can lead to serious consequences, and these complications are not only associated with symptomatic CMV disease, but asymptomatic CMV infections as well.

As the FDA mentioned, to date there are no antivirals which have received FDA approval for treatment of post-transplant CMV. Existing antivirals -- ganciclovir, valganciclovir, foscarnet, and cidofovir -- are used empirically to treat post-transplant CMV infections and, thus, they lack adequate safety and efficacy data from controlled clinical trials in this population typical of FDA-approved therapies.

Each of these agents have severe toxicities that limit their use and can potentially lead to failure to control CMV infection. Because they share the same mechanism of action, they're susceptible to cross-resistance, and 3 of the 4 agents require IV administration, which can necessitate hospitalization and monitoring.

For these reasons, there is an urgent unmet need for an efficacious and safer therapeutic option with a different mechanism of action from these existing antivirals. Maribavir meets that need.

This slide shows a schematic of the viral life cycle, showing points at which CMV antivirals work. The gray box represents currently available therapies, while the three red arrows indicate where maribavir exerts its effects on the viral replication cycle.

All existing agents commonly used to treat CMV infection are DNA polymerase inhibitors, which target the virus at UL54, a specific location on the viral genome controlling viral DNA replication. In contrast, maribavir is the only antiviral that targets CMV at UL97, which not only results in inhibition of viral DNA replication, but also encapsidation and nuclear egress.

Due to this unique and multimodal mechanism of action, strains of human CMV resistant to ganciclovir, foscarnet, cidofovir, or combinations

of these drugs, remain sensitive to maribavir. Let me walk you through the history of maribavir's development.

Maribavir has been well characterized with more than 1500 subjects exposed to maribavir to date. Maribavir, at a dose of 100 milligrams BID, was initially developed for CMV prophylaxis. This 100-milligram BID dose did not meet the primary endpoint in phase 3 studies, and the prophylaxis program was stopped. Accumulated data from limited compassionate use programs suggested that maribavir at higher doses may have potential as a treatment of post-transplant CMV.

In 2011, maribavir was granted orphan drug designation by the FDA, and in 2014, two positive phase 2 studies in resistant/refractory and first-episode CMV infection with maribavir at doses 400 milligrams to 1200 milligrams BID were completed.

In December 2017, the FDA granted maribavir breakthrough therapy designation for the treatment of CMV infection and disease in transplant patients

resistant or refractory to prior therapy.

As there were no previously conducted phase 3 studies for this indication, we worked closely with the FDA on the pivotal studies design. Two phase 3 trials were initiated in December 2016, Study 302 in treatment-naive patients and Study 303 in resistant/refractory CMV, both studies with maribavir 400 milligrams BID. In 2020, we received positive data from Study 303. At this time, Study 302 is ongoing.

Based on the overall available data, the proposed indication for maribavir is for the treatment of adults with post-transplant cytomegalovirus infection and disease, resistant or refractory to ganciclovir, valganciclovir, foscarnet, or cidofovir. The recommended dosing is 400 milligrams BID orally.

This slide shows you our agenda for today. Thank you.

I'll now turn the lectern over to Dr. Camille Kotton, who will discuss the unmet need in post-transplant resistant/refractory CMV.

Applicant Presentation – Camille Kotton

DR. KOTTON: Good morning, everyone. I'm Camille Nelson Kotton, and I'm the clinical director of Transplant and Immunocompromised Host Infectious Diseases at Massachusetts General Hospital and associate professor at Harvard Medical School. I take care of many patients with CMV, and I have led development of all three versions of the international CMV guidelines for organ transplant recipients.

As I'm sure many of you know, stem cell and organ transplants are successful, life-saving treatments. As of 2018, we did almost 10,000 allogeneic bone marrow transplants in the United States. As of 2020, we did over 39,000 organ transplants from both deceased and living donors. Both of these fields are rapidly growing, and we are doing ever more complicated transplants, really advancing the field.

Post-transplant CMV is the most common infection after organ and bone marrow transplant, and it significantly increases the risk of both

transplant loss and also mortality, as shown across multiple different clinical trials. However, when preventing and managing transplant patients at high risk for CMV infection, it's really a series of trade-offs. We both need to give the immunosuppression to manage graft function, prevent rejection, as well as graft versus host disease, but there's always a balance with the increased risk of CMV infection and disease.

As shown on this slide, CMV infection represents a broad spectrum of diseases from asymptomatic viremia to tissue-invasive disease. I'm really pleased that over the past 20 years, we've gotten much better at detecting CMV, usually when it's, as you see on the left, asymptomatic viremia.

Fortunately, the use of CMV prophylaxis or preemptive therapy has significantly reduced tissue-invasive disease after organ transplant, from about 30 percent down to about 5 percent in recent times. The overall goal of prevention and management is really to prevent people from

progressing to tissue-invasive disease because that's really where we see the most problems.

The standard approach to treatment of active disease includes the use of oral valganciclovir for mild to moderate disease, or with more significant disease, intravenous ganciclovir along with consideration for reduction of immunosuppression. The general goal is to treat until CMV has resolved clinically and virologically as per the guidelines.

In general, that tends to go quite smoothly. However, somewhere less than 10 percent of the time we do see development of resistant/refractory CMV. Risk factors for that include the changing renal function that requires frequent antiviral dose adjustment with a risk for suboptimal dosing or treatment lapses, as well as prolonged antiviral drug exposure, as well as those who have ongoing active viral replication or high viral loads, or those who have more potent immunosuppression.

Resistant/refractory CMV includes what we think of as a clinical continuum. Refractory CMV infection is the clinical definition, and that's

where there are signs and symptoms of refractory disease and/or ongoing viremia that fails to improve or actually increases after at least 2 weeks of appropriately dosed antiviral therapy. A subset of those will have genotypic resistance, which is a laboratory definition defined as a viral genetic alteration that decreases the susceptibility to one or more antiviral drugs.

Fortunately, we have not seen person-to-person transmission of resistance reported, and I do want to emphasize that this is among the most vulnerable of all of our post-transplant CMV patients, and they are the ones at highest risk for complications. They tend to be the most immunocompromised with comorbidities and often tend to be more frail and weak as compared with people who are thriving, which is not usually where we see resistant/refractory disease.

In the CMV guidelines, we have the following algorithm recommended for management, which is, first of all, to recognize that there may be clinical drug resistance if there has been at least

2 weeks of ongoing treatment without improvement, at which point we recommended sending a specimen for testing, as well as possibly reducing the immunosuppression.

At this point, it's important to realize that it will take up to 2 to 3 weeks for the resistance testing to result. So in the meantime, if there is severe disease, we recommend empirically switching to foscarnet, and if there is not severe disease, it's reasonable to try high-dose ganciclovir, and then proceeding with treatment until the resistance testing results return, which then drives the remainder of the clinical treatment algorithm.

Unfortunately, there are real challenges with the current management of resistant/refractory disease. For example, with intravenous high-dose ganciclovir, we usually see that this is poorly tolerated due to the neutropenia and cytopenia, which may require the use of G-CSF.

With intravenous foscarnet, we see significant renal and electrolyte toxicities, and

this usually requires hospitalization for safe intravenous administration. I always have my patients in the hospital for at least 2 to 3 weeks for this treatment, which is really challenging for them. Cidofovir also has a serious risk of renal and ocular toxicities, and people either need to be in the hospital or treated at an infusion center for intravenous administration. Also, that is quite burdensome.

Unfortunately, these toxicities often lead to premature discontinuation of the drug, predisposition to resistance development, and may increase the risk of subsequent virologic failure. However, alternative treatments such as decreasing immunosuppression also raises the risk of organ rejection or worsening of graft-versus-host disease. And at this point, there are no FDA-approved treatments or prophylaxis for resistant/refractory CMV, which remains a challenge.

In summary, effective treatments are really needed for post-transplant resistant/refractory CMV

infection, as this is associated with significant morbidity and mortality. The current therapeutic options have significant limitations in toxicity, and there is really an urgent need for treatment with better efficacy, safety, and tolerability, as well as ease of administration. Thank you for your attention.

Applicant Presentation – Martha Fournier

DR. FOURNIER: Thank you, Dr. Kotton.

Good morning. I'm Martha Fournier, medical director for Clinical Sciences at Takeda. I will review the efficacy results demonstrating statistically superior CMV viremia clearance with maribavir compared to investigator-assigned treatment in post-transplant patients refractory to currently available treatment.

The data supporting the efficacy of maribavir 400 milligrams BID in treating CMV infections refractory to current antivirals comes from one pivotal phase 3 study, Study 303, with supportive data from one phase 2 study, Study 202. Study 303 had an active comparator arm and

Study 202 was a single-arm study.

Both studies used confirmed CMV viremia clearance as the primary endpoint. While Study 203 was in a different patient population and will not be reviewed today, it was a randomized, actively-controlled, dose-finding study that also supports the 400 milligram dose of maribavir.

CMV viremia clearance is a validated, objective endpoint that is endorsed by the FDA for assessing clinical outcomes in this indication. CMV viremia is predictive of CMV disease and mortality in transplant recipients.

Per FDA guidance, CMV viremia clearance is listed as a validated surrogate endpoint in post-transplant CMV registration trials. Takeda and the FDA aligned on CMV viremia clearance at week 8 and the composite of CMV viremia clearance and symptom control as the primary and key secondary endpoints for this phase 3 study.

Let's begin with Study 202. Study 202 was a randomized, dose-ranging study designed to evaluate maribavir's ability to treat CMV infections

refractory, with or without resistance to ganciclovir, valganciclovir, or foscarnet. Study 202 was conducted in patients having received either a stem cell or a solid organ transplant.

Refractory was defined as documented failure to achieve greater than 1 log decrease in CMV DNA levels after a 14-day or longer treatment with ganciclovir, valganciclovir, or foscarnet. Resistant CMV infection was defined as a refractory CMV infection and documentation of one or more CMV genetic mutations associated with resistance to ganciclovir, valganciclovir, or foscarnet.

At the time, it was unknown what dose or duration of treatment may be needed for this challenging-to-treat patient population who had already failed another CMV antiviral. Patients were randomized in a 1-to-1-to-1 fashion to receive oral maribavir at 400, 800, or 1200 milligrams BID for up to 24 weeks.

At week 3 and week 6, CMV DNA levels from the prior week were reviewed and comparison was made with baseline CMV DNA levels. If CMV DNA

levels had not decreased, study drug was discontinued. All patients and investigators were blinded to the dose strength.

The primary efficacy endpoint was confirmed undetectable plasma CMV DNA per central laboratory within 6 weeks of treatment. In the phase 2 study of transplant patients with refractory CMV infection, more than 60 percent of patients achieved CMV viremia clearance within 6 weeks at all 3 doses.

The results across multiple studies have demonstrated maribavir 400 milligrams BID as the optimal dose. Two previous phase 3 studies using 100 milligrams BID for CMV prevention failed to meet the primary endpoint. Two dose-ranging phase 2 studies in treatment of CMV infection showed similar efficacy across all doses, from 400 to 1200 milligrams BID. Because the safety profile of the 400-milligram dose was the most favorable in these studies and the efficacy was similar, it was selected as the phase 3 dose.

I will now review our pivotal study.

Study 303 is the first large randomized-controlled study designed to demonstrate the efficacy and safety of maribavir in the treatment of CMV infections in the transplant population with refractory CMV. All patients were required to be refractory to prior treatment with or without resistance, as this is how patients present in clinical practice and the population can't be separated for treatment decision.

Patients were stratified by transplant type and viral load and randomized 2 to 1 to receive oral maribavir 400 milligrams twice daily or to mono or dual therapy with one of the investigator-assigned CMV antivirals for 8 weeks. This was referred to as IAT.

Investigators were allowed to decide which agent to use as an active control against CMV to optimize the efficacy and safety for each patient. Study 303 was an open-label, active-controlled study and included 352 patients 12 years and older. After a minimum of 3 weeks on IAT, patients with an inadequate virologic response to IAT could receive

rescue treatment with maribavir 8 weeks.

Twenty-two patients randomized to IAT entered the rescue period and received maribavir. After the 8-week treatment period, patients were followed up off treatment for another 12 weeks, providing up to 20 weeks of patient data. For the comparator arm, investigators could choose one or two of the four available CMV antivirals: ganciclovir, valganciclovir, foscarnet, and cidofovir.

Investigators could combine products with the exception of cidofovir and foscarnet since combining these agents is prohibited in their labels. This approach enabled physicians to use the same drugs in the study that they would have used otherwise in the real world to treat these patients. Investigators were allowed to switch between IV ganciclovir and oral valganciclovir. However, any other switch to non-study CMV antivirals, besides that selected at randomization, was considered a failure in the primary analysis.

To be enrolled in the study, patients at

least 12 years of age must have undergone a stem cell or solid organ transplant. Patients must have had a confirmed refractory CMV infection. Refractory was defined as a documented failure to achieve greater than 1 log decrease in CMV DNA level after a 14-day or longer treatment period with ganciclovir, valganciclovir, foscarnet, or cidofovir. Patients were also required to have a viral load and acceptable lab parameters as indicated on the slide.

Patients were excluded if they had any other conditions requiring the use of an IAT agent. They were also excluded if they had CMV tissue-invasive disease with CNS involvement or CMV retinitis, as maribavir does not appear to cross the blood-brain barrier. Patients were excluded if they were receiving other CMV antivirals such as leflunomide, letermovir, artesunate or had a marked elevation of liver enzymes. Patients were also excluded if they were pregnant, had active malignancy, or HIV/AIDS.

The primary efficacy endpoint was confirmed CMV viremia clearance at the end of week 8

regardless of whether study-assigned treatment was discontinued before 8 weeks of therapy. To declare viremia clearance, the patient must have been treated exclusively through study-assigned treatment. A key secondary endpoint was a composite endpoint of CMV viremia clearance and symptom control at week 8, plus maintenance of this treatment effect for an additional 8 weeks beyond the treatment phase.

Symptom control was defined as resolution or improvement of tissue-invasive CMV disease, or CMV syndrome for patients who were symptomatic at baseline, or no new symptoms of tissue-invasive disease, or CMV syndrome for patients asymptomatic at baseline. For the key secondary endpoint, the patient must have received exclusively study-assigned treatment. Additional secondary endpoints included resistance development and efficacy of maribavir as rescue therapy.

Patient demographics were generally similar between treatment arms. The median age was about 53 years and the majority of patients were male and

white. Sites in North America accounted for more than half of the randomized patients. The next most common geographic location was Europe, followed by a smaller percentage of patients from Asia.

Solid organ transplants accounted for approximately 60 percent of patients in each arm, and stem cell transplants were approximately 40 percent of patients in each arm. As expected, the most common solid organ transplant type was kidney, followed by lung and heart transplants. In agreement with the low reported rate of symptoms mentioned by Dr. Kotton, most patients did not have baseline symptomatic CMV infection. Seven to 10 percent of patients had confirmed acute graft-versus-host disease at baseline.

Baseline disease characteristics were also similar between arms. At baseline, most patients in both arms had the presence of CMV mutations resistant to ganciclovir, foscarnet, or cidofovir, and were in the low category of CMV DNA level. A large percentage of patients in both groups had the

CMV serotype associated with a high risk for CMV infection after solid organ transplant; that is donor positive/recipient negative. Likewise, for stem cell transplant patients in the study, most patients in both arms had the high-risk serostatus of recipient positive.

Study 303 met the primary endpoint and the result was highly significant. Maribavir was statistically superior to IAT in achieving confirmed CMV viremia clearance at the end of week 8 in post-transplant recipients with resistant/refractory CMV infection. The proportion of maribavir-treated patients who achieved confirmed CMV viremia clearance at week 8 was more than two-fold greater than patients who received conventional treatment with IAT.

Given the fixed time point at week 8, it is not surprising that they were a lower response rate than what may be seen in clinical practice, where clearance of CMV viremia at an earlier time point may be considered clinical success.

Several sensitivity analyses were performed

to confirm that the results for the primary efficacy outcome were not a function of the study design. I will review three of these sensitivity analyses.

First, if subjects in both arms who met the criteria of confirmed clearance at the time of treatment switch or study discontinuation are included as responders, maribavir still had a higher rate of viremia clearance compared to IAT.

The second sensitivity analysis counted subjects who had viremia clearance within week 8 as a responder. This measures clearance in the absence of other factors such as tolerability. Again, maribavir had a higher rate of viremia clearance compared to IAT.

Finally, we performed a sensitivity analysis looking at the response regardless of the use of alternative anti-CMV treatment, including rescue therapy. This analysis assessed efficacy at week 8 even if alternative anti-CMV treatment was utilized. In this analysis, maribavir subjects also had a higher rate of CMV clearance at week 8.

Let's look at the results across key subgroups. Like most randomized-controlled trials, Study 303 used a sample size sufficient to provide adequate power for the overall study population while lacking adequate power for the consideration of some subgroups.

There was no expectation that the treatment effect should be the same in all subgroups, however, the trend in the response was consistent across subgroups, favoring maribavir over IAT. The benefit of maribavir was observed for the primary endpoint regardless of IAT agent chosen by the investigator, the type of transplant, or the baseline CMV viral load.

The cohort of refractory CMV infection without documented resistance was relatively small for the IAT arm, as mentioned by the FDA, yet the trend in the outcome for the baseline refractory-only subgroup was consistent with the overall result; that is, a greater proportion of refractory-only subjects in the maribavir arm achieved a primary endpoint compared with IAT, the

active control.

Now, let's look at the key secondary endpoint for the study. Maribavir achieved statistically superior CMV viremia clearance and CMV infectious symptom control compared to IAT at week 16. This represents a maintenance of effect 8 weeks after the treatment phase.

The proportion of responders that achieved CMV viremia clearance and CMV infectious symptom control through weeks 12, 16, and 20 off treatment was approximately two-fold higher for maribavir-treated patients than for the IAT group. Of note, the proportion of responders in both arms at week 16 is much less than what we saw at week 8. This is not surprising, as CMV is a latent virus, transplant patients continue to have significant immunosuppression, and patients were no longer on CMV antiviral therapy after week 8.

Now I'll review results from other secondary endpoints starting with resistance development. In the 303 study, there was extensive sampling for viral resistance. This is more comprehensive and

performed more frequently than is typical for clinical practice. Throughout the study, samples were genotyped every 4 weeks, as well as for CMV recurrence or rebound. Rebound was defined as an increase in viral DNA load greater than 1 log above the nadir without prior viremia clearance.

Entire genes were sequenced at a central specialty laboratory. In current clinical practice, treatment is empiric, and testing for resistance is typically performed for increasing viral load for deterioration and clinical condition. Overall, baseline resistance to maribavir was rare in patients with CMV infections resistant and refractory to conventional agents.

320 patients had a genotyped sample at baseline that could be evaluated. Approximately 60 percent had a UL97 or UL54 mutation, conferring resistance to IAT. Only 1 percent had a mutation at UL97 that confers resistance to maribavir. This is not surprising, as maribavir is not yet commercially available.

The only characteristic that was predicted a

maribavir resistance development was baseline viral load. Overall, 58 patients treated with maribavir developed a resistance mutation at UL97 while on the study. Of the 58 cases that developed maribavir mutation, 23 had mutations that conferred cross-resistance to ganciclovir, 3 contained an F342Y mutation, and 20 contained a C480F mutation. Of the 23 patients with ganciclovir cross-resistant mutations, only one patient achieved viremia clearance at week 8. Of the 35 patients with non-cross-resistant mutations, 10 patients achieved the primary endpoint.

Susceptibility is expressed as a drug concentration required to reduce growth by 50 percent, otherwise known as the half maximal effective concentration or EC50. The F342Y mutation EC values demonstrate low-grade resistance for maribavir and ganciclovir.

However, the C480F mutation EC values demonstrate that there is a high-grade resistance to maribavir but low-grade ganciclovir resistance. This suggests that CMV infections with the C480F

mutation may be cleared by ganciclovir. This is consistent with the clinical Study 303 results. All mutations conferring maribavir resistance have been previously described in the phase 2 studies.

CMV treatment failure due to maribavir mutations can be effectively treated with alternative CMV antiviral. Of the 48 patients randomized to maribavir that developed a maribavir mutation and were subsequently treated with an alternative CMV antiviral on the study, 63 percent went on to clear viremia following treatment with an alternative CMV antiviral. For these patients, treatment options utilized on Study 303 included foscarnet, letermovir, ganciclovir, or valganciclovir. Some patients were treated with more than one agent.

Let's now look at the response in patients that received maribavir rescue therapy. As a reminder, patients with a poor response to IAT could receive maribavir at week 3 to 7 of the treatment period. The rescue treatment period with maribavir was for 8 weeks. Overall, 22 patients in

the IAT arm received maribavir as rescue therapy. Of these, half achieved confirmed CMV viremia clearance at week 8 with maribavir rescue treatment.

In summary, maribavir cleared post-transplant CMV infection in patients with refractory CMV infection with or without resistance. Efficacy was demonstrated by pivotal Study 303, and Study 202 supports treatment with a 400-milligram BID dose. In pivotal Study 303, maribavir met its primary endpoint, demonstrating statistical superiority to IAT with respect to CMV viremia clearance at week 8. These beneficial effects were also observed across multiple key subgroups.

In addition, maribavir was statistically superior to IAT with regards to the key secondary endpoint, showing that maribavir is not only effective in viremia clearance, but also in improving or resolving CMV symptomatic disease.

I will now turn the presentation over to Dr. Adefuye to discuss the safety results.

Applicant Presentation – Adedeji Adefuye

DR. ADEFUYE: Good morning. My name is Adedeji Adefuye, and I'm the vice president and head of Medical Safety for Rare Diseases at Takeda. I'm pleased to be here today to review the safety data for maribavir.

Transplant patients will have comorbidities and take many concomitant medications with accompanying side effects. As stated in the FDA briefing book, the currently available treatments have toxicities that limit their use.

Adverse events were presented as the most commonly seen in the transplant population. The review will show similarities and differences between treatment arms. However, maribavir provided a favorable safety profile with an advantage over currently available CMV antivirals. It avoids myelosuppression and renal treatment-limiting toxicities of IAT.

The rates of treatment discontinuations due to adverse events were also substantially lower in the maribavir arm compared to IAT. Dysgeusia, the

most frequent adverse events which drove the overall rate of adverse events, was mild to moderate in severity and rarely led to discontinuation.

The absence of treatment-limiting toxicities and lower discontinuation allows patients to remain on maribavir for a longer period of time and benefit from treatment. Maribavir has a well-characterized safety profile over the entire clinical development program, and the total of 1,555 patients have been exposed to maribavir across several different doses and durations, ranging from 50 to 2400 milligrams and 8 to 24 weeks. Approximately a third of the patients have been dosed with the 400-milligram BID or higher.

Adverse event rates reflect the adverse events, including lab abnormalities of special interest such as neutropenia and acute kidney injury that were collected at the points of care, some of which were not captured in our case report forms. The per protocol labs were collected every

2 weeks, therefore this explains the absence of a beneficial effect in the [indiscernible] laboratory values. It's important to note that maribavir was well tolerated, allowing patients to stay longer on maribavir than other available anti-CMV antivirals.

In pivotal Study 303, patients remained on maribavir about 50 percent longer than they did on other treatments. The mean duration of exposure was 52.5 days for maribavir and 36 days for IAT. Staying longer on treatment allowed for a longer period of follow-up for safety observations or in patients who were treated with maribavir.

I'll now review Study 303 that best represents the maribavir safety profile. On this slide, we have separated the IAT arm into individual drugs to highlight the differences in safety and toxicity between maribavir and those drugs. Overall, the maribavir safety profile allowed patients to stay longer on treatment. Importantly, none of the adverse events incidence rates I will share have been adjusted to account for a 46 percent longer duration of exposure,

therefore, the data shall be interpreted in this context.

Almost all patients in each group experienced at least one adverse event. Adverse event rates were high in both groups, which was not surprising given the underlying disease and associated treatment in this patient population. Patients in the maribavir arm reported more adverse events than patients in the IAT group, driven largely by dysgeusia, which I will discuss more on the next slide. However, the adverse events reported were less severe in the maribavir arm.

Slightly more maribavir-treated patients reported a serious adverse event, however, there were more related serious adverse events and significantly more related severe treatment-emergent adverse events in the IAT arm. Patients on maribavir were also less likely to discontinue treatment and had fewer adverse events leading to study withdrawal.

