Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
December 16, 2020

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

Topic: The committee discussed spironolactone for the proposed treatment of heart failure with preserved ejection fraction (HFpEF), a serious and often fatal condition for which no drug is approved to improve outcomes. The data supporting the new indication are post-hoc analyses of the National Heart, Lung, and Blood Institute (NHLBI) sponsored TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, which nominally failed to meet its primary endpoint. Spironolactone is currently marketed in the US for the treatment of heart failure with reduced ejection fraction, hypertension, primary hyperaldosteronism, and for the management of edema.

These summary minutes for the December 16, 2020 meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration were approved on January 28, 2021.

I certify that I attended the December 16, 2020 meeting of the CRDAC meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Joyce Yu, PharmD	Julia Lewis, MD
Designated Federal Officer, CRDAC	Chairperson, CRDAC

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
December 16, 2020

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 16, 2020. 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. The meeting was called to order by Julia B. Lewis, MD (Chairperson). The conflict of interest statement was read into the record by Joyce Yu, PharmD (Designated Federal Officer). There were approximately 350 people online. There were two 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 spironolactone for the proposed treatment of heart failure with preserved ejection fraction (HFpEF), a serious and often fatal condition for which no drug is approved to improve outcomes. The data supporting the new indication are post-hoc analyses of the National Heart, Lung, and Blood Institute (NHLBI) sponsored TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial, which nominally failed to meet its primary endpoint. Spironolactone is currently marketed in the US for the treatment of heart failure with reduced ejection fraction, hypertension, primary hyperaldosteronism, and for the management of edema.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting): Jacquline D. Alikhaani, BA (Consumer Representative); C. Noel Bairey Merz, MD, FACC, FAHA, FESC; Thomas D. Cook, PhD, MS, MA; C. Michael Gibson, MD, MS; Edward K. Kasper, MD, FACC, FAHA; Julia B. Lewis, MD (Chairperson); David J. Moliterno, MD; Paul M. Ridker, MD, MPH, FACC, FAHA; Ravi I. Thadhani, MD, MPH

Cardiovascular and Renal Drugs Advisory Committee Members Not Present (Voting): Javed Butler, MD, MPH, MBA; Peter E. Carson, MD

Temporary Members (Voting): Cynthia L. Chauhan, MSW (Patient Representative); Scott Emerson, MD, PhD; Steven E. Nissen, MD, MACC; Christopher M. O'Connor, MD, MACC, FESC, FHFA, FHFSA

Acting Industry Representative to the Committee (Non-Voting): Jerome A. Rossert, MD, PhD

FDA Participants (Non-Voting): Ellis F. Unger, MD; Norman Stockbridge, MD, PhD; Aliza Thompson, MD, MS; Mary Ross Southworth, PharmD; Ququan Liu, MD, MS

Designated Federal Officer (Non-Voting): Joyce Yu, PharmD

Open Public Hearing Speakers: Vandana Sachdev, MD & Jerome Fleg, MD (National Heart, Lung, and Blood Institute); Meg Seymour, PhD (National Center for Health Research)

The agenda was as follows:

Call to Order and Introduction of Committee	**Julia B. Lewis, MD** Chairperson, CRDAC
Conflict of Interest Statement	**Joyce Yu, PharmD** Designated Federal Officer, CRDAC
FDA Opening Remarks	**Norman Stockbridge, MD, PhD** Director Division of Cardiology and Nephrology (DCN) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) Office of New Drugs (OND), CDER, FDA
GUEST SPEAKER PRESENTATIONS	
Spironolactone for HF with Preserved Ejection Fraction: Effectiveness and Safety Results	**Martin Rose, MD, JD** Member, Rose Regulatory Consulting, LLC
TOPCAT	**Bertram Pitt, MD** Professor of Medicine Emeritus University of Michigan School of Medicine Division of Cardiology
Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)	**Marc A. Pfeffer, MD, PhD** Distinguished Dzau Professor of Medicine Harvard Medical School Senior Physician, Cardiovascular Division Brigham and Women's Hospital
FDA PRESENTATION	
TOPCAT: Spironolactone vs. placebo for the treatment of heart failure with preserved ejection fraction	**Ququan Liu, MD, MS** Mathematical Statistician Division of Biometrics II (DB-II) Office of Biostatistics (OB) Office of Translational Sciences (OTS) CDER, FDA
Clarifying Questions	
BREAK	

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Please comment on the various pre-specified and post-hoc analyses. Which ones contribute to the strength of evidence supporting an indication? Which ones do not?

   Committee Discussion: *Although members generally agreed that the pre-specified primary endpoint was not met, most members found the reduction in the secondary endpoint of heart failure hospitalization to be compelling. Several members added that patients with lower ejection fraction appeared to benefit most. However, there were differences in opinions on the exclusion of data from certain sites. Some members did not favor the exclusion of data, while others referred to doing so as "unusual" but not "unprecedented." There was a general acknowledgement that certain sites exhibitied potential noncompliance. Most members believed the TOPCAT trial showed a benefit in secondary outcome without having to exclude data from any sites. One member also commented that the TOPCAT trial, sponsored by National Heart, Lung, and Blood Institute (NHLBI), differed in some ways from that of an industry-sponsored study. Another member voiced concerns over missing data. Please see the transcript for details of the committee discussion.*

2. **VOTE:** Does the TOPCAT trial provide sufficient evidence to support ANY indication?

   Vote Result: Yes: 8 No: 4 Abstain: 1

   Committee Discussion: *The majority of committee members agreed that the TOPCAT provides sufficient evidence to support an indication. These members described such an indication as for the "reduction in heart failure hospitalization" as evidenced by the secondary outcome. Members who voted "Yes" also believed that benefit of spironolactone outweighed potential risk. Members who voted "No" expressed concerns over missing data and/or selective data presented. These members were also concerned about potential precedent-setting, and cited hyperkalemia as a significant adverse effect of spironolactone. The member who voted to "Abstain" noted that the reduction in heart failure hospitalization was a compelling indication, but was concerned about precedent-setting. Please see the transcript for details of the committee discussion.*

3. **DISCUSSION:** If an indication for spironolactone were not granted on the basis of available information, what would be necessary to augment the support for approval?

   Committee Discussion: *Several members noted that use of the Randomized Aldactone Evaluation Study (RALES) dataset in conjunction with TOPCAT could augment the support*

for approval. Some members proposed that an additional follow-on study be conducted in order to confirm the results from TOPCAT. Members proposed several considerations for a future study, such as greater ethnic diversity, improved site monitoring, and a focus on those with mildly reduced ejection fraction. Please see the transcript for details of the committee discussion.

4. **DISCUSSION:** If spironolactone warranted an indication, how would you describe the patients in whom such benefit applies?

   Committee Discussion: *Several members thought that the data presented from TOPCAT could support an indication for spironolactone in heart failure with mildly reduced ejection fraction for the reduction of heart failure hospitalization. There were some comments made about ejection fraction ranges of 45-55% or up to 57%. One member expressed support for the re-classification of heart failure with "mid-range" ejection fraction into a separate diagnostic category. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 1:37 p.m.