Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting November 9, 2022

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 the request for Emergency Use Authorization 113, for sabizabulin oral capsule, a tubulin polymerization inhibitor, submitted by Veru Inc., for the treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk of acute respiratory distress syndrome. A focus of the discussion included the treatment effect size in the context of the high placebo mortality rate, the limited size of the safety database, and identifying the proposed population.

These summary minutes for the November 9, 2022 meeting of the Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration were approved on 1/9/2023.

I certify that I attended the November 9, 2022 meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	/s/
Takyiah Stevenson, PharmD	David H. Au, MD, MS
Designated Federal Officer, PADAC	Chairperson, PADAC

Final Summary Minutes of the Pulmonary-Allergy Drugs Advisory Committee Meeting
November 9, 2022

The Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 9, 2022. 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 Veru Inc. The meeting was called to order by David H. Au, MD, MS (Chairperson). The conflict of interest statement was read into the record by Takyiah Stevenson, PharmD (Designated Federal Officer). There were approximately 1470 people online. There was one Open Public Hearing (OPH) speaker presentation.

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

Agenda:
The committee discussed the request for Emergency Use Authorization 113, for sabizabulin oral capsule, a tubulin polymerization inhibitor, submitted by Veru Inc., for the treatment of SARS-CoV-2 infection in hospitalized patients with moderate to severe COVID-19 infection who are at high risk of acute respiratory distress syndrome. A focus of the discussion included the treatment effect size in the context of the high placebo mortality rate, the limited size of the safety database, and identifying the proposed population.

Attendance:
PADAC Members Present (Voting): David H. Au, MD, MS (*Chairperson*); Scott E. Evans, MD, FCCP, ATSF; Edwin H. Kim, MD, MS; Janet S. Lee, MD, ATSF; Susanne May, PhD

PADAC Members Not Present (Voting): Leonard B. Bacharier, MD; Emma H. D'Agostino, PhD (Consumer Representative); Brian T. Garibaldi, MD, PhD; Fernando Holguin, MD, MPH; John M. Kelso, MD; James M. Tracy, DO

PADAC Members Present (Non-Voting): Dawn M. Carlson, MD, MPH (*Industry Representative*)

Temporary Members (Voting): Lindsey R. Baden, MD; CAPT Daniel S. Chertow, MD, MPH, FCCM, FIDSA; Daniel L. Gillen, PhD; Jennifer A. Schwartzott, MS (*Patient Representative*); Nitin Seam, MD; Steven D. Shapiro, MD; Pamela Shaw, PhD; Roblena E. Walker, PhD (*Acting Consumer Representative*)

FDA Participants (Non-Voting): Joseph G. Toerner, MD, MPH; Banu A. Karimi-Shah, MD; Robert Busch, MD, MMSc; Rebecca Rothwell, PhD; Karen Higgins, ScD; Sai Dharmarajan, PhD

Designated Federal Officer (Non-Voting): Takyiah Stevenson, PharmD

Open Public Hearing Speakers Present: Ealena Callender, MD, MPH (National Center for Health Research)

The agenda was as follows:

Call to Order	**David H. Au, MD, MS** Chairperson, PADAC
Introduction of Committee and Conflict of Interest Statement	**Takyiah Stevenson, PharmD** Designated Federal Officer, PADAC
FDA Opening Remarks	**Banu A. Karimi-Shah, MD** Deputy Director Division of Pulmonology, Allergy, and Critical Care (DPACC) Office of Immunology and Inflammation (OII) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Veru Inc.**
Introduction	**Mitchell Steiner, MD** Chief Executive Officer and Chief Medical Officer Veru Inc.
Efficacy and Safety	**K. Gary Barnette, PhD** Chief Scientific Officer Veru Inc.
Sensitivity Analysis	**Lee-Jen Wei, PhD** Professor of Biostatistics Harvard University, T.H. Chan School of Public Health
Benefit/Risk Assessment	**Christian Sandrock, MD, MPH** Division Vice Chief of Internal Medicine and Director of Critical Care University of California, Davis, School of Medicine
Concluding Remarks	**Mitchell Steiner, MD**
Clarifying Questions to the Applicant	
BREAK	

FDA PRESENTATIONS

Overview of the Clinical Program and Review of Safety	**Robert Busch, MD, MMSc** Medical Officer DPACC, OII, OND, CDER, FDA
Statistical Review of Efficacy	**Sai Dharmarajan, PhD** Senior Mathematical Statistician Division of Biometrics VII Office of Biostatistics, Office of Translational Science CDER, FDA
Uncertainties and Clinical Considerations	**Robert Busch, MD, MMSc** **Sai Dharmarajan, PhD**
Clarifying questions for FDA	

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee	**Banu A. Karimi-Shah, MD**
Questions to the Committee/Committee Discussion	

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the strength of the all-cause mortality data, specifically considering the uncertainties raised by the Agency in Study 902, including the high observed placebo mortality rate, potential for unblinding, differences in standard of care before and during the trial, differences in timing of enrollment, potential differences in goals of care decision-making, and defining the studied population.