Here you see adverse events reported by 10 percent or more of patients in either arm. The

most commonly reported adverse event for maribavir was dysgeusia, which is unique to maribavir and is driving the higher overall incidence of adverse events. The dysgeusia cases were grade 1 or 2 in severity and resolved while patients remained on therapy or within a median of 7 days after discontinuing treatment.

The other major difference between the groups was much higher rates of neutropenia in the IAT arm. Neutropenia occurred predominantly in patients who received ganciclovir or valganciclovir, which is consistent with a known side-effect profile.

Discontinuation of therapy was also much lower with maribavir, with 13 percent of patients, compared with IAT, for which we have 32 percent for ganciclovir and valganciclovir and 36 percent for foscarnet.

CMV infection was the most frequently reported type of infection that led to discontinuation of maribavir, followed by CMV viremia. No patients in the maribavir arm

discontinued treatment due to myelosuppression or renal events. Serious adverse events were comparable with similar percentages reported by patients in both groups. In both treatment groups, serious adverse events were reported for one patient only.

Here we show the all-cause mortality for Study 303. Please note that the majority of the deaths were assessed by investigator as unrelated to maribavir. All-cause mortality was low and comparable in both arms. Attributable mortality was even lower, as only one death in each treatment arm was assessed as related to study treatment.

I'll next review the adverse events of special interest. Here, the adverse events, including dysgeusia, are well-documented adverse events of maribavir treatment. They occurred in half of patients receiving the 400-milligram twice daily dose. The majority of these events were mild to moderate in severity and did occur early in treatment. Despite the frequency of taste disturbance, only two patients in Study 303

discontinued treatment due to dysgeusia. Additionally, the events of dysgeusia did not lead to loss of weight.

I will now move on to immunosuppressant events. It is well known that co-administration with maribavir may increase the concentration of tacrolimus and other immunosuppressants. Consistent with this known drug-drug interaction, an 8 percent higher occurrence of maribavir-treated patients had an increase in immunosuppressant concentration levels during the on-treatment observation period or periods with patients who received IAT. This was reported as a treatment-emergent serious adverse event in one maribavir-treated patient. Maribavir's approval and proposed label will recommend therapeutic drug monitoring when maribavir is co-administered with tacrolimus type drugs.

Let's now review neutropenia since that's a known risk for ganciclovir and valganciclovir. Maribavir-treated patients had much lower adverse event rates of neutropenia than patients treated

with ganciclovir and valganciclovir during the on-treatment observation period, even with longer treatment exposure for maribavir. Nine percent of maribavir-treated patients reported neutropenia events compared to 34 percent of patients on ganciclovir and valganciclovir. Febrile neutropenia occurred in 7 percent of patients in this population.

As expected, due to the known ganciclovir risk, severe neutropenia and febrile neutropenia were also much greater in the comparator arm. We also see differences when looking at treatment-emergent neutropenia serious adverse events and adverse events leading to discontinuation. No patients discontinued maribavir due to neutropenia. In comparison, 13 percent of patients on ganciclovir or valganciclovir had serious adverse events and 20 percent needed to discontinue due to their neutropenia events.

Moving now to renal events and known risks with foscarnet and cidofovir, renal events were

much lower for maribavir-treated patients compared to patients treated with foscarnet, even with longer treatment exposure for maribavir. Renal adverse events and severe adverse events occurred less frequently with maribavir.

We also see significant differences when looking at treatment-emergent renal and serious adverse events leading to discontinuation. Seven percent of patients on maribavir experienced renal serious adverse events compared to 17 percent on foscarnet. No patients discontinued maribavir due to renal events compared to 21 percent for patients who were on foscarnet.

In summary, maribavir provides a safety advantage over currently used agents. Importantly, maribavir avoids the two most concerning treatment-limiting adverse events known to be associated with currently available treatments, namely neutropenia and renal events. The most common adverse events in the maribavir group was taste disturbance, which was grade 1 or 2 in severity, non-serious, and rarely led to

discontinuation.

Patients were able to tolerate maribavir for up to 24 weeks at doses up to 1200 milligrams twice daily, and the tolerability of maribavir allows patients to be on treatment longer, which allows them to continue to get treatment benefits.

Thank you. I'll now invite Dr. Avery to provide a clinical perspective.

Applicant Presentation – Robin Avery

DR. AVERY: Good morning. I'm Robin Avery, professor of medicine in the Division of Infectious Disease at Johns Hopkins. I want to thank you for the opportunity to provide my clinical perspective on how maribavir will help with the treatment of post-transplant CMV infection.

As a transplant infectious disease physician with almost 30 years experience, I can tell you that post-transplant CMV infections and disease are some of the most challenging scenarios that patients and clinicians can encounter. These include episodes that do not resolve in 3 months; result in 2 or more recurrences or tissue-invasive

disease with complications; high viral loads with multi-organ dysfunction; and severe intolerance to standard drugs.

Importantly, treatment decisions are typically made before testing for resistance. Resistance testing is highly specialized, involves viral genome sequencing, and is frequently sent out to reference labs. Consequently, it takes a long time to get results and we generally don't wait before making treatment decisions.

As you have heard this morning from Dr. Kotton, existing CMV therapies are problematic in terms of efficacy, toxicities, and some are only available in the IV formulation. As clinicians, we feel there's a major unmet need for an effective and less toxic treatment for CMV.

To illustrate the challenges we face with the existing therapies for treating refractory CMV infections, let me provide you some real patient examples. Once patients become refractory, we are urgently adapting treatments to resolve the infection and prevent graft loss and other

complications.

Patient 1 was a 20-year-old woman with acute myelogenous leukemia; status, post to stem cell transplant; and CMV donor negative/recipient positive. She was admitted at 5-weeks post-transplant with fever nausea, vomiting, hypotension, and tachycardia. Cultures were negative except a positive CMV PCR initially with low viral load. The CMV viral load rose on ganciclovir.

The genotype was negative for resistance mutations. Neutropenia worsened. Ganciclovir was changed to foscarnet with improvement but not clearance of the CMV viral load. On foscarnet, she developed acute kidney injury requiring renal replacement therapy, progressed to profound neutropenia and graft loss. And, unfortunately, she died of multi-organ and respiratory failure and sepsis, although her CMV viremia ultimately cleared.

I also have personal clinical experience that aligns with the efficacy and safety benefits

of maribavir over available therapies in post-transplant patients with refractory and resistant CMV infection. Patient number 2 is a lung transplant recipient with CMV pneumonitis resistant and refractory to valganciclovir, ganciclovir, foscarnet, leflunomide, and CMVIg, with renal dysfunction from foscarnet with very poor performance status. He, fortunately, had an amazing response and cleared CMV with maribavir, demonstrated marked clinical improvement, and was maintained on maribavir for secondary prophylaxis. He was alive and CMV-free five years later.

Patient number 3 is another lung transplant recipient who had symptomatic CMV with high viral load, then developed an L595S UL97 ganciclovir resistance mutation and had very poor tolerance of foscarnet with acute kidney injury, severe nausea, weight loss, and malnutrition.

He also had an excellent response. He cleared CMV with maribavir with marked clinical improvement. His nausea resolved, he gained weight back, and also was successfully suppressed for

months on maribavir secondary prophylaxis, which was allowed in Study 202.

In conclusion, this is why we need maribavir. Over the past 28 years, I have seen far too many patients with CMV infection who've had inadequate responses or who experienced harmful toxicities on currently available therapies. Even if CMV clears, its therapies may cause long-lasting morbidity that impairs the lifespan of allograft and the quality of life of the transplant recipient.

No other drug for CMV treatment combines efficacy with lack of hematologic and renal toxicity and is available orally. These benefits are for both refractory and resistant infections since our treatment decision follows the same process, and patients with CMV often express desire for a drug like maribavir and frustration with side effects of available therapies.

In summary, maribavir will be a truly valuable addition to our antiviral armamentarium and will transform the landscape of CMV treatment

for resistant/refractory CMV infection. Thank you very much for your attention.

DR. UMEH: Thank you, Dr. Avery.

Good morning. My name is Obi Umeh. I'm the vice president and global program lead for maribavir at Takeda. I'll be the moderator for today's Q&A session, and we're very happy to answer your questions during this session or at any point during the meeting. In situations where we have data to support your discussion or can address a question later during the day, I will be emailing to indicate my request to be acknowledged. Thank you.

Clarifying Questions

DR. BADEN: I would like to thank the applicant for a terrific set of presentations, outlining the data available and that we need to consider, and your incredible precision on staying on time that is greatly appreciated.

We will now take clarifying questions for Takeda, for the panel members. Please use the raised-hand icon to indicate that you have a

question and remember to lower your hand by clicking the raised-hand icon 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.

I assume, Dr. Umeh, you will help guide the responses.

DR. UMEH: That's correct.

DR. BADEN: If you wish for a specific slide to the panel members 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 of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

If you would like to chime in to add your thoughts on what another panel member or Takeda is stating, please use the green check mark icon. When you are done chiming in, please remember to clear the check mark.

I will ask the panel members to start

raising your hands to ask clarifying questions.

I see Dr. Hardy. Please ask your question.

(No response.)

DR. BADEN: You are on mute, Dr. Hardy.

DR. HARDY: Thank you. This is Dr. David Hardy from Los Angeles, California, adult infectious disease specialist and long-term treater of persons with CMV infection.

Could you describe in a little more detail what you know about the resistance to maribavir? Has that been worked out? And what kind of mutations have you found that cause resistance to maribavir when you've actually been able to characterize this?

DR. UMEH: In our co-presentation, we have a slide that shows the resistance breakdown.

Put that up. The two main resistance mutations that are consequential are the C480F and the F342Y; the C480F, especially, because 19 out of 20 patients have that mutation.

For the rest of them -- these are the mutations -- the thing to know is that this study

did not bring up any new resistance mutations that weren't previously identified in phase 2, and all of these patients who had mutations were successfully treated in about 60 percent of cases across the board.

DR. HARDY: May I ask a follow-up question?

DR. BADEN: Yes, please.

DR. HARDY: Have you found CMV that is resistant to maribavir, a combination of mutations, or any other mutations that cause genetic resistance to mariba -- to your drug?

DR. UMEH: Maribavir.

DR. HARDY: Maribavir.

DR. UMEH: The mutations I just put up on the slide are the major ones that have been seen, and all of these were previously in our phase 2 studies. I can show you a long list, but you'll see that the more consequential ones are the ones that I already mentioned, are the ones that occur frequently.

DR. BADEN: Thank you.

DR. HARDY: Thank you.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: Thanks very much. George Siberry, USAID. Thanks for these presentations.

First, I appreciated that your inclusion criteria went down to age 12. I wanted to clarify if you had any enrollees who were between 12 and 17 that could make us consider this for adults and adolescents. Then second, the dysgeusia, is that a problem, that taste disturbance, that persists after cessation of treatment or that resolves? Thank you.

DR. UMEH: I'll take the second question first. Dysgeusia was transient, and in only 2 patients out of 235 that were treated with maribavir was it discontinued.

With regard to pediatrics, yes, you're right. We did open up this study to patients age 12 and above, and we had a lot of transplant centers that have children in them. Unfortunately, despite our efforts over four years, we could not enroll any pediatric patients, however, we are in discussion with the agency for a pediatric program.

DR. SIBERRY: Thank you.

DR. BADEN: Doctor Flatau?

DR. FLATAU: Hi. This is Arthur Flatau, and I wanted to ask about the washout periods that were mentioned in the briefing document, the various washout periods depending on what drug they're on. I'm wondering if that is expected to be used in clinical practice, and if not, what effect on efficacy and safety that might have.

DR. UMEH: No, we have the washout just to prevent confounding. So we're not recommending that people have a washout before they go on to maribavir, but we didn't want a situation where any of the effect that was observed was attributed to the agent that was previously given. So for those agents that went on standard use or conventional-use treatment, we had a washout period.

DR. FLATAU: Okay. So you don't expect any drugs to now be overlapping if you switch to maribavir?

DR. UMEH: No requirement. Our label will

include areas where you don't co-administer, like with ganciclovir.

DR. FLATAU: Okay. Thank you.

DR. BADEN: I would remind the panel members and others, when you're done speaking to uncheck your raised hand and to go on mute to minimize background sound. Thank you.

DR. FLATAU: And I've done so.

DR. BADEN: Dr. Le, you're next.

DR. LE: Hi. This is Dr. Jennifer Le. I wanted to ask, I know maribavir is not active against the herpes and the varicella zoster, so that's why you needed to add a acyclovir in your 303 study. I'm just curious. In your 202, did you see any reports of these infections while patients were on maribavir?

DR. UMEH: No, not beyond the risk. We know that maribavir is active, in vitro, against EBV and CMV. We have a human study in CMV, and we've always asked that people use prophylaxis for other types of herpes viruses if they need to.

DR. LE: Okay. Thank you.

DR. BADEN: Dr. Gea-Banacloche?

DR. GEA-BANACLOCHE: Yes. Thank you. This is a question regarding slide CO-41. Is that the number that caught my attention? Yes. This is in Study 303.

In Study 303, you have 48 patients who developed resistance to maribavir and you rescued 63 percent of them with the alternative treatment. But that is actually better than the alternative treatment, leaving the general group that was randomized to even 303.

How do you explain that?

DR. UMEH: That is the observation that the study showed us. The 303 is an 8-week trial in which you had to maintain your clearance all the way to 8 weeks. Here, we have evidence of people who had a resistance mutation, had virus present, and then cleared the virus. They were not necessarily subjected to the same 8-week standard to demonstrate their primary endpoint.

DR. BADEN: Thank you. I will ask the next question. In conducting the trial, when you

initiated the randomization to IAT versus maribavir, was there manipulation of the host immunosuppression and how was that managed and accounted for?

DR. UMEH: There was no prospective manipulation of the host immune system. We relied on randomization to balance out people with different levels of immunocompetence and the fact also that we had different centers. I think our baseline demographics showed that most of the key predictive factors were balanced between the two treatment arms.

DR. BADEN: But you did not measure if there was a decrement or a change in hosting immunosuppression. That was not tracked so you could actually compare it.

DR. UMEH: Not systematically, no.

DR. BADEN: Okay. Randomization hopefully takes care of that concern.

DR. UMEH: That's correct.

DR. BADEN: Thank you.

Dr. Haidar?

DR. HAIDAR: Hi. This is Ghady Haidar from the University of Pittsburgh. I just had a clarifying question. I know that in the trial you guys gave the drugs for 8 weeks, but in one of the safety slides, you talk about patients tolerating maribavir for up to 24 weeks. Is that based on some of the older trials or compassionate-use cases?

DR. UMEH: Thank you. That was from the phase 2 studies. So in the phase 2 studies, in Study 202, which is a supportive study for this submission, a cohort of patients went as far as 24 weeks of therapy, and some of them up to 1,200 milligrams. So we mentioned that as data that we have that demonstrates that a safety signal at increased doses and increased durations is essentially the same as the safety signal from the phase 3 study -- I'm sorry, the absence of safety signal from the phase 3 study.

DR. HAIDAR: Thank you.

DR. BADEN: Dr. Perez?

DR. PEREZ: Thank you. This is Federico

Perez from the Cleveland VA. My question is, were all the baseline characteristics of the resistant and the refractory groups comparable? Thank you.

DR. UMEH: We did this study by the baseline characteristics of everybody that was comparable, and this was also consistent in the subgroups, more or less, other than the fact that there was resistance in the resistant group and none in the refractory group.

DR. PEREZ: I have a follow-up question.

DR. BADEN: Please, go ahead.

DR. PEREZ: Similarly, were the frequency of mutations conferring resistance to maribavir similar in the resistant group and the refractory group? Thank you.

DR. UMEH: I believe most of the mutations we calculated for that of the overall population. I don't believe we broke it down. I mean, I think the context to give here is that we had extensive and serial sampling. So unlike clinical practice, we had scheduled times that we would look for resistance, and we would also track for resistance

when there was an increase in viral load. So this is tracking much more than you would have done in clinical practice, as the slide I showed up here showed. But no, we didn't have that broken down by refractory versus overall population.

DR. BADEN: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. I just want to make sure I understood the outcomes slide. I think you had some bar graphs that showed the percentages, and it seemed that one of the bar graphs showed at 8 weeks what the percentage of responders was, no matter what treatment they got.

I was wondering if you could put that up. I didn't quite catch the number of the slide, but it looked like there wasn't much --

DR. UMEH: Is it --

DR. HUNSBERGER: Oh, sorry.

DR. UMEH: No. I was asking you if it was the primary endpoints slide. That would be C -- the primary endpoints are the subgroups. Do you know which one you're referring to?

DR. HUNSBERGER: It was the slide that had the overall percentages, and then it showed what happened if you didn't take out the people who crossed over, essentially, to the experimental arm. So it looked like --

DR. UMEH: Can I show --

DR. HUNSBERGER: Sorry.

DR. UMEH: Can I show you some slides? And then maybe you can tell me the one.

DR. HUNSBERGER: I didn't get the number. Sorry.

DR. UMEH: This is CO-33, and it's the primary endpoint slide.

Is it this one?

DR. HUNSBERGER: Go down. I think it was the next one where it had several different groups. This one I think it is.

DR. UMEH: Okay.

DR. HUNSBERGER: So at the last line, that's saying that at week 8 it doesn't matter what treatment they got. So essentially for the IAT arm, that would be people who crossed over and

got --

DR. UMEH: Yes.

DR. HUNSBERGER: -- maribavir.

Okay. So this is showing that some of the people who crossed over actually did improve when they got it. Okay. I thought that the numbers were closer. Well, it's the 43 percent versus the 42 percent, so it doesn't seem to reflect the fact that people who maybe got maribavir after the IAT then improved.

Am I understanding that right?

DR. UMEH: That slide is the last slide of the efficacy presentation, where we look at the rescue patients and we show that we were able to rescue some of those patients. The point of the sensitivity analysis is to show that any potential confounding in the study, either due to the perceived early discontinuation or the perceived absence of switching to other agents, that despite that, if you let the outcome be whenever they cleared the virus, or if you let them switch to any number of therapies, maribavir was still the same.

But if you're asking for this slide on the rescue patients, I can pull that up for you.

DR. HUNSBERGER: But I'm wondering why it's not reflected in that 42 percent. Is it that it wasn't long enough?

DR. UMEH: I'm not sure I follow the question. That analysis included people who switched over because they got maribavir after rescue. So a treatment switch would be anybody who took a treatment other than that they were randomized to.

Those people who were in the IAT arm were randomized to the IAT, but when they met prespecified criteria for failure to improve, they could be switched over to maribavir rescue therapy. And we're saying if we allow the IAT arm to have the benefit of maribavir therapy and still look at the outcomes, we're still better than the comparator.

DR. HUNSBERGER: I understand that, but I'm wondering if what you're seeing is true, I don't understand why that percentage didn't increase. I

thought what you were advocating was that when they crossed over, they improved, so why isn't that 42 percent increase? And I think it's just because I'm not understanding the slide, but can you explain that?

DR. UMEH: No. The IAT outcome was 24 percent in the primary analysis. I think in the one you're talking about, it's 42 percent.

DR. HUNSBERGER: Okay.

DR. UMEH: Could you put up the slide again?

So it did increase. The IAT did much better when you allowed maribavir patients. If you allowed maribavir treatment in the IAT to count towards the effect of the IAT, the number would increase.

DR. HUNSBERGER: Okay. I got the baseline wrong. Okay, I see it. It went from 24 to 42. Got it. Okay. Thank you so much.

DR. BADEN: Please keep that slide up. Dr. Weina has a follow-up question.

DR. UMEH: Okay.

DR. WEINA: Yes. I just want to be clear

about some numbers, and that is Trial 303, there were 22 patients that failed IAT and were put into a rescue arm with maribavir. But there were also in that same trial 48 patients who failed maribavir and were then rescued with IAT.

Is that correct?

DR. UMEH: No. I think you're using the word "rescue" interchangeably. For the purpose of the study design -- can you still see our screen? We have a blank screen?

DR. WEINA: No.

DR. BADEN: No. We see blank.

DR. UMEH: Is that from our end? Are we fixing it? Okay, we're fixing it, but I'll keep talking in the meantime.

So the study design had maribavir versus IAT, 8 weeks/8 weeks. Then for a proportion of patients who had been treated for at least 3 weeks, because of the fact that the patients who raised up their hand for this study really wanted to get maribavir, what we did was is we said if you have stayed in the study long enough, received enough

IAT, and you're not doing better, on an ethical basis, we will allow you to proceed to this other group called the rescue arm.

So that was rescue with maribavir based on not meeting the criteria for improvement within the study. That's separate from the results we showed you, which is answering the question what happened to patients who had cross-resistance, and should I be concerned that when there's cross-resistance, people can be treated? And I think the answer is no; there isn't a concern because this remains very susceptible to ganciclovir and the other agents. We're not to confuse the word "rescue" in that sense with "rescue" in the design.

DR. WEINA: Yes. I just wanted to be clear -- whatever term you use, whether you use "rescue" or any other term -- that there were 22 patients that went from the IAT arm and were then put into the drug of choice arm, and on the other side, there were 48 patients that were originally out of 235, or 20 percent of them, who were then subsequently treated with IAT.

Is that correct?

DR. UMEH: In the post-follow-up period. And the reason for that is that maribavir was available only for 8 weeks. So there was no post-trial access to maribavir. So even if Dr. Avery or Dr. Kotton wanted to treat that patient with additional therapy with maribavir, they couldn't do that. So they could only use what they had, which was IAT, and that's why we're presenting that data to you.

DR. WEINA: Okay. Thank you.

DR. BADEN: Dr. Green, you have a follow-on question. And I'll remind panel members after you ask your question, please uncheck your box and also go on mute.

Dr. Green, a follow-on.

DR. GREEN: Yes. Thank you. This is Mike Green, Children's of Pittsburgh. Just to follow up on what Pete was just talking about, for those who were originally on maribavir, and it seems like they're now in that post 8-week time period and then seemed to respond to ganciclovir or

valganciclovir, I'm just going to double-check. Was that a group of individuals who at onset of the study did not have resistance mutations against ganciclovir and valganciclovir? Thank you.

DR. UMEH: No. This was a group of individuals who at the beginning of the study did not have any maribavir mutations and they developed treatment-maribavir mutations.

I think I want to make sure I re-emphasize that. So the primary outcome of this study was to demonstrate virologic clearance against IAT. Maribavir was superior to that. There were a number of recurrences, some of which were caused by resistance. If I show you our week 16 slide, which is despite the recurrences, the maintenance of effect at week 16, maribavir was still statistically significantly better than the comparator with respect to clearance of viremia.

So never mind that there was resistance, never mind this accord. The potential for maribavir to be better than the comparator at week 16, 8 weeks after treatment had ended, was

still superior. So our recurrence rates, or sustained cure rates at week 16, still demonstrated a benefit of maribavir, and I think that's really the message that we have.

Maybe I'll invite Dr. Avery here. What we're looking at when we look at resistance is we're comparing the pretreated population with the population of patients naive.

Dr. Avery, do you want to comment?

DR. AVERY: Sure. I think it's also important to draw a distinction here between, for example, antimicrobial resistance in bacteria or resistance in HIV. I think the clinical significance of resistance mutations in this setting, it does not always portend a failure of therapy, as you've seen a number of these patients were successfully treated. And I guess from the clinical perspective, we really don't feel that the resistance is the major issue. We feel that the potential benefit for this extraordinarily sick population with poorly tolerated drugs is very high.

DR. BADEN: Thank you.

We have come to 10:41. We were supposed to break at 10:40. There are still multiple panel members with questions. What we shall do is take the break. The agency will give their presentation, we'll have clarifying questions with the agency, and then I ask my Takeda colleagues to be available for more clarifying questions later in the presentations, as I want to make sure all panel members get their issues addressed.

DR. UMEH: Thank you. Will do.

DR. BADEN: So we will take a quick 10-minute break. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. We'll reconvene at 10:51 sharp. Thank you.

(Whereupon, at 10:42 a.m., a recess was taken.)

DR. BADEN: It is now 10:51, and we shall resume. I would like to remind the committee members to please take down their hands and check

boxes, as we have noted who has further clarifying questions, and we will resume the questions to the applicant later in the meeting.

At this time, we will now proceed with the FDA presentation, starting with Dr. Pikis.

