Food and Drug Administration

Center for Drug Evaluation and Research

Final Summary Minutes of Cardiovascular and Renal Drugs Advisory Committee Meeting
December 13, 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: On December 13, the committee discussed new drug application (NDA) 216401, for omecamtiv mecarbil tablets, submitted by Cytokinetics, Inc. The proposed indication is to reduce the risk of cardiovascular death and heart failure events in patients with symptomatic chronic heart failure with reduced ejection fraction. The committee discussed whether the phase 3 trial (GALACTIC-HF) establishes substantial evidence of effectiveness of omecamtiv mecarbil and whether the benefits of omecamtiv mecarbil outweigh the risks when used according to the Applicant's proposed dosing regimen.

These summary minutes for the December 13, 2022 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on January 17, 2023 .

I certify that I attended the December 13, 2022 meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Rhea Bhatt, MS
Acting Designated Federal Officer,
CRDAC

/s/
Julia B. Lewis, MD
Chairperson, *CRDAC*

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
December 13, 2022

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on December 13, 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 Cytokinetics, Inc. The meeting was called to order by Julia B. Lewis, MD (Chairperson). The conflict-of-interest statement was read into the record by Rhea Bhatt, MS (Acting Designated Federal Officer). There were approximately 599 people online. There were a total of thirteen 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) 216401, for omecamtiv mecarbil tablets, submitted by Cytokinetics, Inc. The proposed indication is to reduce the risk of cardiovascular death and heart failure events in patients with symptomatic chronic heart failure with reduced ejection fraction. The committee discussed whether the phase 3 trial (GALACTIC-HF) establishes substantial evidence of effectiveness of omecamtiv mecarbil and whether the benefits of omecamtiv mecarbil outweigh the risks when used according to the Applicant's proposed dosing regimen.

Attendance:
Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting): C. Noel Bairey Merz, MD, FACC, FAHA, FESC; Csaba P. Kovesdy, MD, FASN; Julia B. Lewis, MD, (*Chairperson*); David J. Moliterno, MD; Christopher M. O'Connor, MD, MACC, FESC, FHFA, FHFSA; Ravi I. Thadhani, MD, MPH

Cardiovascular and Renal Drugs Advisory Committee Members Not Present (Voting): Jacqueline D. Alikhaani, BA (*Consumer Representative*), Javed Butler, MD, MPH, MBA; Peter E. Carson, MD; Thomas D. Cook, PhD, MS, MA; Edward K. Kasper, MD, FACC, FAHA

Cardiovascular and Renal Drugs Advisory Committee Member Present (Non-Voting): Jerome Rossert, MD, PhD (*Industry Representative*)

Temporary Members (Voting): Michael J. Blaha MD, MPH; Debra Dunn (*Patient Representative*); Daniel L. Gillen, PhD; Steven E. Nissen, MD; Thomas J. Wang, MD

FDA Participants (Non-Voting): Hylton V. Joffe, MD, MMSc; Norman Stockbridge, MD, PhD; Tzu-Yun McDowell, PhD; William Koh, PhD; Li Wang, PhD

Acting Designated Federal Officer (Non-Voting): Rhea Bhatt, MS

Open Public Hearing Speakers Present: Juddson Rupp (Milestone Pharmaceuticals USA, Inc.); Nefertari Nelson Williams; Nina Zeldes, PhD (Public Citizen); Ealena Callender, MD, MPH (National Center for Health Research); Gregory Lewis, MD; George Archer; Michael Ashworth; Maggie Teliska, PhD; Jacob Abraham, MD; Denise Duch Widzgowski (The Mended Hearts, Inc.); Donna Hacker Smith; Kirkwood F. Adams, Jr., MD; Susan Ashley Moore (American Association of Heart Failure Nurses)

The agenda was as follows:

Call to Order	**Julia B. Lewis, MD** Chairperson, CRDAC
Introduction of Committee and Conflict of Interest Statement	**Rhea Bhatt, MS** Acting 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
APPLICANT PRESENTATIONS	**Cytokinetics, Inc.**
Introduction	**Rachel E. Melman, MBS, RAC** Senior Director, Regulatory Affairs Cytokinetics
Unmet Needs in Heart Failure with Reduced Ejection Fraction (HFrEF)	**G. Michael Felker, MD, MHS, FACC, FAHA, FHFSA** Vice-Chief of Cardiology Director of Cardiovascular Research Professor of Medicine Duke University School of Medicine
Efficacy of Omecamtiv Mecarbil in HFrEF	**Fady Malik, MD, PhD, FACC, FHFA** Executive Vice President Research & Development Cytokinetics
Safety of Omecamtiv Mecarbil in HFrEF	**Stuart Kupfer, MD** Senior Vice President, Chief Medical Officer Cytokinetics
Dosing Strategy	**Stuart Kupfer, MD**
Benefit/Risk	**Scott D. Solomon, MD** Professor of Medicine, Harvard Medical School Brigham and Women's Hospital

