Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
October 7, 2021

Location: Please note that due to the impact of this COVID-19 pandemic, all meeting participants joined this advisory committee meeting via an online teleconferencing platform.

Topic: The committee discussed new drug application (NDA) 215596, for maribavir oral tablets, submitted by Takeda Pharmaceuticals USA, Inc., 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.

These summary minutes for the October 7, 2021 meeting of the Antimicrobial Drugs Advisory Committee were approved on November 17, 2021.

I certify that I attended the October 7, 2021 meeting of the Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Moon Hee V. Choi, PharmD	Lindsey R. Baden, MD
Acting Designated Federal Officer, AMDAC	Chairperson, AMDAC

Final Summary Minutes of the Antimicrobial Drugs Advisory Committee Meeting
October 7, 2021

The Antimicrobial Drugs Advisory Committee (AMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on October 7, 2021. The meeting presentations were heard, viewed, captioned, and recorded through an online teleconferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Takeda Pharmaceuticals USA, Inc. The meeting was called to order by Lindsey R. Baden, MD (Chairperson). The conflict-of-interest statement was read into the record by Moon Hee V. Choi, PharmD (Acting Designated Federal Officer). There were approximately 381 people online. There were a total of 8 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda: The committee discussed new drug application (NDA) 215596, for maribavir oral tablets, submitted by Takeda Pharmaceuticals USA, Inc., 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.

Attendance:

Antimicrobial Drugs Advisory Committee Members Present (Voting): Lindsey R. Baden, MD *(Chairperson)*; CAPT Timothy H. Burgess, MD, MPH, FACP; Michael D. Green, MD, MPH; W. David Hardy, MD; Sally A. Hunsberger, PhD; Jennifer Le, PharmD, MAS, FIDSA, FCCP, FCSHP, BCPS-ID; Richard A. Murphy, MD, MPH; Federico Perez, MD, MS; George K. Siberry, MD, MPH; Roblena E. Walker, PhD; Peter J. Weina, PhD, MD, FACP, FIDSA

Antimicrobial Drugs Advisory Committee Members Not Present (Voting): Ighovwerha Ofotokun, MD, MSc; Sankar Swaminathan, MD

Antimicrobial Drugs Advisory Committee Member Present (Non-Voting): Richa S. Chandra, MD, MBA (*Industry Representative*)

Temporary Members (Voting): Catherine Bollard, MD, FRACP, FRCPA; Nancy D. Bridges, MD; Arthur Flatau, PhD *(Patient Representative)*; Juan Gea-Banacloche, MD; Ghady Haidar, MD; Lauren Lee, MD

FDA Participants (Non-Voting): John Farley, MD, MPH; Debra Birnkrant, MD; Yodit Belew, MD; Mary Singer, MD, PhD; Andreas Pikis, MD; Takashi Komatsu, PhD, RAC

Acting Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers Present: Bret Ambrose; William Watson; Fernanda P. Silveira, MD, MS, FIDSA, FAST; Thomas Paolo; Genovefa Papanicolaou, MD; Willa V. Cochran, MSN, CRNP; Michael J. Boeckh, MD, PhD; Ronak Gandhi, PharmD, BCPS

The agenda was as follows:

Call to Order	**Lindsey R. Baden, MD** Chairperson, AMDAC
Introduction of Committee and Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Acting Designated Federal Officer, AMDAC
FDA Opening Remarks	**Debra Birnkrant, MD** Director Division of Antivirals (DAV) Office of Infectious Disease (OID) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Takeda Pharmaceuticals USA, Inc.**
Introduction	**Michael Cronin, PharmD** Director, Global Regulatory Lead Takeda
Overview of Post-Transplant Resistant/Refractory CMC Infection and Unmet Needs	**Camille Kotton, MD** Clinical Director of Transplant and Immunocompromised Host Infectious Diseases Massachusetts General Hospital
Maribavir Clinical Efficacy	**Martha Fournier, MD** Executive Director Global Clinical Development Lead Takeda
Maribavir Clinical Safety	**Adedeji Adefuye, MD, MPH, FRIPH, FRSPH** Vice President Head of Medical Safety, Rare Diseases Takeda
Clinical Perspective	**Robin Avery, MD** Professor of Medicine Division of Infectious Disease Johns Hopkins
Clarifying Questions	

BREAK

FDA PRESENTATION

Background; Efficacy	**Andreas Pikis, MD** Medical Officer DAV, OID, OND, CDER, FDA
Virology	**Takashi Komatsu, PhD, RAC** Clinical Virology Reviewer DAV, OID, OND, CDER, FDA
Safety; Conclusions	**Andreas Pikis, MD**
Clarifying Questions	