Dr. Pikis?

(No response.)

DR. BADEN: You're on mute if you are talking, Dr. Pikis. We cannot hear you.

DR. PIKIS: Sorry.

FDA Presentation – Andreas Pikis

DR. PIKIS: Good morning, everybody. My name is Andreas Pikis. I'm the medical reviewer for this new drug application, and together with Dr. Komatsu, the virology reviewer, we'll present the data submitted under this NDA to support the approval of maribavir for the treatment of CMV infection and disease, resistant or refractory to at least one of ganciclovir, valganciclovir, foscarnet, or cidofovir.

The agenda includes the background, trials targeted to a limited population: refractory CMV

infection or disease with or without genotypic resistance; efficacy and safety data from the phase 3 trial, 303; efficacy and safety data from the phase 2 trial, 202, which is a supportive trial; and the virology data from the phase 3 trial.

In the next two slides, I will try to summarize the drug development milestones for the use of maribavir for prophylaxis or treatment of CMV infection in transplant patients. The applicant initially developed maribavir for prophylaxis. First, they conducted a phase 2 trial, Trial 200. That was a randomized, placebo-controlled, dose-ranging trial, comparing 3 doses of maribavir -- 300 milligram BID, 400 milligram QD, and 400 milligram BID -- against placebo for CMV prophylaxis and CMV seropositive stem cell transplant recipients.

The results of that phase 2 trial demonstrated fewer CMV infections or disease with maribavir compared to placebo. However, there was no-dose response. Based on those results, the

applicant selected the 100-milligram BID dose for the two phase 3 prophylaxis trials, Trial 300 and Trial 301.

The two phase 3 prophylaxis trials, one was a stem cell transplant recipients superiority study comparing maribavir to placebo, and the other one was a noninferiority trial comparing maribavir to oral ganciclovir in liver transplant recipients. Both studies failed to meet the primary and key secondary endpoints.

The lower dose selected, the 100-milligram BID dose, was considered by the applicant as a possible explanation for why the two phase 3 prophylaxis trials didn't meet the primary and key secondary endpoints.

Subsequently, the applicant conducted two new phase 2 trials with higher maribavir doses: 400-milligram BID, 800-milligram BID, and 1200-milligram BID. They conducted Trial 202 in CMV resistant or refractory patients and Trial 203 in patients with asymptomatic CMV viremia.

Although no dose response was observed in

the phase 2 trials, the applicant selected the 400-milligram BID dose for further evaluation in two phase 3 treatment trials, Trial 303 in patients with CMV resistant/refractory and Trial 302 in patients with asymptomatic CMV viremia. This is an ongoing trial comparing maribavir versus valganciclovir in stem cell transplant recipients with CMV viremia. The NDA is based on the phase 3 trial, 303, and supportive data from the Trial 202.

In the next several slides, I will try to summarize the efficacy initially for the phase 3 trial, Trial 303. First, I will describe the trial design that was a randomized, open-label, positive-controlled trial, maribavir versus investigator-assigned treatment in transplant recipients with CMV infections resistant or refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir.

The treatment duration was up to 8 weeks. The selected maribavir dose was 400-milligram BID. The IAT dose was based on drug labels with dose adjustment at the discretion of the investigators,

and of course the patients' clinical condition. Upon completing the 8-week treatment, the patients entered a 12-week follow-up period.

Patients randomized to the investigator-assigned treatment were started on one or two of the agents. If the patient was started on two agents, they were allowed to discontinue one of the two agents. Changes between the ganciclovir and valganciclovir were permissible, as well as changes in the dose or dosing regimen.

Patients in the IAT arm were not allowed to add another agent. Also, switches to another agent, with the exception of ganciclovir and valganciclovir, were not allowed. Patients who received the prohibited medications were considered for the primary endpoint as failures.

The study included a maribavir rescue arm for patients randomized to the investigation-assigned treatment. Subjects were eligible for maribavir after at least 3 weeks of treatment if any of the following criteria were met: increased CMV viral load; 1 or more log; subjects with

tissue-invasive CMV disease after being on treatment for 3 weeks and met both of the following criteria: had a decrease in viral load less than 1 log from baseline and symptoms of CMV disease didn't improved or worsened.

The third point was CMV viremia clearance was not achieved and the subjects demonstrated intolerance to the IAT drug. For example, the patients had severe neutropenia or increased creatinine levels. Subjects who switched to the rescue arm were considered failures in the primary analysis.

The definitions of resistant/refractory for the purpose of this trial is resistant/refractory CMV patients were defined as follows: for resistant, documented failure to achieve more than 1 log decline in CMV DNA levels either in the whole blood or the plasma after at least an interval of two or more weeks of treatment with IV ganciclovir, oral valganciclovir, foscarnet, or cidofovir; patients that had documentation of one or more CMV resistance-associated amino acid substitutions to

ganciclovir, valganciclovir, foscarnet or cidofovir.

Refractory patients had the same criteria for the documented failure, however, genotypic analysis didn't demonstrate any resistance-associated amino acid substitutions related to resistance to at least one of the four drugs.

Stratification was based on two factors: the transplant type, stem cell or solid organ, and baseline CMV viral load. We have three brackets: low, intermediate, and high viral load. The low viral load was between 910 and 9100 international units per mL; the intermediate, between 9100 to less than 91,000; and the high viral load, more than 91,000.

For population, all subjects had refractory CMV infection with or without genotypic resistance. The primary efficacy endpoint was the proportion of subjects with confirmed clearance of plasma CMV DNA at the end of study week 8. The clearance was defined as two consecutive samples separated by at

least 5 days with DNA levels below the lower level of quantification.

The key secondary endpoint applies to patients who met the primary endpoint and confirmed CMV viremia clearance and control of CMV symptoms at study week 8 and maintenance through week 16, which was 8 weeks off treatment. The primary analysis population is all subjects randomized to the study treatment.

This slide summarizes the primary efficacy analysis, and it is clear that maribavir performed much better compared to the IAT arm. Grossly, 56 percent of the subjects in the maribavir arm met the primary endpoint compared to 24 percent in the IAT arm, and of course that one was statistically significant.

We were a little surprised with the very low response in the IAT arm. Actually, we were expecting more than 24 percent. We tried to find the reasons for the failures, and we made a comparison between the two treatment arms, the maribavir and the IAT arms.

The results are shown in the next slide. Overall, we had counted for subjects in the maribavir arm who failed the primary endpoint, which was 44 percent, and 89 subjects in the IAT arm, which was 76 percent. We tried to group the failures into two groups, those due to the virologic failure and those to drug or study discontinuation.

The virologic failure was similar between the two groups, 34 percent and 36 percent in the IAT arm. It was mainly due to some of the patients; they never achieved levels lower than the LLOQ, 20 percent in the maribavir, 30 percent in the IAT. The breakthrough was higher in the maribavir arm, 10 percent compared to 6 percent in the IAT.

The failures due to study drug discontinuation were significantly higher in the IAT arm, 58 percent compared to only 9 percent in the maribavir arm. That was mainly driven by the adverse events, 22 percent in the IAT compared to only 3 percent in the maribavir arm. The deaths

were similar between the two groups. However, withdrawal of consent was much higher in the IAT arm, 8 percent compared to less than 1 percent in the maribavir arm. Other reasons were also higher in the IAT arm compared to maribavir. A few patients, three in each arm, remained in the study, but were considered failures.

Two lines of this graph summarizes and shows that the major effect of maribavir was mainly due to drug study discontinuation rather than to the virologic effect.

In the next two couple of slides, I will try to present the sensitivity analyses of the primary endpoint. This slide includes the subjects who met the criteria of CMV viremia clearance at the time of early discontinuation, and it still shows that maribavir performed much better compared to the IAT, 60 percent versus 44 percent. The adjusted p-value was 0.001.

The next slide shows the confirmed CMV viremia clearance at week 8 regardless of prohibited anti-CMV treatment or maribavir rescue

therapy. Again, the gap is less compared to the primary endpoint, but is still significantly favoring maribavir. It was 59 percent versus 43 percent, with a p-value of 0.001.

I have two slides about the subgroup analyses of the primary endpoint. The first one is showing the results for the solid organ and the stem cell transplant recipients. The effect is similar between the two major groups, 56 percent, and is much better compared to the IAT arm. The IAT arm is relatively low, around 26 and 21 percent.

I don't have any slides for this, but the efficacy was consistent across the type of solid organ and the age groups, including patients more than 65 years of age.

I would like to bring your attention to this slide because one of the questions is mainly based on this slide, and this is whether the provided data support the approval of maribavir for the treatment of patients who were refractory to treatment without genotypic resistance. It's

obvious that in the resistant patients, the efficacy of maribavir was significantly higher in studies compared to the IAT. It was 63 percent versus 20 percent. That one was very statistically significant with a p-value less than 0.001.

With regards to refractory, the results were favoring maribavir, 44 percent versus 32 percent. It was not statistically significant, but the study was not powered to show statistical significance. However, the patients comprised with refractory were about, totally, 40 percent of the total of the study population.

Also, I will show that the Breslow-Day p-value for interaction was statistically significant, adjusting for the transplant type and the baseline CMV DNA level. Grossly, this test demonstrates the magnitude, that there was some difference in the response between the two groups, even though the refractory was heading in the same direction as with the resistance.

Here we have some group analyses based on the CMV syndrome or disease at baseline. We have a

very small number of patients with tissue-invasive CMV disease or CMV syndrome. Totally, there were only 29 subjects with CMV syndrome. We had 16 with CMV syndrome and 13 with a tissue-invasive CMV disease. Of the 16 with CMV syndrome, 9 were assigned to maribavir and 7 to the IAT. Of the tissue-invasive CMV disease, we had 13 subjects, 12 assigned to maribavir and only one to the IAT.

For patients who either had CMV syndrome or disease, the efficacy was 57 percent in maribavir compared to 25 percent in the IAT. For the patients with CMV syndrome or before disease, it was in the same direction, almost reaching statistical significance as 0.07. However, as I noted before, the number of patients was very small, totally only 29 subjects.

Here we have the analysis by baseline viral load, which was the second classification factor. For starters, for less than 5,000 international units per mL at baseline, the efficacy was -- okay. Sorry. The IAT was more or less similar to all groups, ranging around 25 percent, so I will

emphasize the results for the maribavir groups, which is obvious that the lower the level, the higher the efficacy.

For patients less than 5,000, the efficacy was 67 percent; between 5,000 and 20,000, it was 46 percent; between 20,000 and less than 50,000, 43; and for patients more than 50,000, it was only 30 percent. It is obvious that we don't have too many patients, particularly for the levels above 20,000.

Two points for this slide are that we had an inclusion criterion that the minimum baseline CMV DNA levels were supposed to be more than 1,000 copies per mL. However, approximately 20 percent of the subjects in each treatment arm had the lower levels, and that was based on the TaqMan assay. Also, among the subjects with baseline CMV DNA levels below 5,000, more than 60 percent of those had CMV DNA levels less than 2,000. It was 67 percent in the maribavir group and 62 percent in the IAT group.

In this slide, we have done the most

conservative approach of analysis and compared the patients who completed 8 weeks of treatment. This is, I can say, a little unlikely, for example, for patients who received total 8 weeks of treatment with cidofovir or with foscarnet. Totally, we have only 37 subjects out of the 117 in the IAT who completed 8 weeks of treatment. On the other hand, we have 183 in the maribavir arm. The difference was not statistically significant, even though it was numerically favoring maribavir. It was 70 percent versus 59 percent.

The key secondary endpoint was the confirmed CMV viremia clearance and control of the CMV disease symptoms at study week 8 and maintenance through week 16. Again, maribavir performed better compared to the IAT, 19 percent versus 10 percent. That one was statistically significant. However, it is obvious that most of the subjects in both groups couldn't maintain the CMV viremia clearance through week 16.

Of the 131 subjects who met the primary endpoint in the maribavir arm, only 44 maintained

the clearance through week 16, 8 weeks of treatment. Also, for the 28 subjects who met the primary endpoint in the comparator arm, the IAT, only 12 were able to maintain the CMV viremia clearance through week 16. Most of the failures in both arms were due to CMV viremia relapses, off treatment, with about 75 percent in the maribavir arm and 69 percent in the IAT arm.

The next slide summarizes the all-cause mortality and the timing of deaths. Mortality was similar between the two treatment arms. We have totally 27 subjects in the maribavir and 13 subjects in the IAT. Half of the patients died -- almost half -- during the first 8 weeks.

The next slide summarizes the new onset of symptomatic CMV infection; no difference between the two treatment options. It was totally 6 percent of new onset symptomatic CMV infection.

In the next two slides, I will try to summarize the phase 2 trial. Trial 002 was a phase 2, randomized, dose-ranging trial in subjects more than 12 years of age who underwent stem cell

or solid organ and had CMV infection, resistant or refractory to treatment with ganciclovir, valganciclovir, or foscarnet. The eligible subjects were stratified by the transplant types, stem cell or solid organ, and they were randomized to one of the to one of the three maribavir doses: 400-milligram BID, 800-milligram BID, and 1200 milligram BID.

The subjects who received maribavir were blinded, as well as the investigators. However, it is obvious that there is no comparator arm in this trial. The primary efficacy endpoint was the proportion of subjects with undetectable CMV DNA levels. For this study, it was defined as less than 200 copies per mL in two consecutive samples separated by at least 5 days, at any time, within the first 6 weeks of treatment.

The efficacy results show no difference between the three maribavir doses. Overall, maribavir was efficacious for 70 percent of the subjects. There were no appreciable differences in the safety among the three treatment groups,

however, we had about 35 percent of CMV viremia recurrence or relapse.

Now, I will invite Dr. Komatsu to present the virology data from the phase 3 trial, and then I will follow up with the safety summary.

FDA Presentation – Takashi Komatsu

DR. KOMATSU: Thank you, Dr. Pikis.

Good morning. My name is Takashi Komatsu, and I am the clinical virology reviewer for this NDA, and I will go over the virology data.

So first, a little bit of background for maribavir. Just to remind you, maribavir is an inhibitor of the protein kinase activity of HCMV UL97, which results in the inhibition of the phosphorylation of proteins.

Resistance to maribavir occurs as a result of substitutions in both UL97 and UL27. Resistance to ganciclovir occurs as a result of substitutions in both UL97 and UL54, so important characteristics of maribavir is that cross-resistance can occur between maribavir and ganciclovir due to substitutions in the UL97.

Over the next couple of slides, I will go over the cross-resistance data between these two. First on this slide, I will go over the ganciclovir resistance-associated substitutions and the cross-resistance data for maribavir. The top panel represents the resistance-associated substitutions of ganciclovir that confers substantial reduced susceptibility to maribavir. We expect these to impact maribavir treatment.

The bottom panel represents the ganciclovir resistance-associated substitutions that confer substantially less reduced susceptibility to maribavir, and at the moment, we do not expect any of these to impact maribavir treatment.

Of course, cross-resistance can occur in both directions, so on this slide is maribavir resistance-associated substitutions and the cross-resistance data with ganciclovir. So again, the top panel represents the maribavir resistance-associated substitutions that confer a substantial decreased susceptibility to ganciclovir, and we expect that these will impact

ganciclovir treatment.

The bottom panel represents the maribavir resistance-associated substitutions that confer substantially less reduced susceptibility to ganciclovir, and at the moment, we do not expect any of these to impact ganciclovir treatment; although we do note that a couple of these, specifically the V353A and L397R, are within the ball park for the shift in reduced susceptibility that is considered clinically meaningful.

We looked at, from Study 303, the summary of efficacy based on the presence of baseline ganciclovir resistance-associated substitutions, and the good news is that the presence of most of the known ganciclovir UL97 resistance-associated substitutions -- including those at position M460, H520, C592, A594, L595, and C603, and these are positions that are most frequently reported to confer ganciclovir resistance -- did not appear to have a significant impact on the efficacy of maribavir.

Now, there were a handful of substitutions,

specifically the UL97 A594P or T, L595W, or the recent net position, 597, where the efficacy was numerically lower. But please note that numbers for each of these substitutions were small. And furthermore, we do not have a shift in susceptibility to maribavir for any of these substitutions, so we really can't make any definitive conclusions for any of these.

Now, taking all of the data together, note that subjects with ganciclovir of resistance-associated substitution, conferring less than 2.5-fold reduction in susceptibility to maribavir, responded to maribavir therapy. The reduction in susceptibility for maribavir treatment-emergent, resistance-associated substitution generally ranged from 4.5 to 81.

So taking these two ranges together, these ranges indicate that the minimum fold shift for maribavir associated with treatment failure due to cross resistance, or breakpoint, is in the 2.6 to 4.5-fold change and may explain the variable response that we saw at the positions that I

highlighted in the previous slide.

Now, we have a couple of examples that seem to support this range. The first is that there was one subject that had the UL97 L193F maribavir resistance-associated substitution at baseline. This substitution confers 2.64 reduced susceptibility to maribavir, and this subject did not meet the primary endpoint.

The second example is the UL97 F342Y substitution. This substitution emerged in ganciclovir treatment failures and is selected clinically by maribavir. It confers 4.5-fold and six-fold reduced susceptibility to maribavir and ganciclovir, respectively.

This substitution emerged in 3 subjects who failed maribavir treatment in Study 303. There were 3 subjects in this Study 303 that had this substitution at baseline. All three of these subjects were initially in the IAT arm. One of these subjects was rolled over to the maribavir rescue arm, and this subject also failed in the maribavir rescue treatment.

Additionally, there was one subject in Study 202 who had this substitution at baseline, and this subject failed to meet the primary endpoint. So these two examples seem to fit the proposed range at days in treatment.

I will now turn over to the treatment-emergent maribavir-resistant substitutions from Study 303. As Dr. Pikis has mentioned, maribavir was superior to achieving viral load less than LLOQ at week 8. However, there were a subset of these patients in the maribavir arm who were a virologic failure, 84 of these patients.

Among these 84 virologic failures, the applicant provided 76 paired sequences, and 62 percent of these had one or more UL97 treatment-emergent maribavir resistance-associated substitutions. Of note, of these, 47 percent had maribavir resistance-associated substitution that was cross-resistant to ganciclovir.

Additionally, 36 percent of the treatment failures in the maribavir arm were virologic failures and 9 percent failed for other reasons.

In comparison, in the IAT arm, 44 percent treatment failures were virologic failures and 32 percent failed for other reasons, for example, discontinuation.

Now I will describe a little bit of the relapse data from the subjects who achieved confirmed viral load less than LLOQ at week 8. As was already described by Dr. Pikis, there were a substantial number of patients that relapsed once they were taken off treatment. Most of the relapses in both treatment arms occurred during the first 2 weeks off of treatment, and by week 12, or 4 weeks off, at least 90 percent from both treatment arms had relapsed. This is overall not terribly surprising given that most of these patients are still immunosuppressed.

The applicant has provided 48 paired sequences among the subjects who experienced a relapse in the maribavir arm, and 23 percent of these patients had treatment-emergent maribavir resistance-associated substitutions, among which 9 percent had maribavir resistance-associated

substitutions that is cross-resistant to ganciclovir; so a substantially less rate compared to the rate that was present in the on-treatment virologic failures that were presented in the previous slide.

I will now turn over to Dr. Pikis, who will go over the safety data from the study.

FDA Presentation – Andreas Pikis

DR. PIKIS: Thanks, Takashi.

This slide provides an overview of the treatment-emergent adverse events during the treatment period. Almost all patients in both arms, we had at least one adverse event. This is not surprising, knowing the underlying disease and too many medications that these patients are taking.

Any treatment-related adverse event was higher in the maribavir arm. It was 60 percent compared to 49 percent in the IAT, and that one was mainly driven by the taste disturbance, which is a known common adverse event of maribavir from the previous prophylaxis phase 2 treatment trials.

The serious adverse events were similar between the two groups, 38 percent versus 37 percent in the IAT group. But serious adverse events attributed to any relationship to the study drug, it was much higher in the IAT, 14 percent compared to only 5 percent in the maribavir arm.

Similarly, it was for the severe adverse events a little higher in the IAT, 38 percent versus 32 percent. But when the serious adverse events were related to the study drug, it was much higher in the IAT arm compared to maribavir, 21 percent versus 4 percent, and similarly was for the adverse events leading to study drug discontinuation. These differences cannot rule out any potential bias in the study.

In this slide, we have the most common adverse events in the maribavir arm. We have events that occurred in more than 10 percent of the subjects, and the most common was the taste disturbance. It was 47 percent versus 4 percent. This number is higher than the 36-37 percent that Takeda presented, and this is because the taste

disturbance, we included all the occurrence of ageusia, dysgeusia, hypergeusia, and taste disorder. The next most common was the nausea, 21 percent; diarrhea, 19 percent; vomiting; and fatigue, and these adverse events were similar in incidence between the maribavir arm and the IAT arm.

Here we have the most common adverse events which led to the permanent discontinuation of the study drug. Totally, we had 32 percent in the IAT compared to only 13 percent in the maribavir arm. The most common adverse events leading to study drug discontinuation were those related to the blood and lymphatic system disorders; for example, neutropenia or thrombocytopenia. We have totally 11 percent in the IAT and no patients in the maribavir arm. Similarly, the renal and urinary disorders were much more common in the IAT arm, 10 percent, and no patients in the maribavir arm. Infections and infestations mainly driven by CMV infections were similarly between the two groups, as well as gastrointestinal disorders.

In this slide, I summarize the selected laboratory abnormalities, and we have measured ones from our experience with the ganciclovir, valganciclovir, and foscarnet. We have the neutrophils, hemoglobin, platelets, and the creatinine levels.

From this slide, you can see that the differences between IAT and maribavir were not significant. For subjects with less than 500, we had 2 percent in the maribavir arm compared to 3 percent in the IAT; between 500 and 750, it was a little higher, 6 percent versus 3 percent in the maribavir arm; and between 750 to 1000 neutrophils per microliter, it was similar between the two groups.

For the hemoglobin, the most severe form was less than 6.5 and was similar between the two groups, and between 6.5 and 8, it was 15 in the maribavir arm compared to 20 percent in the IAT. The most severe, thrombocytopenia less than 25,000, it was similar between the two groups, 5 percent, and between 25,000 and 50,000, it was a little

higher -- similar, I can say, between maribavir and IAT, 12 versus 9 percent.

Creatinine levels, more than 2.5 milligrams per dL, were slightly higher in the IAT, 10 percent compared to 7 percent in the maribavir arm. Between 1.5 to less than 2.5 milligrams per dL, it was slightly higher in the maribavir arm compared to the IAT.

These laboratory abnormalities are not consistent with the huge differences in the adverse events, which led to study drug discontinuation; for example, those related to the urinary chart abnormalities and those related to the blood discretions.

On this slide, I summarized Trial 303, which had the strengths and the limitations of this trial. Clearly, statistically, there was a significant treatment effect on maribavir versus the IAT arm for the primary endpoint. Also, most of the sensitivity analyses supported the primary endpoint. The taste disturbance was the most common adverse reaction, but treatment

discontinuation due to that event was very, very infrequent.

The limitations was the open-label design and potential bias resulting in imbalance in drug study discontinuation due to adverse events, withdrawal of consent, or other reasons. Overall, the treatment effect was due to drug/study discontinuation. The proportion of virologic failures was similar between the two arms, 34 and 36 percent.

Here we have a summary of the phase 2 trial in the resistant/refractory, Trial 202. For the strengths, we had similar activity with maribavir in the same population as compared with the phase 3 trial, 303. The safety profile was similar to the phase 3 trial. The limitations, of course there was the absence of a comparator arm, no dose response was demonstrated, and the baseline resistance was very poorly defined in the phase 2 trial. We cannot differentiate resistance or refractory for most of the enrolled subjects.

Here we have the overall conclusions of this

new drug application. Trial 303 demonstrated that maribavir was statistically superior to the IAT in the primary endpoint analyses. It was 56 percent versus 24 percent. Sensitivity analyses supported the superiority of maribavir over the IAT for the primary efficacy endpoint. The study was limited by the open-label design and potential bias.

Analysis of failures for the primary efficacy endpoint demonstrated that the virologic failure rates were similar in both arms, 34 percent versus 36 percent. Overall treatment effect was influenced by the imbalance in drug/study discontinuation, which was 13 percent in maribavir compared to 32 percent in the IAT. The treatment effect was consistent across transplant type, age groups, and CMV syndrome and disease, despite the very small number of patients with these characteristics.