Conclusion	**Fady Malik, MD, PhD, FACC, FHFA**
Clarifying Questions	

BREAK

FDA PRESENTATIONS

Omecamtiv Mecarbil Efficacy and Safety	**Tzu-Yun McDowell, PhD** Clinical Reviewer DCN, OCHEN, OND, CDER, FDA **William Koh, PhD** Statistical Reviewer Division of Biometrics II Office of Biostatistics Office of Translational Sciences (OTS) CDER, FDA **Li Wang, PhD** Clinical Pharmacology Reviewer Division of Cardiometabolic & Endocrine Pharmacology Office of Clinical Pharmacology OTS, CDER, FDA
Clarifying Questions	

LUNCH

OPEN PUBLIC HEARING

Charge to Committee	Norman Stockbridge, MD, PhD
Questions to the Committee/Committee Discussion	

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the proposed benefits of omecamtiv mecarbil and whether there is adequate evidence for concluding these benefits. Include a discussion comparing the findings for the heart failure and cardiovascular mortality components of the primary efficacy endpoint in the GALACTIC-HF trial. What role does the phase 2 trial play in your assessment of the benefits?

   Committee Discussion*: The Committee members generally agreed that omecamtiv mecarbil, a first-in-class drug, is intended to treat a sick population of patients with advanced heart failure with an unmet need who often have intolerance to existing therapies. However, Committee members expressed several concerns with omecamtiv mecarbil's effectiveness, including the findings based on GALACTIC-HF alone and general consensus that the phase 2 trial does not provide sufficient confirmatory evidence of effectiveness. One member stated that the therapeutic effect was small for the primary efficacy endpoint in GALACTIC-HF. Another member noted that there was no benefit in the cardiovascular death outcome in GALACTIC-HF despite being powered for that endpoint. Several Committee members expressed concerns about relying on subgroup findings from GALACTIC-HF for approval. These members noted that approximately 20 subgroups were examined, which limits the interpretation. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** If omecamtiv mecarbil were approved, what should the labeling say about use as a function of left ventricular ejection fraction?

   Committee Discussion*: Members were generally in agreement that, if approved, the labeling should state that use is for patients with severely reduced left ventricular ejection fraction, such as less than 25%. One member expressed concern about whether there was harm at a higher ejection fraction. Another member noted that cardiovascular death may not belong in the indication, because there was no benefit on that endpoint. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** If omecamtiv mecarbil were approved, what should the labeling say about use in patients with atrial fibrillation or atrial flutter?

   Committee Discussion*: The Committee members generally agreed that if approved, the labeling should address the potential risk observed in patients with atrial fibrillation and atrial flutter. Several members noted that the labeling should state not to initiate omecamtiv mecarbil in patients with atrial fibrillation or atrial flutter. Members were uncertain about how to manage someone who develops atrial fibrillation while on treatment. Please see the transcript for details of the Committee's discussion.*

4. **DISCUSSION:** Discuss whether omecamtiv mecarbil is safe enough to support its proposed use; consider safety with and without pharmacokinetic-based dosing.

***Committee Discussion**: The members generally agreed that if the drug were to be approved, pharmacokinetic-based dosing would be an important component of safety. Some members recommended using the same assay that was used in the GALACTIC-HF trial. A few members expressed concerns about managing risks from drug-drug interactions, although others thought GALACTIC-HF was large enough to have demonstrated such harm if such harm existed. Please see the transcript for details of the Committee's discussion.*

5. **VOTE:** Do the benefits of omecamtiv mecarbil outweigh its risks for the treatment of heart failure with reduced ejection fraction?
    - Provide rationale for your vote.
    - If you voted yes, comment on whether pharmacokinetic-based dosing is essential for the safe and effective use.
    - If you voted no, provide recommendations for additional data or analyses that may support a positive benefit/risk assessment.

Vote Result: Yes: 3 No: 8 Abstain: 0

***Committee Discussion:** The majority of the Committee members stated that the benefits of omecamtiv mecarbil do not outweigh its risks for the treatment of heart failure with reduced ejection fraction. While some members acknowledged the role for omecamtiv mecarbil for the subset of patients who are not served by existing therapies, the members who voted "No," expressed uncertainty about the small treatment effect size despite a large trial, the absence of a cardiovascular mortality benefit, and the lack of improvement on the patient-reported outcome endpoint. Additionally, several members of the Committee noted that there was a modest effect on heart failure hospitalizations. Many members voiced concerns about relying on the results from the subgroup analyses.*

The Committee members who voted "Yes", stated that the single trial established sufficient effectiveness in the very sick population with an unmet need. It was further commented that many advanced heart failure patients are intolerant to many medications that are currently available.

Members expressed overwhelming support to require pharmacokinetic monitoring for dosing decisions if omecamtiv mecarbil were approved.

Many members commented that given the modest benefit and residual uncertainties from the single clinical trial, there is the need for a new, confirmatory trial that is targeted to patients with low ejection fraction. Members suggested a shorter and smaller study in an enriched population should be sufficient. Please see the transcript for details of the Committee's discussion.

The meeting was adjourned at approximately 5:30 p.m. ET.