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee	**Debra Birnkrant, MD**

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the efficacy outcome in 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:

   a. Population – narrow population with unmet medical need

      Committee Discussion: *Overall, the Committee members agreed that the study population was overwhelmingly white adults and noted a lack of African American and pediatric representation. One Committee member added that cytomegalovirus (CMV) serum positivity has a higher prevalence among African Americans, which is why it would be beneficial to include more efficacy data from this population in future studies. Some Committee members expressed the need for additional data in patients with graft versus host disease (GVHD), given the small percentage that was represented in these trials. Other Committee members noted that despite the lack of pediatric and African*

American representation, this study was composed of a narrow population with an unmet medical need, given the rarity of the disease and high risk of the population.

b. Trial design and limitations, including potential bias

Committee Discussion:

Although some Committee members expressed that a stratified, double-blind, placebo-controlled study would have been ideal, these members agreed that the data from the open-label was ethical and sufficient given the patient population. One Committee member stated that the study was stratified in its design given the difference in transplant population characteristics (stem-cell transplant vs. solid organ transplant), and expressed that the effects favoring maribavir was robust in each study population individually, which speaks to adequate design and adequate reassurance that it wasn't simply time and immunosuppression manipulation that impacted the results. However, it was noted that a better understanding of how the alterations of the immunosuppressive medication and time from transplant (especially in SCT patients) impacted the results would be of value. Another Committee member stated that more research would need to be done beyond the fixed time point as 8 weeks is not enough time to gather information on how to manage a patient in the case that they do develop resistance to maribavir.

c. Primary efficacy outcome

Committee Discussion: *The Committee members agreed that the Applicant used an FDA validated surrogate endpoint; however, it was noted that the combination of virologic efficacy and tolerability as the primary outcome made it hard to isolate for just the anti-viral effect of maribavir. One Committee member expressed the need for future studies with a hard endpoint (such as death or tissue disease) as this might reduce the possibility of an immune reconstitution effect. Another Committee member stated that using death and tissue invasion as an endpoint could be a major attribution and adjudication problem because the approximate cause of death for someone with CMV disease is not always the CMV disease as death in these patients is more so related to factors such as multiple comorbid conditions, low white cell counts, and other complications of therapy, to name a few. Overall, the Committee members agreed that the rarity of events such as death and tissue disease make it difficult to design a study that can be achieved in a reasonable amount of time, which make virologic markers and toxicity assessments a reasonable endpoint for this condition/study.*

d. Results from the sensitivity and subgroup analyses

Committee Discussion: *The Committee members agreed that the sensitivity and secondary subgroup analyses all seem to point in a favor of maribavir. One Committee member expressed that the study demonstrated non-inferiority rather than superiority explaining that the patients receiving the investigator assigned treatment (IAT), who had already demonstrated to be refractory or resistant to the IAT, showed a higher success rate and the maribavir naïve patients demonstrated a lower success rate than one would expect. Some of the Committee members expressed that the results did show maribavir to*

be effective based on sensitivity analysis; however, they noted that when looking at the virologic failures, all the drugs in the study performed about the same (which demonstrated the effectiveness of maribavir when compared to a 'failing' antiviral, but not to its superiority when compared to other anti-virals).

e. Maribavir safety profile in comparison to other antivirals for cytomegalovirus (CMV)

Committee Discussion: *Many of the Committee members agreed that the safety profile of maribavir was favorable when compared to ganciclovir, valganciclovir, foscarnet or cidofovir. Most of the Committee members also agreed that the ease of administration and favorable toxicity profile of maribavir will improve outcomes and quality of life in this population. Some Committee members expressed that more research is needed to get data on the tolerability, efficacy, and safety profile of maribavir in comparison to other antivirals in African American and pediatric populations.*

Please see the transcript for details of the Committee's discussion.

2. **VOTE:** 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?

   a. If you voted "No", what additional information would be needed for the benefit-risk assessment to be favorable for the use of maribavir in this population?
      i. If a new clinical trial is recommended, please comment on trial design

Vote Result: Yes: 17 No: 0 Abstain: 0

Committee Discussion*: The Committee unanimously agreed that the overall benefit-risk assessment is 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. The Committee members provided the following recommendations: 1) additional data post-licensing for the bone marrow transplant/GVHD population; 2) phase 4 studies in younger adolescents, pediatric and African-American populations; 3) additional language in labeling for hematologic and renal laboratory monitoring; and 4) studies of resistance patterns, pharmacokinetics and other potential drug-drug interactions post-licensing. Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** 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?

   a. If you voted "No", what additional information would be needed for the benefit-risk assessment to be favorable for the use of maribavir in this population?
      i. If a new clinical trial is recommended, please comment on trial design

Vote Result: Yes: 17 No: 0 Abstain: 0

Committee Discussion*: The Committee unanimously agreed that the overall benefit-risk assessment is 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. The Committee members recommended post-market surveillance, therapeutic drug-monitoring, and removal of the clinical distinction between refractory disease with or without genetic resistance as it might be confusing in practice and to patients. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:00 p.m. ET.