The treatment effect was lower in subjects without genotypic resistance. Refractory CMV was 44 percent versus 32 percent. The primary efficacy endpoint results table in the maribavir arm were

mainly driven by subjects with baseline CMV DNA levels less than 5,000 international units per mL. It was obvious from the presentation there was an inverse relationship between maribavir efficacy and the baseline CMV DNA level.

There was no difference in mortality and no difference in the new onset of symptomatic CMV disease. We had a high rate of maribavir resistance among the on-treatment virologic failures, 62 percent. In many of those, almost half of those, they had conferred cross-resistance to ganciclovir or valganciclovir. Relapse of treatment was observed in both arms, 50 percent in maribavir compared to 39 percent in the IAT arm.

At this point, Takashi and I would like to thank all of the people who helped in the review of this challenging new drug application. We also would like to thank the applicant for their cooperation and their prompt responses whenever we needed it.

I would like to thank everybody for your attention.

Clarifying Questions

DR. BADEN: I would like to thank Dr. Pikis and Dr. Komatsu for very clear and informative presentations of complex data, and for being ahead of schedule. It's always appreciated, as we have many questions, I am certain.

We will now take clarifying questions for FDA. Please use the raised-hand icon to indicate that you have a question and remember to lower your hand by clicking the raised-hand icon again after you have 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 the end of your follow-up question with, "That is all for my question," so we can move on to the next panel member.

If you would like to add your thoughts on

what another panel member or FDA staff is stating, please use the green check mark icon when you are done chiming in. Please remember to clear the check mark. When you are done speaking, remember to also go on mute.

I will start with the first question, while my co-panel members raise their hands, and this is to you, Dr. Pikis.

If we can go to slide 24, please, on slide 24, Dr. Pikis, I think you give a very clear presentation of the --

(Call Interrupted.)

DR. BADEN: Can somebody please clear the -- you are on an FDA advisory committee meeting call, so if you can please mute your line so we can continue our deliberations.

On slide 24, if we can go to slide 24, Dr. Pikis' talk, in this image, Dr. Pikis, I think you present very nicely the analysis of failures of the primary endpoint, showing -- somebody is not scrolling the slides very well.

It is analysis of failures of primary

efficacy endpoint. On that image, you lay out that the failures were both virologic and due to adverse events from discontinuation. It appears, that due to virologic failure, it was equivalent between the two treatment arms, while drug discontinuation was dramatically different.

Is that the correct interpretation, that there isn't evidence of differential efficacy; it's really tolerability that is driving the result? Is that the correct interpretation?

DR. PIKIS: Yes.

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

Thank you, and Dr. Green, you have a follow-on question.

DR. GREEN: Yes. Thanks, Dr. Baden. This would be following up on your question.

If we could look at slide 30, which is now looking, I think -- I'm going to get at the same question that you asked. But now on slide 30, we have stratified by the presence or absence of resistance mutations, and therefore resistant

versus refractory, and I'm wondering if we could have the same analysis that Dr. Baden was just asking about; that is the percentage of failure versus success in maribavir versus IAT, in those with resistance and those without resistance, to determine whether we're seeing a difference in the subsets of response to therapy in terms of virologic response versus a tolerability issue.

So really, just a follow-on to Dr. Baden's question, but now as you've stratified results by the presence or absence of resistance, if we can stratify the results of why they failed in these two subsets. Thank you.

DR. PIKIS: Thank you, Dr. Green. We did not have enough time. Actually, the [indiscernible] plans to do the same analysis for the refractory as the slide we represented before, but we still haven't done it. Thank you for the question. It's really challenging, but I apologize for not having the data.

DR. BADEN: Thank you. No. Thank you for having the data you do have available and being

direct as to what data are available at this time.

Dr. Gea-Banacloche has another follow-on question.

DR. GEA-BANACLOCHE: Yes. It's not really related to that, and I don't know if it was mentioned before frequently.

This is Dr. Gea-Banacloche from the NIH. Frequently the FDA advises the sponsor on what kind of design they will want, and in this particular case, I wonder why they chose as the primary endpoint, and if the FDA was involved in recommending this, the result at 8 weeks; because we almost never treat CMV for 8 weeks, particularly CMV without disease, CMV viremia.

So frequently, in part because of the toxicity of the drugs that we have, we create for a few weeks until the viremia clears, and then we stop. Precisely, because in this trial what we see is a superiority of maribavir because of tolerance, I wonder if there are data at 4 weeks and if the FDA said, "No, no, we want to see the results at 8 weeks."

Can you answer either of those two questions?

DR. PIKIS: I will try. Thank you for the question. Look, this is a very challenging population to do for the study design. Each one has pluses and minuses, and I agree with you strongly about the study design.

I mean, when you go to the treatment guidelines, they say to treat the patients until you have 2 negative cultures, and then you stop. Of course, the company will say -- the applicant -- I have a drug that is relatively, according to them, safer to the other, and how I will take advantage of that.

If I got the chance to do the study again as a division, probably I would have done it a little differently. Add-on therapy looks much better in this population, and it's much more, I can say, clear results. For example, you can use for 2-3 weeks foscarnet, then you add on one side the maribavir, and the other side, the placebo, and it will be much clearer to see the effect of

maribavir.

I think also my colleague Dr. Komatsu has something on this to your questions.

DR. KOMATSU: Alright. Thank you. Part of the reason why we wanted to go longer than 4 weeks was we were looking at the viral decay kinetic data from phase 2 studies, and we noted that based on the decay kinetics, we didn't think that 4 weeks was going to be sufficient to suppress or achieve less than LLOQ in a substantial number of patients by just from 4 weeks of treatment.

So on top of all the things that Dr. Pikis has mentioned, another reason for going longer was because of the decay kinetic data from the phase 2 study. Thank you.

DR. GEA-BANACLOCHE: Thank you.

DR. BADEN: Moon, you pointed out that Dr. Umeh may be able to clarify one of the questions the committee members had.

Dr. Umeh, are you able to provide a point of clarification?

DR. UMEH: Slide up.

So I think the conclusion that the cure rates are equal may be a mistaken conclusion. The failure rates are equal. Essentially, what we're saying is that in 40 percent of the patients with IAT, we didn't have a viral load. So the presumption that the efficacy is driven by tolerability only assumes that all the missing viral loads are cleared. We don't know that.

But let's put that aside for a moment. Let us look at all the patients when they actually had a viral load. So every patient in the analysis you're looking at now had a viral load, so the question about discontinuation does not even arise in this particular analysis. What you see is everybody's cure rate got better, and maribavir remains statistically, significantly better than the comparator, eliminating tolerability as an issue.

Now, tolerability in this indication is very favorable because of the long-standing condition caused by immunosuppression of which it continues to go on. But even when you'd remove tolerability

as an advantage, we still have a true virologic effect.

And maybe, Dr. Avery, you want to comment on this.

DR. BADEN: No. I'm sorry. We will have a chance to clarify with the applicant when we come back to the applicant. This is a discussion with the agency. I thought you had an on-point clarification for one of the questions one of the panel members had. We will come back and have further discussion with the applicant. This is the time to clarify things with the agency.

So I will go back to the clarifying questions from the panel members, and, Dr. Umeh, there will be time for you to explain this when we come back to discuss with the applicant.

DR. UMEH: Thank you, Dr. Baden.

DR. BADEN: Thank you.

Dr. Bridges, I think you were next with clarifying questions for the agency.

DR. BRIDGES: Yes. Thank you.

I have a question about a slide that I

believe was presented by Dr. Pikis. It's the slide that shows the hematologic laboratory abnormalities compared between the two treatment groups.

Can we bring that slide up? And my question is, specifically, how the values for this comparison were chosen. I think it's important because the issue of whether there was bias in evaluating hematologic abnormalities or choosing to discontinue drug because of hematologic values, given that this study was unblinded, I think is one of the key questions in addressing a potential weakness in this study.

I'm sorry. I'm just waiting for the slide to come up.

I don't know if these numbers represent an average of the values obtained per patient over the course of the study versus the lowest value that was ever seen in a patient or how these numbers were derived. And without knowing that, I don't really know how to interpret them.

DR. BADEN: Dr. Bridges, do you know the slide number, again, that you are looking for?

DR. BRIDGES: I'm sorry, I don't. It was the second presenter, and it was a presentation of --

DR. KOMATSU: Fifty-four.

DR. PIKIS: Fifty-four.

DR. BRIDGES: Thank you.

DR. BADEN: Fifty-four. Thank you.

(Pause.)

DR. BRIDGES: It may be that the FDA can address the question even without having the slide in front of us.

DR. PIKIS: Okay. The slide that is presented, it has the laboratory abnormalities based on the central labs. We did a single analysis based on both the central labs and the local labs because the central labs would run [indiscernible] these tests every 2 weeks. So we analyzed the same things based on both, the local and central labs, and the results were almost identical with slight differences.

We were very surprised, to be honest, to see that neutropenia was not too much different between

the two arms.

DR. BRIDGES: Well, that's --

DR. PIKIS: It was very surprising to us. And similarly, it was surprising to us there was no difference in the nephrotoxicity because of the foscarnet, but that's what we got.

DR. BRIDGES: But that doesn't quite answer my question; I'm sorry. For example, if we look at neutrophils less than 500 and we say 2 percent of patients had that in the maribavir arm, does that mean that a single patient had that as their -- no; a patient had that as their lowest value one time versus some kind -- if you look at over time, how much time did they --

(Crosstalk.)

DR. PIKIS: Yes. These are the lowest values.

DR. BRIDGES: So that might account for the surprising results, right? Because you wouldn't discontinue a drug for one abnormal reading, but you would discontinue it for a persistent very abnormal reading.

So I think it would be important to understand how much time did a patient spend with these abnormal values, and that might unveil a difference between the two groups.

DR. PIKIS: Your question?

DR. BRIDGES: That's the end of my question.

DR. BADEN: Thank you, Dr. Bridges.

If the agency doesn't have any direct response, because I think that's a clarifying framing that Dr. Bridges provided, then we can go to Dr. Bollard?

DR. BOLLARD: Yes. Thank you so much. Mine's a clarifying question from previously for slide 30. Just as context, I am a bone marrow transplant physician in addition to my other day jobs. I note that in the study, 40 percent of your patients are bone marrow transplant recipients. Furthermore, this patient population seems a relatively good prognosis with pretty low rates of graft-versus-host disease in the range of 7 to 10 percent, which is low in this patient population.

So my question here is, I know on slide 29, you don't show any difference between the solid organ transplant recipients and the BMT patients, but in this slide, do we have breakdown where the resistant group was skewed to a BMT population or not?

The reason I'm asking this is because, as you know, BMT patients, especially if they don't have GVHD over an 8-week period, will be weaning their immune suppression. So especially if they were recipients of donors who were CMV positive, and half of your BMT patient population was, then they will be recovering endogenous CMV-specific, T-cell immunity; so again, would give a better prognosis or outcome.

So I know the numbers are small, but I'm interested if we have that data.

DR. PIKIS: I --

DR. BADEN: If the agency -- I'm sorry. Go ahead, Dr. Pikis.

DR. SMITH: I can answer, Andreas.

DR. PIKIS: Okay. My colleague, Dr. Smith,

will reply to this.

DR. SMITH: So for refractory subjects without resistance, approximately 70 percent were stem cell transplant recipients, whereas with resistance, about 80 to 85 percent were solid organ transplant, recipients. They had a lot more solid organ transplant recipients. So you had a lot more solid organ transplant recipients who had resistance at baseline, and a lot more stem cell transplant recipients who were refractory without resistance.

DR. BOLLARD: That's helpful.

DR. BADEN: Thanks.

Dr. Haidar, I see you have a follow-on question.

DR. HAIDAR: Yes. This is Ghady Haidar from the University of Pittsburgh. I just have a follow-up -- and not to belabor the point about the lab abnormalities table -- and I'm just confused about the renal failure data. I mean, given that a lot of foscarnet and maribavir were used in the IAT arm, I'm not sure how you can have the numbers be

so close to the maribavir arm. I was wondering if someone could comment on that. Thanks.

DR. PIKIS: I want to project one of the backup slides.

DR. BADEN: While you are pulling up the backup slide, just to the applicant, if there are additional clarifying data that you would like to present based on the questions you are hearing, we will have time to do that after lunch and when we come back to clarifying questions to the applicant. So please do consider any clarifying information that you think will be helpful for the committee.

DR. UMEH: Thank you. Will do.

DR. BADEN: Back to you, Dr. Pikis.

DR. PIKIS: Can you project, please, slide 72?

Here we look on a similar thing. We look on the grade 3 and grade 4 abnormalities, and we see that we had 3 percent in the maribavir arm compared to only 2 percent for the grade 3 creatinine increase. For the grade 4, the most severe, we had no patients from either arm.

Also, slide 73, the next slide, sometimes because these patients, they have abnormal values at baseline because of the underlying disease and the different drugs, we don't know what they have, so we tried to do an analysis of the shifts of three grades or four grades compared to the baseline.

Here, we have for the creatinine increase, we had for the three-grade shift -- for example, if the patient was at grade 1 for example at baseline, and then he moved to grade 4, which is the most severe, or he got zero at baseline, normal, and he moved to grade 3, we had only three subjects in the maribavir arm and no one in the IAT. Similarly, for four-grade shift, there was no subjects either in the maribavir arm or in the IAT arm. It was very surprising to us, but that was the data.

DR. BADEN: Thank you.

I see Dr. Banacloche has a follow-on question.

DR. GEA-BANACLOCHE: Yes. Do you think that that could be because of the open-label design,

that the physician sees a trend of the creatinine or a trend of the neutrophils, and then declares failure of the foscarnet, or intolerance to foscarnet or ganciclovir, and then switches the patient to maribavir?

DR. PIKIS: That may cause a potential bias in the study, there is no doubt. How much, I cannot answer. I don't have any measuring tape to say this person was biased and the other one was not biased, but clearly there is bias in the study, and you are correct.

DR. BADEN: Thank you.

I see Dr. Bridges has a follow-on question.

DR. BRIDGES: Yes. Thank you very much.

I guess I would like to ask the FDA if they agree that we would really need to see the persistence of these laboratory abnormalities to have it contribute to any evaluation of bias, because I am concerned that the way that the data are presented might suggest bias, but don't really give us the whole picture.

DR. PIKIS: We absolutely agree with your

remark that we don't have the complete picture. As I said before, there is a bias. How much is the bias, I don't know. But clearly, I mean, you cannot rule out any of the bias in this kind of trial, and it's normal, considering that it's an open-label study. The IAT drugs have characteristics adverse events; I mean, all drugs -- valganciclovir, ganciclovir, foscarnet, and, cidofovir. Because of the experience for so many years, we know there are adverse events.

DR. BIRNKRANT: This is Debbie Birnkrant.

DR. BADEN: Thank you. And I think we have one last question, and then we can work on the lunch timing.

Dr. SIBERRY: Thanks very much, Chair. George Siberry here.

Back on slide 30, I understood Dr. Birnkrant at the beginning to say the FDA guidance for trials of refractory and resistance CMV disease should be powered for overall effects and then have subgroup consistency. And what I note here is that we have the overall effect, that the point measurements are

in the same direction but of lower magnitude for refractory, and that you highlighted the interaction.

So I wanted FDA to comment directly on whether this meets the expectation set out in that guidance, or not.

DR. PIKIS: As your input, from our perspective, as we presented before, yes, numerically it's higher in the refractory. It's a very complicated issue. It's in the same direction. There are some limitations in the trial, and that is the major issue that we really ask your input.

I mean, it's easy for me to say my opinion, or anyone, but I think for us, the job is to try to present the data objectively and let the experts in the field -- again, the advisory committee -- to make the recommendations on this issue.

I think Dr. Birnkrant before made a couple of comments.

DR. SIBERRY: I'm sorry. Did you say somebody else was going to make a comment?

DR. PIKIS: Yes. Dr. Birnkrant would like to comment.

(No response.)

DR. BADEN: You are muted if you are talking, Dr. Birnkrant.

DR. PIKIS: They are trying to arrange the problem while we wait.

DR. BADEN: Thank you.

DR. BIRNKRANT: Okay. I can respond now.

DR. BADEN: Thank you.

DR. BIRNKRANT: Thank you.

That is true what Dr. Siberry said, that Trial 303 does meet the standard that was outlined in the guidance document on cytomegalovirus and transplantation. Keep in mind that this is a guidance document.

The other thing I wanted to bring up again with regard to the adverse reactions/adverse events that were seen and the question raised about why are they seen in both arms, I think we have to still keep in mind that this is a very sick patient population with multiple comorbidities in addition

to polypharmacy of perhaps toxic therapeutics. I think we should also keep in mind that those on the maribavir arm were able to tolerate maribavir for almost twice as long as those receiving IAT therapeutics. Thank you.

DR. BADEN: Thank you.

DR. SIBERRY: Thank you, Dr. Birnkrant.

And, Chair, I have one quick final question. May I?

DR. BADEN: Please.

DR. SIBERRY: Slide 44, that is about the resistance mutation pUL97 C480F. I heard FDA claim that this would have an impact on ganciclovir activity. I thought I heard the sponsor suggest that ganciclovir could still be expected to be active and note the fold change is a bit at the borderline.

So could FDA clarify the certainty about the impact of this mutation on clinical ganciclovir activity? Thank you.

DR. KOMATSU: Sure. Thank you.

First of all, I thank you for the question.

Generally speaking, overall, ganciclovir resistance-associated substitutions, the general rule of thumb is anything above two-fold is generally considered to be clinically meaningful, and C480F certainly fits that criteria.

Now, I definitely agree with the applicant that with patients with this substitution, especially if they had this substitution, probably can be first treated with ganciclovir again for what is typically considered low-grade resistance to ganciclovir. Anything less than five-fold, the treatment guideline is to change the ganciclovir dose to treat such patients.

Now, with respect to the applicant's data, I would say the idea for the 48 patients -- we just recently received this, so we haven't been able to do a thorough analysis of this. So I would definitely ask the applicant to clarify if I misrepresent any of their data. But when we dissect those 48 patients, at the end of the day, what we were really concerned about for these substitutions is specifically the cross-resistance

to ganciclovir.

We do know mechanistically, foscarnet and cidofovir are not cross-resistant to maribavir and certainly are, of course, an option, so we were really more focused on ganciclovir; specifically on ganciclovir.

Now, amongst those 48 patients that were re-treated, our understanding is that eight of those patients were treated with ganciclovir only and, again, all eight of those patients had the C480F substitution. So again, I agree with what was done, and they probably can be treated with ganciclovir.

I should note that of those eight patients, seven of those patients were refractory, so they didn't have preexisting ganciclovir resistance-associated substitutions. So when they failed maribavir, this substitution was the only substitution that they had that would be resistant to ganciclovir for 7 of the 8 patients.

Now, it was certainly encouraging that all eight responded, so that's definitely great news.

But one of the things that typically happens with quote/unquote, "low-grade ganciclovir resistance substitutions," is that they may respond initially when they get dose-adjusted ganciclovir. But a subset of those patients is going to get additional ganciclovir resistance-associated substitutions, and ultimately may end up failing.

Now again, based on the 8 patients, none of those patients acquired additional ganciclovir substitutions, so that's certainly encouraging. But based on 8 patients, I don't think we can definitively say that cross resistance will not be an issue. I think we will need a little bit more, a bigger denominator, to make that conclusion. Thank you.

DR. SIBERRY: Thank you very much, and thanks to the chair.

DR. BADEN: Thank you for clarifying those issues.

We will now break for lunch. We will reconvene at 1:00 p.m. Eastern time. Panel members, please remember that there should be no

chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin around 12:45 to ensure you're connected before we reconvene at 1 [o'clock].

I will also just ask the applicant to prepare any clarification, as we will come back to clarifying issues with the applicant and potentially the agency after the open public session, which is approximately 1 to 2 o'clock.

Thank you all, and we will restart at 1 o'clock sharp.

(Whereupon, at 12:17 p.m., a lunch recess was taken.)

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

(1:00 p.m.)

Open Public Hearing

DR. HOFFMAN: It is now 1 o'clock, so it is time for us to resume. We will now begin the open public hearing session.

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

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

meeting.

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

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 speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected

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

Speaker number 1, please.

MR. AMBROSE: Yes. Good afternoon, and thank you for the opportunity to speak before this committee today. My name is Bret Ambrose. I have no financial disclosures to acknowledge. I'm a 60-year-old retired electronic sales manager in the military and aerospace industry and a volunteer ambassador for my local organ procurement organization, Midwest Transplant Network.

Today, I am pleased to be representing myself, as well as those future patients who might benefit from my experience. I'm speaking to you from my home on the Lake of the Ozarks in Central Missouri, where I reside with my wife of 31 years, Brenda, and our Goldendoodle, Body [ph].

As a young child, I was diagnosed with cystic fibrosis in the mid 1960s at a time when the life expectancy for a CF patient was approximately 10 years of age. I was blessed to lead a

reasonably normal life despite my continuously declining lung function, which had plummeted to less than 10 percent by December of 2013.

On September 23, 2014, I was fortunate to receive a life-saving double-lung transplant at the University of Pittsburgh Medical Center. I was administered two years of oral valganciclovir prophylactically for CMV, per protocol, for a high-risk, CMV-positive donor/CMV-negative recipient case. During that time, I also developed chronic kidney disease due to my immunosuppressant medications that eventually required me to be listed for a kidney transplant.

Within two weeks after discontinuing prophylaxis, that would be October of 2016, I first tested positive for CMV with no symptoms. I immediately restarted oral valganciclovir to no avail. By early November, I had developed severe ulcers and I had lost 15 to 20 pounds in 2 to 3 days due to severe diarrhea as my CMV PCRs topped out at 580,000 international units.

I had a PICC inserted and commenced

IV ganciclovir for several months, and the symptoms subsided. Unfortunately, I could never clear the virus, and a mutation test revealed that my CMV had mutated at UL97 and had become resistant. At that point, I was in a real predicament, as my GFR was not sufficient to be enrolled in the phase 3 maribavir trial, and the only available treatment for my situation, foscarnet, was extremely nephrotoxic and would likely drive me into a lifetime of dialysis. I had also been told that the mutated CMV diagnosis would likely exclude me from receiving a donated kidney.

I was admitted to the University of Pittsburgh Medical Center in early April 2017 and commenced IV foscarnet with aggressive hydration to assist and protect my kidneys. After several days of this treatment, by blood work showed little to no change in CMV levels, but my GFR had improved just enough to qualify for that trial.

I enrolled in the phase 3 trial and randomized, fortunately, to maribavir. Within two weeks, I had a CMV PCR test yield CMV not detected,

the only side effect being mild dysgeusia, which I described as a slightly metallic taste with each dosage; in my opinion, a small price for the achieved result.

I completed the trial over the next several months and discontinued the maribavir. With the exception of a brief breakthrough CMV episode that was cleared with oral valganciclovir two years later, I have had not detected or detected but too low to count CMV PCR since. It's difficult to describe the relief and elation that I experienced following the maribavir trial and my CMV clearance. I'll try to do so for you.

If you're familiar with cystic fibrosis, you can understand that my normal life that I alluded to earlier included multiple time-consuming lung clearance treatments daily, as well as full-time oxygen. Imagine going through the rigors of transplant surgery, experience the joy and freedom of a new life, and then because of a CMV diagnosis and the lack of an approved and safe effective treatment, that you could be forced to revert to a

very limited life style due to dialysis requirement.

Now, imagine how you would feel if there was a safe and effective medication like maribavir that is approved and commercially available that could prevent the negative scenario that I described. I ask that you consider the data to take into account the roller coaster of emotions that patients in a similar situation as me are confronting on a regular basis.

Hopefully, you'll be able to make a positive decision for this medication, maribavir, that was so effective in my case. I thank you very much for your time and attention today.

DR. BADEN: Thank you.

Will speaker number 2 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MR. WATSON: Hello. I am Bill Watson. I have no financial disclosures. I'm an IT professional. I live in Westfield, Massachusetts. Here's my story.

In 1994, I lost my kidney due to IgA nephropathy and went on dialysis. I was 30 years old. After nine months on dialysis, my sister donated a kidney. In 2013, I was diagnosed with CMV retinitis. By the time I was diagnosed, I had lost vision in my right eye and I was losing sight in my left eye.