   Committee Discussion*: Overall, the Committee acknowledged that Study 902 met its primary endpoint of all-cause mortality at Day 60 and that the results were clinically significant. However, the Committee also agreed that the validity and strength of the data in Study 902 are questionable and insufficient to determine efficacy of VERU-111 due to the uncertainties raised by the Agency. Several Committee members expressed their concern with the small study sample size, the precision of efficacy estimates, and that unblinding in the study due to dissimilarities in drug powder appearance may have influenced outcomes and the validity of the results. Additionally, differences in standard of care before and during the trial as well as differences in timing of enrollment were noted to influence the interpretability and applicability of the data by some members. Some members expressed concern regarding the high placebo mortality in the World Health Organization Ordinal Scale for Improvement (WHO) 4 group, however another member noted that the observed high placebo mortality rate may have been due to the small sample size and 2:1 randomization schema. One member noted that even small baseline differences in such a small placebo control group could exert a large impact on the mortality estimate. One member noted that having data on goals of care and other aspects of standard of care (e.g., ventilation strategies) would make a difference in understanding the mortality; another member noted that potential differences in goals of care decision-making may exist widely and will be variable across clinical trials studying this disease. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Discuss your level of concern regarding the limited size of the safety database for this new molecular entity.

   Committee Discussion: *The majority of the Committee members expressed concern regarding the limited size of the safety database given that VERU-111 is a new molecular entity. Multiple members expressed concerns regarding the uncertainty of the safety profile provided, but also noted that these safety concerns may be mitigated by the potential mortality benefit and the proposed context of use of hospitalized patients. Members highlighted that the small safety database may not have captured rare adverse events. One member added that the lack of clarity regarding VERU-111's mechanism of action made it unclear which safety signals should be monitored. Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** Do the known and potential benefits of VERU-111 when used for the treatment of adult patients hospitalized with COVID-19 at high risk of ARDS outweigh the known and potential risks of VERU-111?

a. If yes, discuss the appropriate patient population in which VERU-111 should be authorized.
b. If no, discuss what additional data would be necessary to assess the benefits vs. the risks of treatment.

Vote Result: Yes: 5 No: 8 Abstain: 0

Committee Discussion: *The majority of the Committee members voted "No", indicating that the known and potential benefits of VERU-111 when used for the treatment of adult patients hospitalized with COVID-19 at high risk of ARDS do not outweigh the known and potential risks of VERU-111. Members expressed concerns that the data from the small study sample size lacks robustness and the study design raises more questions and uncertainties. Additionally, members agreed that the uncertainty in the proposed patient population for use and the unclear mechanism of action of this drug in COVID-19 make it difficult to determine the appropriate patient population in which it should be authorized and the appropriate timing of administration. Members recommended that the Applicant conduct additional studies which include patients with a wider variety of demographics, and some members suggested that the Applicant focus on a more narrowly-defined population of COVID-19 patients, to better determine which patients could benefit. In addition, members commented that an emergency use authorization may hinder assessment of the risk-benefit profile in the long term. Some members stated that it would be reasonable to request that a larger clinical trial be conducted to better assess VERU-111's risk-benefit profile given the high prevalence of hospitalized patients with COVID-19 at high risk of ARDS. A couple members commented that the appropriate patient population in which VERU-111 should be authorized might be patients who are hospitalized with a score of a five or six on the WHO Ordinal Scale for Clinical Improvement who failed maximum standard of care therapy.*

Committee members who voted "Yes" agreed the data presented were sufficient to meet EUA criteria. Some of these members expressed their shared concerns that Study 902's small sample size and study design limitations made it difficult to assess efficacy and safety of VERU-111. One member that voted "Yes" noted that they agreed with all the uncertainties advocated by those voting "No" as well. However, since there are patients that could potentially benefit from this drug, members suggested that the EUA could be granted to give these patients facing the high mortality rate of ARDS more options, while larger clinical trials are conducted concurrently. Please see the transcript for details of the Committee's discussion.

4. **DISCUSSION:** If authorized, the Agency believes that additional data are necessary to understand the benefit-risk assessment as a condition of authorization. Please discuss the proposed design aspects of a study to provide this additional data.

Committee Discussion: *Overall, the Committee members agreed with the Agency that additional data are necessary to understand the benefit-risk assessment as a condition of authorization. Several members agreed that understanding the mechanism of action is important to better understand the benefit-risk assessment as a condition of authorization. A couple members recommended measuring biomarkers for host-immune response and biomarkers for VERU-111's hypothesized antiviral mechanism of action. Members stated that correlating findings from biomarkers with a meaningful clinical endpoint would help determine which patient population would benefit from this drug. Another member recommended enrolling patients at earlier stages of COVID-19 to address the issue related to timing of administering VERU-111, while others suggested narrowing the patient population to subjects with WHO 5 or 6 severity for future study. Members noted that enrollment criteria and data collection that addressed the timing of enrollment, goals of care data collection, and elements of standard of care therapy would help reduce the uncertainties in the trial results. Some members also recommended that subsequent studies should further stratify patients who are hospitalized based on diagnosis at time of hospitalization. These members highlighted that comparing those patients who are hospitalized due to COVID-19 versus those hospitalized primarily due to other conditions that are further complicated by coincident COVID-19 is important for evaluating efficacy. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:51 p.m. ET.