Fortunately, and as a retina specialist at Mass Eye and Ear, Dr. Varvares, still says to me today, "I need to thank God, not him, that I can still see." I was treated with valganciclovir. I stayed on this medication as a preventive measure, as I was immunosuppressed due to the transplant and I needed to be protected against the CMV.

In 2017, so about four years later, I became very ill, lost nearly 60 pounds, and it was discovered that I now had CMV colitis. The CMV had become resistant to valganciclovir.

I spent two weeks in the hospital and really began to wonder if this was the end for me, if I was going to end up in a hospice. There was a lot of concern about the impacts of foscarnet on my

transplanted kidney, but there are so few options to treat CMV. Fortunately, I was asked to participate in the trial for maribavir. Within a week, I felt better. After a couple weeks, the CMV wasn't detectable. Life began to return to normal. I returned to work. My weight started to go back up. Then the trial ended, and I no longer had access to the medication.

A few months later, now in 2018, I started to have vision issues in my last working eye. The CMV had come roaring back. This time there were no options, no options for maribavir. So this time I was hospitalized with a line in my chest for two weeks of aggressive foscarnet treatment IV, including foscarnet directly shot in my eye.

To protect the kidney, I was flooded with fluids in between doses of the foscarnet. My creatinine did rise, my legs swelled, my blood pressure rose, but in the end, it did treat the CMV. Without any good alternative meds, I was stripped of all my immunosuppression meds so that my own immune system could re-establish itself to

see if it could fight the CMV. The thinking was better to be on dialysis again than blind or dead. If you have never been on dialysis, this isn't as clear-cut an answer as you might think. I was also put on Prevymis to help hold back the CMV from returning.

Now I live in constant worry with, will my transplant kidney reject, will the CMV return, and can I survive another round of foscarnet? Will I never ever be able to get a transplant again if needed? Will CMV return and strike somewhere else in my body?

It's recommended that I don't get the COVID vaccine due to worry it may trigger a return of the CMV or kidney rejection. So that has completely isolated me from the rest of the world because, for me, the pandemic is still ongoing.

There are so few options to treat CMV. This really wears on you. Maribavir worked for me. It allowed me to return to normal life while also not losing my transplanted kidney or my sight. The transplant is a gift from my sister, and I'm glad

that I was able to retain it.

Taking maribavir was just like taking a couple of Tylenol. I had no notable side effects that I noticed. Myself and all those who suffer from CMV need more options for treatment. Thank you for listening and your time.

DR. BADEN: Thank you.

Will speaker number 3 begin and introduce yourself? Please state your name and any organization you're representing for the record.

(No response.)

DR. BADEN: Speaker number 3, you are on mute. We cannot hear you.

(No response.)

DR. BADEN: We shall move to speaker number 4. Will speaker number 4 please begin and introduce yourself. Please state your name and any organization you are for the record. Thank you, speaker number 4.

DR. SILVEIRA: Okay. Can you hear me?

DR. BADEN: We can. Thank you.

DR. SILVEIRA: Good afternoon. I am

Fernanda Silveira. I am associate professor of medicine, transplant infectious disease physician, and director of clinical operations for Transplant Infectious Diseases at the University of Pittsburgh and University of Pittsburgh Medical Center. I have been in practice for 15 years, and I care for patients who underwent solid organ transplants; patients with hematologic malignancies; patients who received CAR-T; and patients who received hematopoietic cell transplants.

I was a site principal investigator on the Shire-Takeda phase 2 and 3 trials of maribavir for refractory and resistant CMV, SOT, and HCT recipients, and received compensation for participation in a Takeda advisory board meeting. I am not being compensated for my time today.

In my practice, I care for several patients with CMV infection and disease. Besides suffering from the effects of CMV, these patients experience significant side effects from CMV treatment. Occurrence of severe leukopenia and neutropenia with val and ganciclovir is very common and leads

to drug interruptions, need for granulocyte growth factors, and secondary infections.

Furthermore, a subset of patients experience refractory and resistant CMV, requiring the use of foscarnet, which carries a substantial risk of nephrotoxicity, sometimes requiring the need for renal replacement therapy. As an example, I would like to mention two patients who are currently under my care. These are not exceptions, but rather what we commonly see in practice.

The first is a 75-year-old man who received a lung transplant in 2015 for idiopathic pulmonary fibrosis. For the last several months, he has had CMV viremia. He was placed on valganciclovir and tolerated it well, and viral load improved initially. But his viremia rebounded and reached levels higher than prior to therapy.

CMV resistance testing showed the presence of a UL97 mutation that confers ganciclovir resistance. His creatinine was 1.5, consistent with a creatinine clearance of approximately 50 mL per minute. Due to the lack of other options, he

was admitted for initiation of foscarnet, which can't be started as an outpatient due to the need for very close monitoring of renal function, electrolytes, and need for IV hydration.

Nine days after initiation of foscarnet, despite concomitant IV hydration, his creatinine increased to 2.1 and his creatinine clearance decreased to approximately 30 mL per minute. This patient remains without other options, and he's at risk of further progression of renal failure and need for renal replacement therapy.

Another patient is a 57-year-old female who had a previous autologous hematopoietic cell transplant for multiple myeloma and subsequently had two kidney transplants. She was diagnosed with CMV GI disease refractory and resistant to ganciclovir. She's currently admitted into the hospital for IV foscarnet. Her creatinine on admission, prior to foscarnet, was 0.9.

After only a week of therapy, her creatinine increased to 2.1, and foscarnet had to be held due to fear that she will lose her second kidney

allograft. An application for maribavir for compassionate use was submitted and luckily was accepted, and maribavir was started yesterday.

These two cases are not exceptions. Transplant ID physicians encounter situations like these regularly, and the use of foscarnet leads to severe comorbidities, including having patients progress to advanced chronic kidney disease, and even to dialysis. It also adds the burden to the patient due to the need for hospital admission and very frequent blood draws for monitoring.

We clearly need in our armamentarium drugs that are safer and effective. The availability of maribavir will fulfill a large unmet need in the management of CMV. I thank you very much for your time.

DR. BADEN: Thank you.

Will speaker number 5 begin and introduce yourself? Please state your name and any organization you're representing for the record.

(No response.)

DR. BADEN: We shall move to speaker

number 6, as number 5 is not available.

Will speaker number 6 please begin and introduce yourself?

MR. PAOLO: Hello?

DR. BADEN: Please state your name and organization you are representing for the record. Thank you.

MR. PAOLO: Hello. My name is Thomas Paolo. I'm 66 years old. First of all, I would like to thank you for the opportunity to share my story regarding my experience while being treated with maribavir as a participant in a trial in the fall of 2018. I do not have, nor have I ever had, any financial connections with Takeda Pharmaceutical Company, Limited.

Tomorrow, October 8th, will mark my 44th wedding anniversary to my wife, Darlene. We have three children and six grandchildren. I'm a self-employed tax accountant, an enrolled agent. I've been practicing for nearly 45 years.

I was first diagnosed with COPD in 1999. My main issue was emphysema with some fibrosis issues

as well. I was not quite 45 years of age when diagnosed with, at the time, three teenage children. With help of a fabulous pulmonologist who motivated me in many ways, I knew that I would have to take special care of myself if I were to live into my 60s.

After a serious setback in 2016 and pneumonia-induced exacerbation, I was placed on 5 liters of oxygen and knew that a potential lung transplant was going to be the only way I could hopefully extend my life past another year or two. After extensive testing, I was extremely fortunate to be included on the transplant list on December 21st of 2017. And on March 31st of 2018, I received a single-lung transplant at UPMC Presbyterian Hospital in Pittsburgh, Pennsylvania.

According to my records and my knowledge, I was first diagnosed with the CMV virus in the fall of 2018. While in the hospital, I was told that the treatment would be a drug given intravenously over a period of time, valganciclovir, as previously mentioned. That is when I got yet

another gift because Dr. Fernanda Silveira, speaker 4 as a matter of fact, an infectious disease doctor with whom I've grown to respect immensely, was conducting a trial for maribavir.

I was fortunate enough to be part of it, and my CMV numbers dropped immediately. But after a period of time, the trial ended, and since then, the doctors are trying to keep the CMV virus under control with a cocktail of meds that include everolimus 0.75 milligrams twice a day. It now appears that the meds are starting to take their toll on my kidneys. I'm at stage 3A kidney failure.

I hope and pray that maribavir is approved for transplant patients. We survive only as a result of breakthrough meds that are effective and not only prolonging our lives, but enhancing the quality of our lives as well. Thank you again for allowing me to tell my story.

DR. BADEN: Thank you for sharing.

Will speaker number 7 begin and introduce yourself? Please state your name and any

organization you're representing for the record.

DR. PAPANICOLAOU: Good afternoon. My name is Genovefa Papanicolaou. I'm an infectious disease physician at Memorial Sloan Kettering Cancer Center and professor at Cornell University, both in New York City. I have been in practice for 25 years treating adults and children who receive stem cell transplants. I'm also a key participant in many CMV trials, including several of the maribavir trials. I serve as consultant to Takeda and Merck. I'm not compensated for my time today.

Today I'm here to tell you why I'm excited about maribavir. We have come a long way with CMV in transplantation. With letermovir, we now have a safe and effective drug for CMV prevention. And this is great, but some patients still get CMV and need treatment.

For over 20 years, we have two anti-CMV antiviral drugs, ganciclovir and foscarnet. Both have excellent antiviral activity. Their downside is their toxicities, which are well described and quantified. Ganciclovir and its oral prodrug

valganciclovir are myelosuppressive. Foscarnet is only available intravenously and is nephrotoxic.

Today I want to tell you how CMV treatment affects my patients' lives. I will share the story of Diane, a 53-year-old lady with lymphoma. Diane received a stem cell transplant from her brother in early April 2021. Despite letermovir prophylaxis, she developed CMV infection after transplant. She was initially treated with ganciclovir, but after four weeks, she was switched to foscarnet for refractory CMV viremia. She received foscarnet as an outpatient for two weeks, her CMV infection resolved, and foscarnet was discontinued.

Ten weeks later, or five months after her initial transplant, she had progression of her lymphoma. While on treatment for lymphoma, her CMV infection recurred. Her blood counts now were too low to be treated with valganciclovir, so she was treated with foscarnet. Up to now, she has received six weeks of foscarnet as an outpatient. She's still receiving it to prevent CMV recurrence. Her lymphoma is responding to treatment and she is

planning to receive a second transplant.

Now, from the CMV outcomes perspective, Diane is the success story. She did not develop CMV disease, did not require hospitalization for CMV, and actually she did not have any measurable toxicity related to CMV treatment. As a clinician, however, I feel we should be able to do better for our patients.

Since her hospital discharge, Diane spent 25 percent, or one-fourth, of her total days in the clinic tied to an infusion pump for 6 to 8 hours each day. Every day she spends in the clinic is one less day she could be spending at home with her family. Diane's story is not unique. We need a CMV treatment that is oral, well-tolerated, safe, and effective. Maribavir meets this need. Maribavir when approved will replace foscarnet in my practice.

We are at an inflection point in the treatment of CMV. Twenty years ago, we were at a similar point with aspergillosis. Amphotericin was the only treatment option for aspergillosis.

Amphotericin, like foscarnet, is nephrotoxic and available only by vein. Voriconazole is an oral drug spectrum as well that is not nephrotoxic. After approval, voriconazole replaced amphotericin for treatment of aspergillosis. Maribavir has the potential to replace foscarnet for treatment of CMV and improve the quality of life of our patients.

Stem-cell transplantations have to jump over many hurdles. Graft-versus-host disease, organ toxicities, and relapse are just to name a few of them. Getting treatment for CMV should not be another hurdle.

On behalf of our patients and their families, I respectfully request the committee consider these factors in its review of the new drug application for maribavir oral tablets. Thank you for your time and for the opportunity to provide my comments.

DR. BADEN: Thank you for sharing those comments.

Will speaker number 8 begin and introduce yourself? Please state your name and any

organization you're representing for the record.

MS. COCHRAN: Good afternoon. My name is Willa Vroman Cochran. I'm an infectious disease nurse practitioner at Johns Hopkins Hospital's Comprehensive Transplant Center. I have been caring for liver and kidney transplant patients for about six years. I have no financial disclosures, and I am not being compensated for my time today.

In 2014, the Hopkins Transplant Center conducted an internal assessment of kidney and liver transplant recipients who required hospital readmission post-transplant, and they found that the most common reason for readmission was, quote/unquote, "infection." While this is to be expected to some extent, as transplant recipients are immunosuppressed, to prevent rejection, certain infections stood out as being preventable. The most common of these was cytomegalovirus infection or CMV.

I was hired in May of 2015 and dually trained in transplant and infectious disease medicine, and I was tasked with reducing CMV

infection in collaboration with both the infectious disease program and with the transplant center. At our center, around 80 patients a year are CMV antibody negative prior to transplant and receive an organ from a CMV antibody-positive donor. Per protocol, these patients take valganciclovir in 900 milligrams daily for CMV prophylaxis for a total of six months.

I review all 80 patients once a week for a year to ensure that their dose of valganciclovir is adjusted accordingly based on their most recent creatinine clearance. I spend on average 8 hours a week re-dosing valganciclovir. Many of these patients experience valganciclovir-induced neutropenia. This puts them at very high risk for opportunistic infections. The transplant team is then faced with the choice to either stop CMV prophylaxis and check CMV PCR once a week or to administer granulocyte colony-stimulating factor, G-CSF, to boost the neutrophil count and continue the prophylaxis dose of valganciclovir.

Both of these choices pose potential risks

and costs to the patient. Furthermore, as patients develop CMV viremia in the future and have a history of valganciclovir-associated neutropenia, this requires critical conversations around dosing of valganciclovir versus prescribing letermovir, which is often not covered by insurance and is cost prohibitive to many of my patients.

A painful example of this scenario is Mr. A, a 68-year-old man who underwent deceased-donor liver transplant in 2016. Prior to transplant, Mr. A was CMV antibody negative. His donor was CMV antibody positive. He started valganciclovir for prophylaxis immediately post-transplant per protocol. By three months post-transplant, he was noted to have an absolute neutrophil count of 0.3 and his valganciclovir was stopped by his transplant team.

The CMV PCR was ordered to be drawn every two weeks, but unfortunately it was not drawn until one month after stopping valganciclovir, and at this time, his CMV viral load was greater than 100,000 copies. He was admitted to our hospital

for IV ganciclovir and stayed 5 nights until his CMV was low enough that he could transition back to oral valganciclovir.

Once home, his ANC dropped predictably and he required 3 doses of G-CSF again. This injection cost him about $30 out of pocket each time, which was a financial strain for his household, which was on a fixed income. He continued valganciclovir at home until his PCR was negative twice, and we were eager to stop the valganciclovir as soon as it was safe because his ANC was dropping again.

From 2017 to 2019, Mr. A had 6 reactivations of CMV viremia. He had innumerable instances of valganciclovir-associated neutropenia, CMV colitis, CMV pneumonitis, and in the setting of this neutropenia, he was diagnosed with PJP pneumonia.

We requested letermovir in 2019. It was denied by his insurance, and we appealed, and it was finally approved. By this point, however, his net state of immunosuppression was so low that in the setting of severe neutropenia and weakness, he fell at home, sustained an open-foot fracture, the

site of which soon became infected, and required admission for IV antibiotic.

He passed away in July of this year in the setting of C. diff colitis and fungal pneumonia. The majority of his diagnoses can be tied back to his net state of immunosuppression, which was dangerously low since his first instance of valgan-induced neutropenia.

If an antiviral agent with activity against CMV and without potential to cause marked neutropenia had been available for Mr. A, he may have avoided three years of resistant/refractory CMV infection and the multiple opportunistic infections that ultimately cost him his life.

Thank you for the opportunity to share Mr. A's case, and thank you for your time.

DR. BADEN: Thank you for sharing your perspective.

Will speaker number 9 begin, and introduce yourself? Please state your name and any organization you're representing for the record.

DR. BOECKH: Thank you for giving me the

opportunity to speak. My name is Michael Boeckh. I'm a professor of medicine at the Fred Hutchinson Cancer Research Center and the University of Washington Seattle. I'm the head of the Infectious Disease Sciences Program in the Vaccine and Infectious Disease Division at the Fred Hutch, and the medical director of the Infectious Disease Consulting Service at the Seattle Cancer Care Alliance.

I am a clinical researcher and CMV has been my field of interest for more than 30 years. As for disclosure, I've served as consultant and received research support from various pharmaceutical companies that work in the area of CMV drug and vaccine development, including Takeda and the other companies that were involved in the development of maribavir over the years. In my recent years, I have not received consulting fees, and I am also not compensated for speaking here.

You all have reviewed the data on maribavir and heard compelling testimonies today. Since I receive frequent questions on how to best manage

patients with difficult-to-treat CMV from across the United States, I think it might be instructive to illustrate the complexities of treating severe CMV infection by telling you about a recent case that I was involved in.

The patient was a 54-year-old male from the southeast of the United States, was diagnosed with plasma cell leukemia in February of 2020, and received a myeloablative, T-cell depleted HLA mismatch unrelated allogeneic transplant in October 2020. He was CMV-cell positive and so was his donor. Post-transplant prophylaxis consisted of low-dose acyclovir and letermovir, which was given until day 100.

On day 120, so about 3 weeks later, after the stop of letermovir, the patient developed the first episode of CMV reactivation with a viral load of 1450 IUs per mL, which was treated with valganciclovir for a month, which didn't work and led to an increase of the viral load to 5,500, which then required hospital admission and switch to foscarnet. Eventually, the viral load declined

to undetectable levels with one month of foscarnet treatment.

Two additional episodes followed, where both required foscarnet for 4 to 6 weeks, respectively, with hospitalization for the 2 weeks of induction courses in both cases. The C4 count of this particular patient continued to be less than 5 microliters throughout the entire time.

One month later, now about 11 months after transplantation, patient presented with fever and a viral load of 15,000 and was started on foscarnet and valganciclovir, given both at induction dosing. Three days later, the viral load increased to about 50,000. Drug resistance was suspected and his test was sent to a reference lab.

Four days later, the patient developed respiratory failure, and the viral load at that time was 184,000. Letermovir was added empirically and maribavir was requested, due to the dire circumstances, from the company and started 3 days later as monotherapy. Unfortunately, the patient died 3 days later with multiple organ failure, but

the viral load had declined to 40,000 at the day of his death.

This profoundly immunosuppressed transplant patient had depleted CMV reactivation episodes, and the criterion for refractory infection was met already during the first episode, which occurred about 3 weeks after the 100 days of the term of the prophylaxis. Over the following weeks and months, resistance developed against all drugs that are approved for CMV treatment at the moment -- that is ganciclovir, foscarnet, and cidofovir -- but the results became available only a few days before his death.

While the foscarnet in this patient did not cause renal insufficiency, it did require weeks of hospitalization, or maribavir could have been used as early as during the first episodes of CMV reactivation when the viral load was refractory and would have prevented foscarnet use and associated hospitalizations.

I believe our patients do need additional oral drugs to treat CMV with a unique mechanism of

action and a favorable toxicity profile. Maribavir is such drug in my opinion. Thank you for your time and the opportunity to share my thoughts.

DR. BADEN: Thank you for sharing your comments.

Will speaker number 10 begin and introduce yourself? Please state your name and any organization you're representing for the record.

DR. GANDHI: Good afternoon, and thank you for allowing me to participate in today's ADCOM. My name is Ronak Gandhi, and I'm an infectious diseases pharmD and board certified as a pharmacotherapy specialist with six years of experience. I practice at Massachusetts General Hospital with a primary focus on transplant infectious diseases.

I have no financial disclosures, and I'm not being compensated for my time today to provide a statement of why maribavir should be considered for FDA approval for resistant/refractory disease. And though by definition, resistant disease is different than refractory disease, in the

healthcare setting, we consider them as a continuum and one process, so my statement will fall under those pretenses.

As a transplant infectious diseases pharmacist, managing CMV is something I encounter routinely. CMV infection/disease post both solid organ and bone marrow transplantation are common and associated with increased morbidity and mortality. Even though advancements in our therapeutic arsenal have improved outcomes, the risk of developing resistant or refractory disease still remains and can be very burdensome to patients and healthcare providers.

Patients with resistant/refractory CMV face a steep battle to get their disease under control. They're typically managed with potently nephrotoxic and/or marrow-suppressive agents such as foscarnet or cidofovir.

In certain instances, these patients can require combination therapy with either of those agents, along with high-dose ganciclovir, adding to further marrow suppression. And patients who are

already so heavily immunosuppressed, causing further neutropenia can be detrimental to these patients' safety and can lead to other complicated invasive infections. Additionally, all of these therapies require renal dose adjustment, which can be challenging, as many of these patients have acute kidney injury, chronic kidney disease at baseline, or kidney transplant recipients themselves.

Balancing these parameters to achieve therapeutic concentrations without invoking toxicities -- or worse, treatment failure, resistance, or even rejection -- put significant stress on healthcare providers. Furthermore, these therapies are only IV and require frequent lab monitoring, making discharge to a safer environment such as their homes nearly impossible.

Additionally, a fair amount of these patients require maintenance or suppressive therapy once they have cleared their acute infection. Currently, this is challenging with limited oral options and can lead providers to use a preemptive

monitoring strategy, which puts further stress on both the provider and patient to evaluate and be evaluated weekly or monthly.

Maribavir is a novel anti-CMV agent with a unique mechanism of action. This mechanism of action allows for it to retain its activity even against ganciclovir-resistant infection or disease. In all clinical trials available to date, maribavir side effect profile is much cleaner than currently available options, with the biggest side effect being dysgeusia or taste disturbance.

Though taste disturbance can impact nutritional status of these patients, which is important, it's worth noting that a minimal number of patients discontinue therapy based on the side effect, and the side effect resolves in most patients after 1 to 2 weeks.

Additionally, maribavir is primarily hepatically metabolized with less than 3 percent renally excreted, so there is no risk of either under- or overdosing patients with renal impairment or dynamic renal function. Furthermore, maribavir

is being manufactured as an oral formulation, which will help facilitate earlier discharge and potentially can be used in suppressive therapy after initial clearance of infection.

In a multicenter phase 3 study for resistant/refractory disease that has recently just been completed and not yet published, results from prominent abstracts presented at national meetings demonstrated statistically significant clearance of infection at 8 and 16 weeks compared to investigator-initiated therapy for valganciclovir, ganciclovir, foscarnet, or cidofovir for resistant/refractory CMV in both solid organ and bone marrow transplant recipients.

The result of the study, coupled with the complications of traditional therapy and the more favorable safety profile of maribavir, should provide this committee with good evidence to consider approval of this agent.

What I would like this committee to remember today is adding maribavir to our current armamentarium will allow us as healthcare providers

to manage a complicated disease state with an alternative agent when standard-of-care options are not feasible, limited by toxicities, or continued worsening while on treatment. More importantly, this agent can improve patient care, as it is oral and can facilitate discharge from the hospital in cases where patients are receiving IV foscarnet or cidofovir.

Additionally, maribavir is not renally eliminated, providing a more predictable PK profile and a larger margin of safety, as well as potentially prevent the emergence of resistance, toxicities, or acute rejection when traditional therapies are either under- or overdosed in patients with renal dysfunction.

Lastly, maribavir can negate the toxicities of standard therapy such a neutropenia and nephrotoxicity and can be an alternative to decreasing immunosuppression and an unacceptably toxic combination of high-dose ganciclovir plus foscarnet for resistant disease.

I hope this committee takes this into

perspective, and I want to thank all of you for taking a few minutes to listen to me today. Have a great afternoon.

Clarifying Questions (continued)

DR. BADEN: Thank you for sharing your thoughts with us.

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

We will return to the clarifying questions, as we were unable to clarify all issues before lunch. I think we were able to complete the clarifying questions to the agency, but I would like the agency to stay available if questions come up that we would like to address to you.

To the applicant, Dr. Umeh, thank you for returning to clarify matters for us. For the committee members, there are several of you who had

indicated you had more clarifying questions. What I'd like to do is have you raise your hand again, in case your questions were already answered, and we'll continue with clarifying issues with the applicant. I will start with the first question while the committee members queue up.

Dr. Umeh, you reacted to my comment to the agency -- and I would very much like you to clarify -- when I harped on the issue that the agency raised about the efficacy was driven by safety, not virologic activity.

Can you please clarify that issue? I know you had started, but I would like you now to more fully clarify on that point.

DR. UMEH: Thank you to the Chair. I want to start by first showing the slide on treatment duration at any time. The patients who did not have a viral load was because -- the patients did not have a known viral load, and that was assumed to be failure. They didn't come for their weekly visit. However, if you focus only on the patients who had a viral load, there is no guesstimating

what the outcome was. You're focusing on what the viral load shows, and you're giving credit to any patient who had a viral load and cleared the therapy. Maribavir maintains an advantage. Here, the tolerability advantage has been neutralized, and you see that we still show a significant benefit.

I'll show you another slide. This particular slide I show you, the first line is at anytime. If the virus was cleared, you got credit for the virus being cleared, independent if you completed 8 weeks or not. What you see here is the first line I already mentioned.

In the second line, what we've done is to respond to a question during the break, what was the outcome by week 4? Because typically, these patients are treated for about 4 weeks. The idea is that we treat for shorter than they should have been treated, and in which case give maribavir in advance? The answer is no. Even if you look at the week 4 outcomes and do the viral clearance rated by the week 4 outcomes, there is still a

statistically significant advantage for the comparator.

One of the things I would like to show you is the duration of therapy because a lot has been made about the discontinuation rate. But the question is, were patients treated long enough in the IAT arm? This is the mean duration of therapy for the entire study.

What you see here is that the average duration of treatment, the mean duration of treatment, in the IAT arm is 36 days. It is longer than what is done in clinical practice. Dr. Avery is going to come up to speak to her experience in the clinical practice.

DR. AVERY: Yes, just to confirm that this mirrors what we do see in real-life clinical practice, our center, Johns Hopkins, published a retrospective study of patients treated with foscarnet for CMV, 39 patients, and the median duration of therapy was almost exactly the same as this.

DR. UMEH: So we view this as a benefit of

maribavir rather than a bias. The fact that maribavir can be treated for longer is a benefit of a safe drug in this condition that requires immunosuppression rather than a bias against the comparator.

DR. BADEN: Now, understood, and an oral agent that is more easily administered can be taken for longer and potentially have the benefits of longer treatment.

To just push a little bit more on this point to make sure I'm thinking about this properly, in order to get into the study, patient had to have CMV reactivation. They were treated. The treatment failed to control it, and then they were randomized.

So in the IAT arm, individuals may have gotten valganciclovir or foscarnet, be randomized, and continue valganciclovir or foscarnet, while the other half received the maribavir. So we're comparing maribavir versus continuation of a failing therapy.

Am I interpreting this correctly?

DR. UMEH: I'll show you a slide, and then I'll ask Dr. Avery to come up again and speak to her experience.

About half of the patients actually received the therapy they were randomized to, but about half of the patients also received new therapy. And as you can see in the first line of the slide, that did not make a difference. In fact, people who were randomized to valganciclovir did better.

But, Dr. Avery, come speak to your experience as a PI.

DR. AVERY: Right. As investigators, we approached the study subjects in what we felt was in the best interest of the patient. So the choice of IAT was tailored to the patient's prior responses, preexisting lab abnormalities and toxicities, and also patient preference.

There were some patients who entered the study, of course, hoping to be randomized to the maribavir arm, were randomized to IAT, but then did not want to leave their therapy that they were on because of concern that other therapies might be

more toxic. So I think, in general, this just speaks to the rather very limited options, dismal options, we have for IAT in these patients in general.

DR. BADEN: Thank you. No, that makes sense, and the treatment options, as many of the OPH speakers and others have raised, are limited and toxic. But in terms of understanding the superiority, making sure that it's just clear what we're comparing, which the standard of care or IAT is incredibly limited in many circumstances.

I know, Dr. Green, you have a follow-on question to this line of discussion?

DR. GREEN: Yes. Thank you. It's Mike Green. I consider it follow-on because I've looked at the slide that showed a very nice level of response, even at 4 weeks, but I noted in the FDA analysis that 32 of the 80 virologic failures in maribavir occurred in individuals who cleared their load but presumably then developed a new positive load during that 8-week time period.

I wonder if you can tell us a little bit

about the 32 patients who had breakthrough CMV in that 8-week time period on maribavir.

DR. UMEH: So there were 48 patients. What you're speaking to, basically, is the recurrence of therapy and those who are associated with development of resistance.

I think the way to look at this is what actually happened at week 16, which is when we have a differential clearance of viral load, and maribavir being much more able to clear the virus.

DR. GREEN: I want to clarify to make sure that you're correct or I'm understanding the table from FDA, and it's their table, page 24 of what they shared with us. I didn't read that as individuals -- it said, "analysis of failures of primary efficacy endpoint," and I understood primary efficacy endpoint to be the 8-week time point.

So as I read this table, my reading would be that of 80 failures, virologic failures, at the primary efficacy endpoint -- that's 8 weeks -- 32 of 80 had gone to non-detectable or

non-quantifiable and became positive again by that 8-week time period; so not the 9 to 16 week.

I understand reactivation greatly. I do CMV and I do transplant ID for a living as well. I don't understand what's happening in this cohort with primary efficacy endpoint, which, again, I think is talking about the first 8 weeks of therapy. Thank you.

DR. UMEH: Yes, you're correct. So you had to clear the virus at any time, and if you maintain the clearance through week 8, you'll be counted as a success. So that's differentiating between those who cleared it between those who never cleared it at all throughout the 8-week period of treatment. That table is different than those who never did clear it from those who cleared it but couldn't maintain the clearance to week 8.

DR. GREEN: Correct. So I'm trying to understand that group of 32 who presumably stayed on maribavir at that point, unless they were taken off for some reason; so having cleared, having stayed on therapy, they then broke through. And

I'm not sure whether they all had resistance or if you have any further analysis of those 32 patients that respond and breakthrough in the time period leading up to week 8.

DR. UMEH: We know that a lot of the on-treatment recurrence was associated with resistance.

DR. GREEN: Thank you.

DR. BADEN: Thank you.

Dr. Bollard?

DR. BOLLARD: Yes. Hi. Can you hear me?

DR. BADEN: Yes.

DR. BOLLARD: Great.

Yes, I'm back, actually, on -- no, not 32; sorry -- CO-41. I had asked the agency about the breakdown between the bone marrow transplant and the solid organ transplant patients in those that entered the trial with other viral resistance, and we saw that there is a skewing with a preponderance of solid organ transplant patients over 80 percent in the resistant group and over 70 percent of bone marrow transplant patients in the refractory group.

So my question is now about those 48 patients who were randomized to maribavir and developed maribavir mutations. Of those 48, because I'm concerned that the BMT patients are a better prognosis group just inherently, how many of those were BMT patients? And of those 63 percent who went on to clear the viremia, how many of those were the bone marrow transplant patient group?

DR. UMEH: What I have actually is the table at baseline. I don't have the table broken down by outcome. I know, like you mentioned, that in the -- and I'm going to put up the slide to show you.

This is a baseline table which is comparing the proportions of patients with HSCT versus SOT in the resistant versus the refractory population. I can tell you that there were significantly more. It was overpopulated with HSCT patients later on in the refractory group compared to the resistant group, but I don't have that table broken down by those who have outcomes. But again, the -- sorry.

DR. BOLLARD: But I'm asking actually about

those that are resistant to maribavir. Is this resistant to your drug or not? This is baseline, right?

(Crosstalk.)

DR. UMEH: No, that's IAT.

DR. BOLLARD: Yes. No, I'm not talking about that. I'm talking about on slide CO-41, those that actually had maribavir resistance, or mutations should I say. Sorry. I shouldn't have used the word "resistance." Yes.

For those that developed the maribavir mutations, of those 48 patients, how many of them were the BMT patients?

DR. UMEH: We don't have a table for that right now. We didn't break it down by refractory versus resistant subgroup.

DR. KOMATSU: Excuse me. This is Takashi from the FDA. I believe of the 48, I think 32 is SOT; 16 is BMT.

DR. BOLLARD: Sorry. Thirty-two were BMT?

DR. KOMATSU: No. Thirty-two was SOT and 16 were BMT, based on the --

(Crosstalk.)

DR. BOLLARD: Of the maribavir -- of those patients that developed --

DR. KOMATSU: Of the 48 patients in that slide, yes.

DR. BOLLARD: Yes. Okay.

DR. KOMATSU: Yes.

DR. BOLLARD: Then of the 63 percent that cleared, do we know what the breakdown was of them?

DR. KOMATSU: I'm going to need a little bit of time for that. I'll get back to you on that.

DR. BOLLARD: Okay. Thank you.

DR. UMEH: If I may add, the primary endpoint of the study and the secondary endpoint factors in the proportion of patients who would become resistant. So when we go back to week 16, which is basically looking at how durable was the cure rate in the two arms, I think what we see is that despite the development of resistance -- which I might add is taken into context at baseline -- everybody who came into the study had already failed the prior therapy.

So there was a hundred percent genotypic resistance at the beginning of the study, and 60 percent of the time that was associated with genotypic resistance. I think what you're seeing is about the same picture with maribavir. So we're not seeing anything different, but instead what we're seeing is a benefit in terms of viremia clearance, both at week 8 and week 16.

DR. BOLLARD: Thank you. I have no additional questions at this time.

DR. BADEN: Thank you, Dr. Bollard. And I'll remind all speakers when you speak, please state your name, so it's clear who is talking.

I think Dr. Murphy is next on the list.

Dr. Murphy?

DR. MURPHY: Thanks a lot. Richard Murphy, White River Junction VA in Vermont.

My question is a little different. It kind of gets to the issue of the problem of durable virologic response both with maribavir and with other anti-CMV agents. It seems like given the problem of durable response, taken together with

the fact that maribavir is oral and pretty well tolerated, do we anticipate that a large proportion of patients will go on to suppressive or secondary prophylaxis -- and maybe this is for Dr. Avery or Dr. Kotton -- strategy with maribavir?

If that's true, what do we know about long-term safety and tolerability of maribavir potentially from earlier trials? Thank you.

DR. UMEH: Dr. Kotton, and then Dr. Avery.

DR. KOTTON: Camille Kotton. Thank you. I think that that's a great question. This is something that we would have to consider in guidelines and develop the best approach towards this. I do think that we've learned a lot about secondary and tertiary prophylaxis, and those will have to be things we consider.

Obviously, if this drug is not approved for prophylaxis, then I think it would be hard to come by, so we'd have to ponder the next best steps. But it is a really, really important issue for resistant/refractory disease, is how to prevent further disease.

DR. AVERY: Hi. I'm Robin Avery. Thank you. Yes, indeed. As you recall, this population has recurred and recurred, in some cases many times, so they are of the phenotype. They're already of the propensity for recurrence.

Back in 2008 when the compassionate use program was initiated, and again in Study 202, secondary prophylaxis out to 24 weeks was permitted, we saw some very nice responses, and I presented some of those earlier in the day. As Dr. Umeh will tell you, the safety data out to 24 weeks is very good.

DR. UMEH: That is correct. In a limited number of patients, we have data up to 24 weeks at doses up to 3 times the phase 3 dose, 1,200 milligrams BID, and the safety profile is consistent.

DR. BADEN: To panel members, after you've asked your question, please take your hand down unless you have another question.

I think Dr. Le has a follow-on question.

DR. LE: Yes. This is Dr. Jennifer Le.

Following up on the safety side, I believe earlier you mentioned that there were over 1555 patients who are assessed for safety, and one-third of them, which is about maybe 500 patients, received 400-milligram BID or higher.

I'm interested to know did you do a subgroup analysis of these patients who received higher doses -- because I know you started out with 100 BID early on -- and what the toxicity was. And in particular, I want to know more of the renal toxicity, as well as the neutropenia.

DR. UMEH: Firstly, the 500 patients who have been treated are from the treatment studies. We had a phase 2 study with a dose-ranging study. That went from 400 to 1,200 milligrams BID. There were 240 patients in that study. In this particular study, we have 235 patients treated with the 400-milligram dose. There has always been the fact that maribavir has a favorable profile with respect to the development of neutropenia or acute kidney injury.

There was a question that came up actually

during the break about why the laboratory values looked different, and I want to invite Dr. Avery to speak, based on her experience as a principal investigator, why might there have been a difference between the neutropenia reports and the laboratory values.

DR. AVERY: Yes. Again, as investigators, we are keeping the best interest of the patient foremost, and since the safety labs and the central labs were every 2 weeks, many of these patients were getting local labs much more frequently, depending on how far out they were from transplant and whether they were inpatient and so forth; some of them as frequently as every day or several times a week.

So if we saw neutropenia or acute kidney injury developing, we were not waiting for central lab values in order to act with G-CSF, or mitigation of renal failure, or changing or discontinuing therapy.

DR. LE: Okay. Thank you for that.

I also have a question regarding the same

topic of safety. Having certainly a threshold of platelets or serum creatinine makes sense in the evaluation of drugs. But in addition to that, it's always, I think, also pertinent to know where a particular patient [inaudible – audio gap].

Did you evaluate maybe the change from baseline value for each patient in platelets and serum creatinine, and maybe hematocrit, too? And if you did, what were the results for that?

DR. UMEH: Do we have a slide on that?

No, I don't believe we have a prepared slide on that. The labs were too infrequent for us to do the shift table, I think, because they were being collected every 2 weeks.

You have the tables?

DR. LE: Yes. I'm confused with that because on the one hand you said that you got labs frequently there. So I would assume that when a subject enters the study, there would be some baseline labs that are done. So I'm just interested in knowing how did the patient perform at baseline, and then throughout maybe at 4,

8 weeks, or even 16 weeks, to see if there was a change and was it increasing/decreasing. So it's more patient-specific than it is more of just a general blanket threshold.

DR. UMEH: No. I think maybe I need to clarify something. We had safety labs mandated by the study only every 2 weeks. Dr. Avery was speaking to the fact that they did a lot of local labs in the management of the patient based on the unique patient situation. There was no requirement to capture these labs, local labs, in this area.

So all we would have had in the vast majority of cases -- there were a few times on scheduled visits they were captured as local labs, but for the vast majority of the time, we did not capture the local labs. So we wouldn't see the minute-to-minute changes in the parameters that could have been observed by somebody who collected the local labs. But again --

DR. LE: Okay.

DR. UMEH: -- I'm sorry.

DR. LE: No, go ahead.

DR. UMEH: I was going to say the one question that could be asked was, well then, how then did you make sure the reports were based on actual labs? And that's because we had an AE reconciliation process where we had a team make sure that laboratory values are reported twice.

DR. LE: Okay. Thank you. But it's certainly something that I would recommend if you can draw that data. It's really looking to more patients with specific changes.

Now, along the same lines of safety here, you mentioned also that there were drug interactions with the immunosuppressant drugs, and there were four that you listed. Is there any specific recommendation to adjust these immunosuppressant drugs, based on your experience? Do we decrease the dose by 25 percent or 50 percent with tacrolimus or cyclosporine?

DR. UMEH: There will be a recommendation for therapeutic drug monitoring if these two are co-administered, if tacrolimus or tacrolimus-like agents are co-administered.

DR. LE: Okay. Thank you. That's all I have.

DR. BADEN: Thank you.

Dr. Bridges, did you have a follow-on question?

DR. BRIDGES: Thanks. I decided that probably no new information would result from my asking it, but thanks for noticing that.

DR. BADEN: Okay.

Dr. Lee, do you have a follow-on question? Lauren Lee?

(No response.)

DR. BADEN: You're on mute if you are talking.

DR. LEE: Can you hear me now?

DR. BADEN: Yes, now we can hear you.

DR. LEE: Thank you.

I was just wondering, other than sirolimus, tacrolimus, are there any other suspected drug-drug interactions with the meds that we commonly use post-transplant, like ruxolitinib or anything like that?

DR. UMEH: Dr. Song, our clinical pharmacology leader, will address that.

DR. SONG: With regard to immunosuppressants, that included sirolimus, everolimus, and cyclosporine, in addition to tacrolimus. Other DDI and significant DDI we have found, including digoxin, as well as CYP3A inducers, moderate and a strong inducer, can reduce maribavir exposure significantly, and maribavir dose increase is needed. And all-dose DDI will be in the proposed product label.

DR. LEE: Thank you.

DR. BADEN: Thank you.

Dr. Chandra?

(No response.)

DR. BADEN: You're on mute. Thank you.

DR. CHANDRA: Thank you.

I had a clarifying question to Dr. Obi and Dr. Avery regarding the lab values from local labs. I'm assuming that during medical monitoring, patient profiles for individual patients who discontinued from the therapy would have been

developed, and those should have captured the local lab information and what was the cause for discontinuation of these patients. I assume that you had that.

DR. UMEH: No, we didn't systematically collect local labs in these areas. I mean, we had 80 something sites, in 18 different countries, with different ways to do it, so we had to have a central lab do it. But because of the amount of blood volume drawn at these sites, the labs are every 2 weeks.

DR. CHANDRA: My question was regarding the patients who discontinued. So typically during medical monitoring, you would have individual patient profiles developed for patients who discontinued and the reasons that they discontinued. So I'm assuming those should have captured the local labs because those were the reasons for why those patients were discontinued.

DR. UMEH: No. The discontinuations are captured as AEs, so we had that collected, yes.

DR. CHANDRA: Okay. Thank you. That was

all.

DR. BADEN: Thank you.

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

(No response.)

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

DR. HARDY: This is David Hardy from Los Angeles. I just wanted to follow up a little bit more on the question about the metabolism of the drug-drug interactions with maribavir, because reading about it, it seems it is metabolized by several different cytochrome P450 isoforms.

Therefore, are you recommending that with particularly the commonly used anti-rejection drugs, some of which have already been mentioned and with other drugs, that the level of maribavir be monitored in order to maintain steady levels?

DR. UMEH: It's the other way around, the level of immunosuppressant has to be monitored. Maribavir doesn't need to undergo any changes.

DR. HARDY: Okay. Are there any changes in which the level of maribavir is decreased in a drug-drug interaction?

DR. UMEH: Yes. Dr. Song will speak to that.

DR. SONG: Maribavir is mainly metabolized through CYP3A, and then CYP1A2 as secondary, and only the enzyme inducers for those enzymes can have a potential to reduce maribavir exposure.

DR. HARDY: But there are several potential drugs like that, so is therapeutic drug monitoring going to be recommended with maribavir?

DR. SONG: Yes. The most common CYP3A inducer, moderate and then strong, include carbamazepine, phenobarbital, and phenytoin. So for those inducers, the recommendation is to increase maribavir dose. And then rifampin is the most potent inducer, where recommendation is not to be co-administered.

DR. HARDY: But I take it you're not recommending therapeutic drug monitoring of maribavir.

DR. SONG: No.

DR. HARDY: Thank you.

DR. BADEN: Dr. Bridges, you have a

follow-on question?

DR. BRIDGES: No, I don't. I'm sorry if the screen indicates that I do.

DR. BADEN: Thank you.

Dr. Murphy, do you have a follow-on question?

DR. MURPHY: Yes. Just to clarify, I believe it was stated in the data that there was only a single patient who received maribavir who had an important excursion in concomitant immunosuppressive agents. Would that justify therapeutic drug monitoring of all patients who received this agent? Thank you.

DR. UMEH: No. We said there was 8 percent more in the maribavir. I believe it's 9 versus 1 percent; 9 versus 1 percent immunosuppressant drug changes.

DR. BADEN: Thank you.

I would like to remind committee members that this is a time to ask clarifying questions. We'll go to discussion shortly. I will ask the next clarifying, Dr. Umeh.

In the briefing document you provided -- and I may have misunderstood this -- there seemed to be an increase in GHVD in those treated with maribavir. Is that correct or did I misunderstand those data? And can you please clarify, the relationship between maribavir and graft-versus-host disease?

DR. UMEH: So the number you're referring to is the 9 versus 4 percent incidence of GVHD, and that's actually new or worsening. But actually, what we know is that at baseline, there was already an imbalance. There was more GVHD in the maribavir arm compared to the comparator. And when you look at acute GVHD, or when you denominate by the number of days treated, remembering that we have 50 percent more exposure, the numbers are actually the same.

We don't have any mechanistic explanation. The adjusted rates will show you that the numbers are almost the same, what I have on the slide. We don't have any mechanistic reason to believe that treatment with maribavir will result in increase of

GVHD. We think it's just an imbalance.

DR. BADEN: Thank you.

Dr. Green, you have a new line of questioning?

DR. GREEN: I do. Thank you. It's Mike Green. I just wanted to give the sponsor an opportunity to explain why they, on their slide 49, report a larger event incidence for neutropenia than the CDC [sic] on their slide 54, I think it is.

The sponsor's data says 22 percent neutropenia reported as AEs in the IAT group versus 9 percent in the maribavir group. But when we heard the data presented -- we have selected laboratory abnormalities by FDA -- they were telling us that they were really the same. So the numbers don't match, and I don't understand why they don't match. Thank you.

DR. UMEH: I must show the second slide you're speaking to. Maybe the AES are special interest, where we break them down by the component drugs. I say it is a convenience term we gave to

all the agents that were used in this population, but we know that ganciclovir causes neutropenia. So when we break them down, the numbers look higher. I believe the laboratory values as FDA presented was where they said there wasn't really a difference, but we've provided an explanation for that.

I don't know if that addresses your question that you're asking.

DR. GREEN: I'm not completely understanding. Again, these data, both what FDA is showing and what you're showing on the current slide 49, are presumably your central lab data, so they're included.

You show a 22 percent incidence of neutropenia in the IAT group out of 116. Even going to the group up to a thousand, they report only a percentage of 14 percent and they report only 17 IAT patients getting neutropenia, but 22 percent of 116 would be higher than that.

So I just don't understand that discrepancy. And I recognize these are your data and those data

that they have are their analysis. But the difference might be important because they're inferring that there's not really a difference in that important adverse event.

DR. UMEH: No, you're correct.

So this table that we're looking at is what was reported by the investigator. When the investigator has an event, the laboratory value, however they got it, whether by central lab measurement or by independent measurement at the site, they would call it an AE and they would report it.

Now, what happens is our monitors go out to the site and sources verify that there is actually in the clinical record a laboratory value that matches these adverse events. So when you go by these reported adverse events based on neutropenia, that's what you get.

The FDA focused their table exclusively on the lab data, and that is the lead data that was collected every 2 weeks, which we said and which Dr. Avery explained are probably infrequent to

capture the interval changes between the first report of neutropenia.

DR. GREEN: That that is very helpful, and I thank you for that further explanation.

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

DR. MURPHY: I did not.

DR. BADEN: Dr. Haidar, you have a question.

DR. HAIDAR: Yes. Hi. This is Dr. Ghady Haidar from the University of Pittsburgh, and just a minor question about drug administration. I know that it's oral, but is there an IV form? Is there something that you can give to someone who is intubated? And my third question is, I think it was only looked at in people with a GFR greater than 30. Will there be any dosing or proposed dosing recommendations if the GFR is less than 30?

DR. UMEH: For the first question, no, we don't have an IV formulation as of now. We only have this oral formulation, and the label will be limited. There will be no dosing recommendations for people less than 30 because we didn't study

them in this particular trial.

DR. HAIDAR: And then --

DR. UMEH: Sorry. Go ahead.

DR. HAIDAR: I was just going to ask how about the intubation, and then can you give it down a feeding tube?

DR. UMEH: It will not be in the current label because we have outstanding studies to do. But there is a plan for us to complete those studies and make the data available to guide use through the NG tube.

DR. BADEN: Great. Thank you.

I think we have covered all of the clarifying questions from the committee.

DR. UMEH: Can --

DR. BADEN: Go ahead.

DR. UMEH: May I ask the chair if we could respond to a statement?

In the presentation, the FDA has asked the committee to comment on the value of the data in the refractory patients. I wanted Dr. Avery and Dr. Kotton to speak to their own feelings about

this data.

Dr. Avery?

DR. AVERY: Thank you. It's Robin Avery. Yes. I think as clinicians, we feel that this is a continuum. We don't differentiate into two groups of refractory and resistant. We think of this as a continuum of very, very challenging patients, and we really look forward to the opportunity to have an oral, less toxic, and effective drug for this entire group.

DR. KOTTON: Camille Kotton. I'd like to second what Dr. Avery said. We have a definition paper that was in Clinical Infectious Disease in 2018 by Roy Chemaly, et al, and in that we define the concept of resistant/refractory disease, and we really think of this as a continuum.

As I mentioned, in the guidelines, we first identify that there is likely to be resistant/refractory disease. We reduce immunosuppression. We send resistance testing. And because resistance testing takes several weeks to come back -- in parentheses, especially during

the pandemic when everything seems to be slowed, especially, PCR-based assays -- for patient care, we must initiate appropriate treatment.

So for me as a clinician in the field who often manages these patients, and I get emails from all over the world about these patients, it would be heartbreaking if we divided this into resistant disease only but not management of refractory patients, because we really think of this as sort of one in the same process.

Furthermore, there are issues that I won't go into with diagnostics, but we do think that many of the refractory patients may well have resistance that isn't yet diagnosable with the current testing we're doing. But I think that likely in the next five years, we may have diagnostic capacity such that we're able to realize that what we're calling refractory, but not officially diagnosed as resistant patients, may well have that resistance.

DR. BADEN: Thank you for those comments. I think that we appreciate all of the information shared by the speakers, the applicant, the agency,

and really appreciate everyone's input, so thank you.

What we'll now do is proceed with the charge to the committee, to Dr. Birnkrant.

Charge to the Committee

DR. BIRNKRANT: Thank you very much, and thank you for the discussion.

Well, you've heard from both the applicant and the FDA, and data have been presented from Trials 303 in refractory patients, most with genotypic resistance, and from Trial 202. The primary endpoint was met in Trial 303 and showed superiority with respect to confirmed CMV viremia clearance at week 8, and was most favorable in the population with genotypic resistance with a numerical trend in the setting without genotypic resistance.

First, we would like you to discuss the presentations as part of discussion question number 1, and then we will move to the voting questions 2 and 3. Again, we would like you to discuss your evaluation of the efficacy outcome in

the phase 3 trial, 303, and data from the phase 2 trial, 202, and the overall risk-benefit assessment for maribavir for this new indication.

In your discussions, please consider the population that is narrow with an unmet medical need; the trial design and limitations that we presented; the primary efficacy outcome and the results from sensitivity and subgroup analyses, and the maribavir safety profile.

Thank you very much, and I'll turn it back to Dr. Baden.

Questions to the Committee and Discussion

DR. BADEN: Thank you, Dr. Birnkrant. I think a lot of what you just raised is part of question 1, the discussion. So I think that we'll turn our attention to the discussion question and cover the exact issues, Dr. Birnkrant, that you raised.

So 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 comment. We'll proceed with the

questions to the committee and panel discussions.

I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. After I read each question, we'll pause for any questions or comments concerning its wording, then we'll open the question to discussion.

What we will do, committee members, is we will look at question 1, and then take Dr. Birnkrant's comments to heart as we discuss question 1, which raises all the issues about the types of data we have seen, the complications in this population, and what kind of data are helpful in our deliberations and in establishing safety and efficacy.

Now we have the question. Question 1, which is a discussion question, discuss the efficacy and outcome in the phase 3 trial, SHP620-303, and data from the phase 2 trial, SHP620-202, and the overall risk-benefit assessment for maribavir. Include in the discussion the following: population; trial

design; efficacy; sensitivity and subgroup analyses; and safety.

Are there any questions about this discussion question? And then I will open it up to discussion among the committee members. But are there any questions about the charge to us regarding discussing these issues?

(No response.)

DR. BADEN: So if there are no questions or comments concerning the wording of the question, we'll now open the question to discussion. To the committee members, please raise your hand as you wish to start the discussion. I see Dr. Bridges. Please start.

DR. BRIDGES: Thank you. Nancy Bridges from NIAID. I am reluctant to start with what sounds like a negative comment because I do think that, overall, the data are very persuasive in support of approval. But I just wanted to mention that the study participants were overwhelmingly white, so I guess this comes under the topic of population.

We know, actually, that CMV serum positivity

has a much higher prevalence among African Americans, so within the context that I do hope that this drug is approved, I would like to see some requests to the company to gather data about efficacy in African Americans because I don't think we have any data really on that.

DR. BADEN: Thank you.

Dr. Le?

DR. LE: I'm just going to piggyback on the content of minority populations. I guess pediatric would fall into that. I was happy to hear that the company did make some attempts to look into pediatric data, although there was no enrollment. But I hope you can encourage to continue to particularly look into the PK data. I'm interested in knowing what the dosing would be like in pediatric patients, and maybe even consider down to neonates as well, at least with the PK data.

I'm trying to put all of this in perspective in terms of the data presented to us is open-label. How realistic is it for us to do a full-blind, placebo-controlled trial that's blinded? Is it

realistic in this population to even do that?

DR. BADEN: I think that's a great question. I think from what I heard from the sponsor was the taste was so distinctive that they were concerned about the ability to be double-blind, let alone the toxicities of the IV options, foscarnet and ganciclovir. But your point -- and this is for discussion with us. The sponsor and the agency doesn't come in here, so these are committee members to discuss.

So I think that it was some of the challenges of the options and of the product, was my understanding. But your point from my perspective is well taken, which is an open-label trial with the incipient biases is problematic, but whether or not a truly double-blind/double-dummy study could have been done is unclear. But reasons were given why that may have been difficult.

I think we have follow-on questions.

Dr. Flatau?

DR. FLATAU: Yes. I would say I think that even if maribavir, the results were only because it

was more tolerable, that that would be a step in the right direction. But as far as the population, I agree with it. It seems like it hasn't been studied at all or very little in the pediatric population. It seems like something that would be important to do.

The thing that also got me was the idea of a placebo-controlled trial. We have drugs for CMV, and I think using a placebo against maribavir would be unethical in treating CMV. I understand the need for blinded trials and the problems with them, but I don't think using a placebo would be ethical in this situation. Thanks.

DR. BADEN: Thank you.

Dr. Bollard? And please state your name right before you talk just so that the record is clear.

DR. BOLLARD: Yes. Hi. It's Catherine Bollard here, Children's National, Washington DC. Just to capitalize on the question about potential bias and populations we're missing, I completely agree. Obviously, if the population is

predominately white and adults, we're missing ethnic diversity and the pediatric population.

But again, going to the BMT population, bone marrow transplant population, with such a few percentage less, 7 to 10 percent having graft-versus-host disease, that is the major problem patient population in the bone marrow transplant setting. I also urge the company to get more data in that particular setting, especially GVHD.

DR. BADEN: Thank you, Dr. Bollard.

Dr. Bridges, you have a comment?

DR. BRIDGES: Yes, just a follow-up comment in this area. I would say, first of all, while I stand by my concerns, I also think we need to be careful not to let better be the enemy of good in this setting. Also, on the issue of a blinded trial, I think probably everybody would agree you can't have a placebo-controlled trial in this setting, but I would argue that in the absence of an approved therapy for CMV, it would be equally unethical to have a blinded-controlled trial.

I think that once you've reached this

setting where patients are refractory, physician judgment is really all we have left for such a group of patients, and I don't really think that you can ethically take that away from patients in this dire situation. So I happen to believe that the design that was chosen is probably the best that we can do.

DR. BADEN: Thank you.

Dr. Hardy? And again, please state your name before you make your comments.

DR. HARDY: Hi. This is Dr. Hardy, David Hardy from Tech School of Medicine and USC in Los Angeles. I just want to support the fact that in a patient population like this, that is at high risk and immunocompromised, doing a clinical trial that is not strictly placebo controlled, because you do have to treat the CMV somehow, would be a double dummy, meaning that one group would get a placebo oral, and the other group would get a placebo IV. Even that kind of design would be problematic in terms of giving patients who are immunocompromised medication or intravenous infusions that are

placebo.

So I think, again, I would really support the fact that in this patient population, trying to do that rigorous of a trial, while a good idea, in trial design it's not practical. So I would think that this is as good as the data we're going to get.

DR. BADEN: Thank you.

Dr. Haidar?

Dr. HAIDAR: Yes. Hi. This is Ghady Haidar from the University of Pittsburgh. I just want to comment on what's been said. Despite the issues with the lack of pediatric population and an over-representation of white people, I think that we can all agree that SOT and BMT recipients are just the highest risk. Actually, they're probably the only individuals who are at risk for refractory and resistant CMV.

In that regard, I think that the fact that the population was narrow makes perfect sense. These are people with an unmet medical need. I think that someone earlier said we shouldn't let

perfect be the enemy of the good, and I completely agree with that.

As far as doing a different kind of trial, as someone who sees these patients all the time -- so all I do is see BMT, CAR-T, SOT, and things like that -- I can tell you since there's no standard approach to managing refractory/resistant CMV, you might end up in a situation where if you really want to double-blind everything, you're going to have to give people sort of fake foscarnet, which involves twice a day intravenous infusions, and giving them magnesium, and giving them all these boluses of normal saline and things like that. So it's just not possible or feasible to do. So I think that the design that was chosen is the only one that works.

DR. BADEN: I'm going to push a little bit on this design issue because your point is well taken, and this gets to some of Dr. Bollard's comments across the day. Are the BMT populations in the SOT populations really the same?

What I think was raised earlier, if the BMT

population is having GVHD prophylaxis tapered over the next hundred days; and they develop CMV; and they get standard treatment for a couple of weeks; and they are declared now refractory or resistant; and they are now switched to another agent while the immunosuppression is being tapered, how much can we tease apart the antimicrobial effect from the immune reconstitution effect because of how these patients are managed?

What do you think of that consideration, which is different than SOT, where they may be on a stable regimen, or it also may be rejection with some tapering of the immunosuppression? So how do we deal with the immunosuppression manipulation and the timing of the antiviral and the efficacy outcomes? To the group, so please feel free to comment.

Dr. Haidar?

DR. BOLLARD: Maybe I can comment --

DR. BADEN: Dr. Bollard? Yes, Dr. Bollard?

DR. BOLLARD: It's Catherine Bollard here.

Well, thank you very much for summarizing

what I was trying to actually say throughout my questioning throughout the day. You're exactly right. And I am particularly concerned in the BMT population that you might be seeing an immune reconstitution effect.

I say that because it's low rates of GVHD in this population they studied, and half of that population had donors who were CMV seropositive, which is a better risk situation. So I am worried that we're comparing apples and oranges there a little bit.

DR. BADEN: So for others who want to react to what I just said, please do the check box. But the point that I was trying to make in my comment earlier is the immune manipulation is not a trivial consideration, and the BMT and SOT may not be homogeneous.

I see others have chimed in.

Dr. Gea-Banacloche, your comments on this?

DR. GEA-BANACLOCHE: Yes. You're absolutely on target. As you say, there are different populations, and the wiggle room may be different

also because you have brought two things that are kind of opposite. You say the BMT patient who develops graft-versus-host disease and CMV, and in that patient, actually, you cannot decrease immunosuppression; you have to increase the immunosuppression.

So the only weapon that you have against that to be able to interpret anything is the randomization, and you end up saying, well, this is a small study in terms of numbers, particularly when you say that the fraction of patients with graft-versus-host disease is very small. Only 40 percent of the patients were BMT and a few cases of graft-versus-host disease.

And not only that; when you look at the CMV, these were not terrible CMVs, right? The overall impression that I get looking at the data is that, yes, maribavir is an agent that we should be able to use -- there are no two ways around that -- but in terms of how potent it's going to be, how well it's going to work when someone has GVHD and they're not absorbing the drug and when they have

increasing CMV, and instead of talking of a few thousand copies, we're talking about really high CMV or CMV disease -- in the data they show that it works worse for CMV disease or for CMV syndrome.

So I think that that there are many unknowns still. So I think that in terms of refractory/resistant, as you say, the new manipulation is a big part of it, but I don't know how to fix it. I mean, it would have been nice if they had measured the immune manipulation in some fashion that they had some standard way of saying, oh, yeah; in this percent of patients, they decreased the MMF, or they stopped the MMF, or they aimed for lower toxable [ph] levels. But that is extremely difficult to do.

I think the way to address that is to have a separate study for BMT, a separate study for solid organ, and hope that randomization is going to help you with the differences.

DR. BADEN: Thank you.

I'm going to preferentially call on those who have spoken less in this discussion first.

Dr. Burgess?

CAPT BURGESS: Thanks, Dr. Baden. My comment to the question that you raise is I realize that bone marrow transplant and solid organ transplant are obviously different and the issue of GVHD is different. But couldn't you also say that amongst solid organ transplant recipients, that there is considerable heterogeneity?

I think Dr. Gea-Banacloche just alluded to that. In a lung transplant recipient, for example, a difference between CMV syndrome and CMV pneumonitis might also introduce reasonable heterogeneity that would suggest if one were going to make perfect the enemy of sufficient, that you'd need to even further subdivide or have additional studies.

So how much is sufficient? And I would concur with the comment that you just have to rely on randomization.

DR. BADEN: Thank you.

Dr. Perez?

DR. PEREZ: Thank you.

Federico Perez, Cleveland VA. On the issue of trial design limitations, I think the discussion has convinced me that the open label is reasonable, but I am following the discussion on the differences between these two populations of solid organ and bone marrow transplants.

The design solution for that would be a stratified, randomized-controlled trial, but I don't know if any post hoc analysis is possible at this point or what type of recommendations would come from this committee in that regard, other than real-life studies to see how the drug performs in the populations of more concern. Thank you.

DR. BADEN: Thank you.

Dr. Flatau?

DR. FLATAU: Yes. I wanted to say that any effect of reducing immune suppression presumably would have been on both sides of the trial, both in the IAT group and the maribavir group. Others have said we can't let the perfect be the enemy of the good, so I think we need to look at it the best we can. It would be nice to have just an HSCT trial,

but I think probably what we have now is as good as we're gonna get. That's it.

DR. BADEN: Thank you. No. These are very difficult trials to do.

Dr. Siberry.

DR. SIBERRY: Yes. Thanks. George Siberry here, USAID. This was stratified by stem cell transplant versus solid organ transplant in its design, and while we have a lot more to learn, I would emphasize that the effect of maribavir, in favor of maribavir, was robust for both of those groups when looked at separately.

So I think that speaks to not only good design but, at least at this point, adequate reassurance that it wasn't simply time and changing immunosuppression that meant the stem cell transplant patients got better, or you wouldn't have seen the preservation of a difference in favor of maribavir.

I'll just quickly say a couple of other points so that I'm done. I do think the overall design was actually very good and the combination

of refractory and resistance, including refractory without documented resistance, seems like the only feasible way to go since you can't really differentiate those at the time of having to make a decision about this treatment.

I do think even though the magnitude of the effect was less in refractory without resistance, it was still in the same direction, and that I think speaks, again, to the robustness of the findings and the reassurance that it will go well.

But my main questions about study design and what else maybe could have been considered is the duration of treatment. Did we do right by the 8 weeks and not looking at other durations? Do we have enough information about the resistance that emerges in failures of this drug and what to do then? And as mentioned, of course, pediatrics.

I'd end by saying I hope we don't have an artificially low 18-year-old age mark, as if that were biologically relevant, and keep this open to adults and adolescents who are puberty mature. Over.

DR. BADEN: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger.

As I'm following this discussion and separating and having stratified groups, what strikes me is that it almost feels like people don't believe the endpoint. And I'm wondering, when I was hearing the public comments and such, it was avoiding transplant and that kind of thing, that they were arguing that this is why it's important.

It seems that if we had a harder endpoint such as a combination of death and avoiding transplant, then the open label would be less of a problem, and I think right now it's not clear that people believe the endpoint that well.

When you look at the sensitivity analyses -- and the primary analysis shows that there's a strong effect on this endpoint -- all the sensitivity analyses, they essentially did an intention-to-treat analysis, and that was a strong effect. They gave the standard-of-care arm the

best possible option by saying, okay, let's look at their response at any point during the time that they were treated, and all of those showed that there was a benefit, but from the treatment arm.

So the argument seemed to be more around do we believe the endpoint, so I think that's one of the questions you need to grapple with. Over.

DR. BADEN: Thank you, and we'll come back to the endpoint because that'll be its own discussion.

Dr. Bridges?

DR. BRIDGES: Thanks. Nancy Bridges from NIAID. I agree with the sentiment that the efficacy is quite clearly demonstrated despite whatever small objections we might have to the design of the trial. But what I wanted to say is I certainly don't claim to have any more expertise than anybody else on this call, but I'm speaking from my experience of specifically designing trials for transplant patients for the last 20 years; that's what I do for a living.

In general, you have to focus on the big

picture. Does it work and is it going to hurt anybody? And in almost all cases, the nuances of how a new drug will be used in the transplant population are worked out by the transplant clinical community post-approval because the population is so heterogeneous and there are so many moving parts, it's really not possible, and the population size is limited.

So when you take all of those things into consideration -- small population size, high amount of variability, and many things we can't measure at all -- it's inevitable that the clinical use of the drug, many aspects of it are going to be worked out after approval. That's all I had to say.

DR. BADEN: Thank you, Dr. Bridges. So part of what you are suggesting is that this is a relatively closed community of patients and providers, and much will be learned by how they utilize new therapies if those new therapies have a favorable risk-benefit profile in a macro sense.

DR. BRIDGES: Exactly.

DR. BADEN: I see that Dr. Haidar has a

comment on this discussion.

DR. HAIDAR: Yes. This is Ghady Haidar from the University of Pittsburgh. I just wanted to follow up on what's just been said. I think that, one, I do believe the endpoint, even if it's driven by the worse safety profile of the other drugs. I think that's fine.

I think as far as the issue of duration, I completely echo what was just said, in that should this drug be approved, you're going to see the transplant docs and the transplant ID docs just do all sorts of things with it. They might treat for beyond 8 weeks; they might treat for less than 8 weeks.

It just all has to be customized based on the patient's individual risk factors; what organ they've had; what kind of CMV mismatch BMT they've had; what sort of immunosuppression they're on; have they cleared; do they have a positive T-cell response, and things like that.

In a controlled clinical trial setting, they had to pick an end date at some point because

everything else I think would have been too complex, but time will tell how this is going to be used. And I'm pretty sure that, over time, you'll also start seeing more about the resistance to this drug as well, as more important people use it.

Along these lines, I also just wanted to emphasize the point that Dr. Kotton had made earlier, which is about the distinction between resistant and refractory infection, which is a little arbitrary, and I completely agree with what she said in that it's a continuum of conditions. The point that she made about having to wait for the genotype to come back is actually crucial. It does take a very long time for us to get a genotype back, and these patients typically can't wait the many weeks we have to wait for the reference lab to tell us what the genotype is. Thank you.

DR. BADEN: Thank you. But just to the endpoint issue, I think we all would agree that an efficacy endpoint and the toxicity endpoint are different, though equally important, but need to be clearly delineated when we say success or failure

as to why, because the high viral load cases with maribavir didn't have as good an outcome -- if I interpreted some of the data presented -- on the efficacy side as the low viral load.

So I agree that the efficacy endpoint of avoiding dialysis or toxicity endpoint is incredibly important, but it still is very different than the high-level antiviral effect, and that has to be clearly understood and delineated so that as we explore how this may work, we understand its strengths and weaknesses.

Dr. Weina?

DR. WEINA: Hi. Pete Weina. Actually, I'm kind of taking off a little bit on what Dr. Haidar just brought up, and that is discussion point 1E, the safety profile in comparison with the other antivirals.

Well, first of all, we don't have a lot of safety data on maribavir in a fairly large enough population at the intended dose. And as I bring up at just about every meeting, the potential for off-label use -- and that was kind of touched on

several times -- once the drug is approved, even if it's approved with a limited indication, it's going to get used for practically everything. It's going to get used for prophylaxis. It's going to get used for secondary prophylaxis. It's going to get used for longer than 4 weeks, longer than 8 weeks, and longer than 32 weeks. Who knows?

Given the fact that it appears to be a kinder and gentler drug compared to the current therapies that are out there, both in terms of side effects and ease of administration, and everything else, it's going to very quickly gain footing and use other than those cases demonstrated to be refractory or resistant.

So I'm kind of torn. The difference between the actual vote questions and the difference between genotypic resistance and without genotypic resistance I think is truly a moot point here. Over.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Thank you. I've been waxing and

waning between raising a hand and checking whether to comment or not.

I first want to make one comment, as a pediatric ID doctor who does transplant ID, that on the time that I've been on the committee, not a single drug that we've considered has come with pediatric data at that time. So everyone should be hopefully resting assured that the sponsor, or Takeda, will be interested in doing a study in kids. And when they are, I know that myself and many other colleagues would be very happy to try to help them to enroll subjects for it.

I did want to comment on the primary efficacy outcome and including, by definition, sort of a built-in composite score of virologic efficacy and tolerability. While I'm sort of disappointed that a number of patients were probably enrolled knowing that if they got the investigator-chosen regimen, that if they could just tough it out for 3 weeks and they weren't better, that they could be switched, I do think that combining the virologic effect and also the safety effect to judge a

success is relevant and has been done in previous studies that have drugs that are licensed; things like when they were looking at caspofungin versus, I think, amphotericin way back when.

I do also want to say, as was mentioned, that, really, there is some measure and meaning to the fact that the sensitivity analysis, and the primary efficacy analysis, and subgroup analysis all seem to point in a single direction, and even when not statistically different, trends were noted. But not once was maribavir identified as inferior, and the drugs that we currently use are not actually approved for treatment anyhow.

So I think that that's very notable and important to pay attention to. And I think that in taking all that into consideration, I think there was a discussion and a design that was approved by both the sponsor and the FDA. They followed it. They went through the trial following those rules.

I do believe the statements about how the data that FDA could see in terms of safety markers may not completely reflect the evolving impact the

investigator-chosen drugs were having on kidneys and bone marrow because it might act before you could see it, and that makes a great deal of sense.

This is an imperfect population to study. It's tremendously challenging to care for. I give credit and thanks to both the agency and the sponsor for working to try to develop a new option where we are limited in what we can do. And I at least feel that I have data to inform a vote that I'm going to make in a few minutes. Thanks very much.

DR. BADEN: Thank you.

Dr. Siberry?

DR. SIBERRY: Thanks, Dr. Baden.

I just want to note that the sponsor did use the FDA validated surrogate endpoint as their choice, so in these complex and difficult areas, they chose something that was acknowledged as reasonable. And you made the point about the viral load, but even there, even though point estimates or the differential benefit of maribavir against the IAT were smaller for the higher viral load, in

every case it was still higher, still in favor of maribavir.

So I don't think when we're talking about this endpoint that has some sort of required combination of efficacy and safety, we're not giving up efficacy in order to get safety. From everything we've looked at, the efficacy persisted, even when we say took away people who had to stop for AE reasons and just looked at virologic response. It wasn't as if maribavir was worse. Perhaps it was, we can say, at least no better.

So I just want to emphasize that the efficacy measures when stripped away, it doesn't look like we're sacrificing that; and that across viral load, among the other things, that the point estimates really were pretty robust. Thanks.

DR. BADEN: Thank you, Dr. Siberry. I don't disagree, but I want us to also be a little bit careful in the overall interpretation in that the efficacy in IAT may be, in part, due to the drop in immunosuppression, not to virologic activity. We don't know. And that doesn't take away from what

maribavir brings to the treatment, but we have to be careful that we don't have a placebo group to know what just immune manipulation does versus antiviral activity.

I agree with the other comments that the overall constellation of evidence all point in the same direction, as we've seen discussed from many sides. But we are looking at a new agent compared to a failing agent -- and that's the reality of the clinical scenario -- not against placebo. So we have to be careful about overinterpreting, although the data all point in the same direction.

Dr. Walker?

DR. WALKER: Yes. Hi. Dr. Roblena Walker. I've been toggling back and forth. I made my mind up, and then I've been listening to the discussion, and I went back.

So I do agree with some of the comments that have been made, and I do believe that the study design was well. The primary efficacy endpoint indicates that the hypothesis was shown. It indicates effective therapy. There were some

significant findings at 4 weeks.

However, I think my main concern -- especially as the consumer representative, as an African American female, and as a daughter of a mother who was diagnosed with multiple myeloma and had a successful bone marrow transplant -- all things considered, I think the limitation in the population and the concern of how tolerable this drug would be in the African American population, especially African American women, has just not been shown. But it does not negate the findings of the study in the population that was provided.

DR. BADEN: Thank you. No, it's very important that data be extended to all important populations to whom we hope to treat, so your points are very well appreciated.

Dr. Banacloche?

DR. GEA-BANACLOCHE: Yes. Juan Gea-Banacloche from the NIH. Just to say the same thing that you said during the discussion, I think when they studied the failures, there was the same

percent of virological failures in the maribavir arm as the IAT arm. I think that is an important different way of looking at the same data.

I think my overall impression of maribavir is that it is effective. I don't think it's better than the other agents, but I think that it's something that we need to have. As I have pointed before, to be able to give something that is less toxic than ganciclovir and foscarnet is really important.

So in that sense, the endpoint at 8 weeks, which I mentioned before, was a little problematic for me because, in reality, the way we use these medicines, we try to give them as little as possible. I see how they can present that we did a sensitivity analysis, and no matter when they responded, still maribavir was superior. Well, it may be, but when you look at the other virological failures, they were the same.

So it's a design thing, and everybody has said, yeah, this is all that we're going to have. And I think maribavir is a drug that should be

approved, but at the same time, I don't think it's the best possible drug against CMV. It's something we need.

DR. BADEN: So I will ask the committee to avoid saying how you're going to vote, although our comments obviously speak to what we think of the strengths and weaknesses of the data. So thank you very much for those comments.

I want to come back to one of the points that I think Dr. Bridges or Sally brought up about the endpoint and having an endpoint of death or CMV tissue invasion versus viral load or toxicity.

Do the committee members have thoughts on how we can improve the primary endpoint for these studies, given the uneven nature of what we've been talking about with toxicity and efficacy as a virologic measurement? Thoughts on death and tissue disease, and hit the check box if you would like to discuss.

I see Dr. Weina jumped boxes.

So I'll make some first comments on that because I think the primary efficacy outcome is

critically important. And personally, I look at efficacy and toxicity as separate, although co-equal and incredibly important. And as much as I would like death or tissue disease, the rarity of those events make it difficult, in my mind, to design a study that can be achieved in a reasonable amount of time.

So we're left with a virologic marker and then toxicity assessments. And renal failure dialysis, the toxicity, severe neutropenia, these are not trivial toxicities, but at least I consider them quite different, although co-equally important. So it seems reasonable in terms of the primary efficacy outcome, the question 1C, but I'm interested if others have comments.

Dr. Bridges?

DR. BRIDGES: I agree with everything you said, and I would just add that if you used this as an endpoint, it would be a major attribution and adjudication nightmare because many times the proximate cause of death in somebody who has gone through prolonged treatment for CMV disease is not

the CMV disease. But there's a strong sense that they wouldn't have ended up there had it not been for multiple hospitalizations, multiple bouts of low white counts, et cetera, all of the complications of the therapy. So it might not end up being a clearer endpoint.

DR. BADEN: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. This is Sally Hunsberger. I'm a statistician. For me, I would just say we'd have to run the numbers to see how big of a study that would be. And you're right; it might not be feasible.

But I do think that an endpoint that captures both the risk and the benefit -- so if someone died of a toxicity, I think that should go against the drug, and it is a nice way to summarize both the good and the bad of the drugs. So it might not be feasible, but, for me, that would make everything much more clear, if you're using the most clinically relevant. And the problem here is that it's hard to say that this is a clinically

relevant endpoint, but I won't argue too strongly against it. I'm not a clinician.

So just that I put that out there, that a hard endpoint would take away all of these other issues, and I think we would know a lot more about the treatment, but it might not be feasible.

DR. BADEN: No, the point is well taken, the issue of CMV viral load that is used clinically to trigger treatment. So there are clinical standards for how it's used, and it leads to a change in management, preferably before end-organ dysfunction from CMV invasion occurs.

DR. HUNSBERGER: Just to follow up, I do think that this was a good design in that there were criteria for when people would be taken off the treatment. So I think that was a strength of the design. So I think as far as this endpoint for this study goes, I think they did it very well. I think it's a strong study. So with this endpoint, I think they did it as good as they could have done it.

DR. BADEN: Thank you.

Dr. Haidar?

DR. HAIDAR: Hi. This is Ghady Haidar from the University of Pittsburgh. There's actually an article in CID, published in 2018 I want to say, that goes over all of these things. It's about disease definitions for CMV when it comes to trials, and they go over a lot of these nuances.

But one of the issues that I think has also been brought up is if you want to use CMV tissue-invasive disease as an entry criteria, or even an endpoint, that means that you're going to have to subject people to biopsies, where in clinical practice, a lot of the time we don't necessarily nitpick about is this person's liver function abnormality because of CMV or not. You just sort of assume that it is, and you call it probable CMV, so then an added layer of complexity. And even people who have tissue-invasive GI disease, you don't always have to do a colonoscopy and endoscopy. You can, but you don't always.

Then you would imagine that a trial would start to mandate that people do biopsies when the

doctors may not think they're indicated. Aside from sample size and power issues, one of the nightmares would also be the definitions of CMV, because then you start to get into does this person have proven CMV pneumonia, or probable, and things like that.

So I think that having a biomarker in the blood as the main endpoint, is the same as you would do with an HIV viral load or an LDL, for example, I think that's the best way to go with CMV trials.

DR. BADEN: Dr. Le?

DR. LE: Hi. Dr. Jennifer Le from UC San Diego, California. I agree with Dr. Baden's comment in terms of the use of viral load as a primary outcome, given the population feasibility. And it sounds to me until we get to a place where we improve mortality in transplant patients and management of, in general, not just CMV, I don't think we can safely use mortality as a primary outcome. But it doesn't hurt to use it as a secondary to just keep an eye on it. Thank you.

DR. BADEN: Thank you.

Dr. Chandra?

(No response.)

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

DR. CHANDRA: Can you hear me now?

DR. BADEN: Yes, now we can hear you.

DR. CHANDRA: Okay.

FDA guidance on conducting CMV clinical trials does include a composite endpoint as the primary endpoint, which includes both viral load, as well as improvement or resolution of signs and symptoms of CMV disease.

I think the issue in this study was that most patients, 90 percent, were asymptomatic, and also most of them were having very low viral load, less than 5,000 or so. So probably that was the reason they used it as a secondary endpoint. And for resolution of signs and symptoms, they had an adjudication committee to help with that. And that's what I wanted to just add to it.

DR. BADEN: Thank you. I mean, the open-label design also complicates it, as raised

this morning in the discussion, where if somebody's on foscarnet and their creatinine starts to go up, the team may switch, while if they're on another agent that they don't think is renal toxic, then they stick it out longer; the same thing with neutropenia.

So I think there is an implicit bias in the open label with the toxicity impacting the switching endpoint. But to some degree, we're stuck with that, given the reality of this population and the nature of the interventions.

DR. CHANDRA: That's right. Okay. I agree with that.

DR. BADEN: Yes.

Dr. Green, you have a comment?

DR. GREEN: So it's a quick follow-on in case individuals aren't actively involved in the care and management of patients who've undergone transplant, either solid or liquid, who develop asymptomatic CMV loads. There is absolute evidence and a strong mandate to recommend treatment before they develop symptoms.

So to the credit of the design and all, for the clinicians that care for these patients, they're not going to wait for them to get symptomatic to treat. So if they have been treated and they haven't responded in 14 days, as has been mentioned earlier, that is a time point where one thinks about doing something else. And at a minimum, one does think about the possibility of resistance and send it on.

So I just want to emphasize, while we didn't wait for patients to be entered until they had disease, that is standard of care in the practice of transplant infectious disease at this time, and that's worldwide. Thank you.

DR. BADEN: Thank you.

Dr. Weina?

DR. WEINA: Peter Weina. Actually, you saw me switching back and forth because I was following on one of the earlier comments, and then you switched the train on me. But just going back to a point that actually you have made regarding being careful not to overinterpret the data, when I first

looked at this -- and I think that the discussion today didn't change my mind at all.

That is, that I think we focused all on this open-label Trial 303, and the conclusions that I came from this trial is really a demonstration of noninferiority rather than superiority, because what you have are maribavir-naive patients getting maribavir versus patients getting the investigator-assigned treatment with drugs, many of those have already demonstrated could be refractory or resistant to those drugs because, arguably, they all have the same mechanism of action, or at least that's one of the posed strengths of maribavir.

Given that, one would expect the efficacy of maribavir to actually be higher than in the investigator-assigned treatment. In fact, I personally think you should be surprised that the investigator-assigned treatment arm did as well as it did with 24 percent being successful in the primary endpoint when it supposedly was resistant or refractory to it.

So I can see it more as a noninferiority

rather than as a superiority, and I just want to echo the comment made about not overinterpreting the efficacy data that's out there.

DR. BADEN: Thank you. And I will let Dr. Bridges and Hunsberger take you outside later and address the issue of noninferiority versus superiority. There are fundamental structural design issues. However, your point is very well taken about what we can infer from the data that are available.

I think we have exhausted the discussion elements for question 1. Are there any other committee members who filled moved to make any other comments about question 1? at this time?

(No response.)

DR. BADEN: I assume, Dr. Chandra, your check box is you've not taken it down. Okay. That has cleared the board.

What I would like to do, if Dr. Choi agrees, is take a 10-minute break now. If there is no further discussion on this discussion question, we'll now take a quick 10-minute break. Panel

members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. We will reconvene at 3:25, and we will then go into the two questions with formal voting. So at 3:25, we shall reconvene.

(Whereupon, at 3:15 p.m., a recess was taken.)

DR. BADEN: It is now 3:25, and we shall resume.

We will now move to the next question, which is a voting question. Dr. Moon Hee Choi will provide the instructions for voting.

DR. CHOI: Questions 2 and 3 are voting questions. Voting members will use the Adobe Connect platform to submit their vote for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

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. BADEN: As there are no questions, I will now --

DR. GEA-BANACLOCHE: I'm sorry. This is Gea-Banacloche. I need the -- how do we vote?

DR. BADEN: No. We are about to go to the voting process, and --

DR. GEA-BANACLOCHE: Okay.

DR. BADEN: -- I will read the question, and then we will see if there any questions, and then we'll go to the voting room.

DR. GEA-BANACLOCHE: Oh, okay. So there's no button to press yet.

DR. BADEN: No buttons right now. We will go to the voting room after we have all agreed we understand the question that we are voting on.

So question number 2 is a formal voting question. Is the overall benefit-risk assessment favorable for the use of maribavir for the

treatment of transplant recipients with CMV infection and disease refractory to treatment and with genotypic resistance to ganciclovir, valganciclovir, foscarnet, or cidofovir?

If you voted no, what additional information will be needed for the benefit-risk assessment to be favorable for the use of maribavir in this population? If a new clinical trial is recommended, please comment on trial design.

Are there any questions about the wording of this question?

Dr. Hardy, you have a question about the wording.

DR. HARDY: Yes. This is David Hardy from Los Angeles. Is the question reading CMV infection and disease refractory to treatment or genotypic resistance, or both conditions have to be satisfied: infection and disease, refractoriness, and resistance?

DR. BADEN: I will ask our FDA colleague to comment on the exact intent of the wording.

DR. BIRNKRANT: Hi. It's Debbie Birnkrant.

Everyone is refractory. This question in particular, though, asks about refractory to treatment and with genotypic resistance.

The next question --

DR. HARDY: So it's either/or.

DR. BIRNKRANT: No, it's not either/or. It's refractory to treatment with genotypic resistance.

DR. BIRNKRANT: Okay. Thank you.

DR. BIRNKRANT: It's the, quote, "resistant population."

DR. BADEN: Because the next question addresses the underlined part of this question.

DR. HARDY: Gotcha. Thank you. All clear.

DR. BADEN: If there are no other questions or comments concerning the wording of the question, we will now begin the voting on question 2.

(Voting.)

DR. CHOI: The voting has closed and is now complete. Once 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, if any.

For the record, we have 17 yes; zero no; and zero abstentions.

DR. BADEN: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote if you wish to.

Given what is on the screen, I will start with Dr. Murphy. If you're not talking, please put yourself on mute, but we'll follow what's on the screen starting with Dr. Murphy.

DR. MURPHY: Richard Murphy. Yes.

DR. BADEN: Any other comments, feel free to make them; otherwise, we will move down the list.

If you're talking, Dr. Murphy, you're on mute or I assume you have no additional comments.

DR. MURPHY: Yes.

DR. BADEN: Dr. Bridges?

DR. BRIDGES: Nancy Bridges. Yes. No additional comment.

DR. BADEN: Dr. Lee?

DR. LEE: Lauren Lee. Yes. No additional comments.

DR. BADEN: Dr. Weina?

DR. WEINA: Peter Weina. Yes. I'd just like to say that I think that the open-label trial, 303, was necessarily designed, so one might expect the maribavir to do better than the investigator-assigned treatment, and one might be expected to be surprised that the investigator-arm treatment did as well as it did.

I am concerned about 20 percent of the subjects in 303 developing genotypic resistance and genotypically had to be treated with investigator-assigned treatment. My concern is because so many develop genotypic resistance in such a relatively short treatment period on a drug that hasn't been widely available. It's a kinder, gentler drug compared to current therapies, and

despite how we're going to potentially limit its use, it's very quickly going to gain footing and use other than those cases demonstrated to be refractory or resistant.

Given all this, I think other tools in our toolbox are critical. The number of patients exposed to and followed for safety signals with maribavir is relatively small, though, and I think extensive phase 4 requirements for monitoring adverse events with all potential uses should clearly be a requirement. That's all.

DR. BADEN: Dr. Burgess?

CAPT BURGESS: Timothy Burgess. I voted yes. No additional comments.

DR. BADEN: Dr. Bollard?

DR. BOLLARD: Catherine Bollard. I voted yes. I do have some brief comments. I agree with Dr. Weina. I think there were obviously strengths to the study but obvious weaknesses in the design that were necessary, given the complex study and the patient population you are studying.

I would have preferred, if you like, the

bone marrow transplant patients to be studied separately on a different trial, but understand that this is a major area of unmet need, and I assert that that patient population is just as urgent as the solid organ transplant patient population.

That being said, I think additional data and post-licensing would definitely be required, especially for the GVHD population, and most critically those with gut GVHD.

DR. BADEN: Dr. Siberry?

DR. SIBERRY: George Siberry. I voted yes. I'll just note that it's disappointing that no adolescents were included, but I think these data also would support the use in older adolescents, and direct study in younger adolescents and younger children should be moved forward quickly. Thank you.

DR. BADEN: Dr. Walker?

DR. WALKER: Hi. Dr. Roblena Walker. I voted yes. I just want to piggyback on, I think, what Dr. Bollard stated regarding the BMT

population. More data is definitely needed. I'm highly concerned about that, especially among African Americans, and a more point of reference, African American females.

DR. BADEN: Thank you.

Dr. Green?

DR. GREEN: Mike Green. I voted yes. As I noted when I introduced myself this morning, I'm a pediatric infectious disease specialist who cares for children that have undergone transplant, and I have done so for more than 30 years.

Accordingly, I know firsthand that CMV is as important, as has been stated during our committee, and I also know the side effects of all the CMV treatments and that they are real, especially the nephrotoxicity associated with foscarnet and cidofovir.

Maribavir met the primary endpoint and appeared superior for secondary endpoints. Certainly, it was not inferior to the investigator-chosen treatment for any endpoint. If you add to this that maribavir is an oral

medication, which would not be an option for any of the other truly resistant CMV therapies, I think this is a great strength.

While nephrotoxicity was unexpectedly not seen, patients who get foscarnet and cidofovir will definitely develop nephrotoxicity, so having maribavir available for resistant CMV will improve outcomes and quality life in this population.

I do agree that we need phase 4 studies, as have been called for. I definitely want to see studies in pediatrics and also to address populations that weren't included in the current studies. Thank you.

DR. BADEN: Dr. Flatau?

DR. FLATAU: Hi. Arthur Flatau. I voted yes. While we all agree that we wish CMV didn't exist, given that it does, I think the data could be more robust. We wish it were more robust, but it's what it is, and it's better than not having it. And I think this will be an important useful drug in treating CMV. Thank you.

DR. BADEN: Dr. Gea-Banacloche?

DR. GEA-BANACLOCHE: Juan Gea-Banacloche. I voted yes. No further comments.

DR. BADEN: Lindsey Baden. I voted yes. I think these data are messy. There are ways to improve the study design. We have much to learn. The advantages of an oral medication with limited side effects are self-evident. I think we have to be careful not to overinterpret the data as to what we want them to mean. But overall, the sum-total data demonstrate benefit in this population, so I voted yes.

Dr. Le?

DR. LE: Jennifer Le. I express the same concerns as Drs. Siberry and Green and the lack of pediatric data, and want to re-state the unmet need in this population, including neonates. At the minimum, please consider evaluating the pharmacokinetic data to at least inform dosing as early as possible.

In addition, I want to just slightly comment on safety, which is largely of mild adverse effect with some perhaps renal and hematologic effect.

However, with the limited safety data that we have, especially at the doses of 400-milligram BID and higher, I recommend adding some language in the product labeling for hematologic, including platelets, as well as renal laboratory monitoring at baseline and also provide a frequency.

I also recommend just only to consider adding language in the product labeling for the antagonism between maribavir and ganciclovir, or ganciclovir, that was based on in vitro EC50 values.

DR. BADEN: Thank you.

I'll remind all panel members please go back on mute when you're done talking.

Dr. Hardy?

DR. HARDY: Hello. This is Dr. David Hardy. I voted yes. I would just say that in the field of CMV treatment, it's been many, many years since a new product, especially one that can be delivered by oral administration, has come to FDA review. So I believe this is an advance, but certainly an incremental advance, for a very high-need patient

population.

As others have said, there needs to be further clarification of where it works and where it works best. Its resistance patterns need to be worked out, especially as its next phase 3 study is looking at non-resistant/non-refractory patients to better understand that, and also looking more at its pharmacokinetics with other drug-drug interactions. Over.

DR. BADEN: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I voted yes. Given the endpoint that was stated, the study definitely met the endpoint. The sensitivity analyses were very strong. I think for the population that it looked at, it showed a positive study. There are things that could have been changed, but I think as far as the study was designed, it met its endpoint.

DR. BADEN: Dr. Perez?

DR. PEREZ: Federico Perez. I voted yes. No further comment. Thank you.

DR. BADEN: Dr. Haidar?

DR. HAIDAR: Hi. This is Ghady Haidar. I voted yes. No further comments.

DR. BADEN: To summarize the comments, the study, as designed, met the endpoint; key populations, a need to be studied, including pediatrics and greater diversity. There were weaknesses in the open-label design. We need PK data, particularly for neonates, and postmarketing or post-licensing studies will be critical. Overall, 17 in favor of efficacy; a favorable risk-benefit analysis.

We will now move on to question 3, which is also a voting question.

(Pause.)

DR. BADEN: Just waiting for the question to be displayed.

Question 3. Is the overall benefit-risk assessment favorable for the use of maribavir for the treatment of transplant recipients with CMV infection and disease refractory to treatment but without genotypic resistance to ganciclovir,

valganciclovir, foscarnet, or cidofovir?

If you voted no, what additional information will be needed for the benefit-risk assessment to be favorable for the use of maribavir in this population? If a new clinical trial is recommended, please comment on the design.

Are there any questions about the wording of this question?

(No response.)

DR. BADEN: Hearing and seeing no questions about the wording of this question, if there are no questions or comments concerning the wording of the question, we will now begin the voting on question 3.

DR. CHOI: We will now move voting numbers to the voting breakout room to vote only. There will be no discussion in the voting breakout room. Once the vote results display, I will read the results into the record.

(Voting.)

DR. CHOI: 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, if any.

For the record, we have 17 yes; zero no; zero abstentions.

DR. BADEN: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification of your vote if you wish to. We'll start with Dr. Murphy again.

DR. MURPHY: Richard Murphy, yes. And I'll briefly say that I think that given the way the patients present in clinic, refractory disease with or without resistance is a distinction without a difference. And since it's not something that's clear up front, it wouldn't make sense to make that distinction in the approval to me, and may actually result in harm that patients are not given a more

active therapy while waiting for resistance results. Thanks.

DR. BADEN: Thank you.

Dr. Bridges?

DR. BRIDGES: Nancy Bridges. I vote yes. Just two brief comments; that I hope that the FDA will require collection of post-licensing information in minority populations who are not represented in this study, and also that the clear evidence as benefit in adults will prompt the company to move forward expeditiously with a trial in infants and children. Thanks.

DR. BADEN: Dr. Lee?

DR. LEE: Lauren Lee. I voted yes. No further comments

DR. BADEN: Dr. Weina?

DR. WEINA: Peter Weina. I voted yes. I do not think there's adequate data available to differentiate between a refractory and resistant infection and disease, and clinically, I don't think this really matters, given our current diagnostic technology. So I believe it's the same

vote. Thank you.

DR. BADEN: Dr. Burgess?

CAPT BURGESS: Timothy Burgess. I voted yes. No additional comments.

DR. BADEN: Lindsey Baden. I voted yes. I think the totality of the data support efficacy in this setting, and as already mentioned, the pragmatics of care make this distinction untenable.

Dr. Siberry?

DR. SIBERRY: George Siberry. I also voted yes, agreeing that this is one population at the time you need to make the decision. And in the subgroup analysis, there was evidence, if only a trend, that there was still a benefit in this group. Thanks.

DR. BADEN: I will get your name correct one of these days. I apologize.

DR. SIBERRY: No problem.

DR. BADEN: Dr. Walker?

DR. WALKER: Dr. Roblena Walker. I voted yes. No further comment.

DR. BADEN: Dr. Green?

DR. GREEN: Michael Green. I voted yes. I want to endorse the comments made by fellow members of the committee who've spoken before me. There certainly may have been concern that there wasn't the statistical superiority in this cohort, but there certainly was also no inferiority, and clinically you can't separate them. And the safety benefits and the logistical benefits of an oral drug remain really important. Thank you.

DR. BADEN: Dr. Flatau?

DR. FLATAU: Arthur Flatau. I have no further comments.

DR. BADEN: Dr. Gea-Banacloche?

DR. GEA-BANACLOCHE: Juan Gea-Banacloche. I voted yes. No further comments.

DR. BADEN: Dr. Bollard?

DR. BOLLARD: It's Catherine Bollard. I voted yes. No further comments.

DR. BADEN: Dr. Le?

DR. LE: Jennifer Le. I voted yes and only have one comment. I do highly recommend evaluating the need for therapeutic drug monitoring in light

of the potential for the expanded use in the real-world setting, the reported resistance and potential drug interaction that may occur in a population who we know will be affected by polypharmacy. Thank you.

DR. BADEN: Dr. Hardy?

DR. HARDY: David Hardy. I voted yes. No further comments.

DR. BADEN: Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I voted yes. No further comment.

DR. BADEN: Dr. Perez?

DR. PEREZ: Federico Perez, and I voted yes. No further comments.

DR. BADEN: Dr. Haidar?

DR. HAIDAR: Hi. This is Ghady Haidar. I voted yes. Just one quick comment just as a reminder to everyone that there are some transplant patients who have what is known as compartmentalized CMV, which means that they have tissue-invasive disease without evidence of plasma viremia, meaning that you're actually never going

to be able to even get a genotype on them, even though they have resistance. Thank you.

DR. BADEN: Thank you. And I guess that also highlights the blood-brain barrier issue for this medication that we didn't discuss. Thank you.

So the vote was 17 in favor of moving forward for this population as well, those without genotypic resistance, largely driven by the clinical impracticality, and this may be a false distinction clinically and the risk of harm.

There was great interest in postmarketing or post-licensure data with trials in key populations that are underrepresented, particularly pediatric and underrepresented minority groups. The issue of TDM needs to be considered in the real world with polypharmacy and the other complexities of care in this population, and we need to pay attention to tissue-specific disease and the impact that may have with this medication and the diagnostics associated with it.

Thank you to the committee members, and I would like to, before we adjourn, see if the FDA

has any further or last comments for us.

DR. BIRNKRANT: Hi. It's Debbie Birnkrant. I also wanted to offer my thanks on behalf of my colleagues. Thank you for the input today and for the discussion. It was very helpful in addressing not only this application but future applications as well for these patients. We greatly appreciate everyone's participation. Thank you very much.

Adjournment

DR. BADEN: I'd like to thank the applicant and the agency for very clear presentations and helpful discussion. I'd like to thank the committee for your hours and hours of hard work and input, and now we can adjourn this meeting. Thank you all.

(Whereupon, at 4:00 p.m., the meeting was adjourned.)