Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting December 10, 2019

Location: FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland

Topic: The Committee discussed new drug application (NDA) 022034, for vernakalant HCl solution, for intravenous injection, submitted by Correvio International Sàrl, for the proposed indication of rapid conversion of recent onset atrial fibrillation to sinus rhythm for non-surgery patients: Atrial fibrillation ≤ 7 days duration, and for post-cardiac surgery patients: Atrial fibrillation ≤ 3 days duration.

These summary minutes for the December 10, 2019 meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration were approved on January 28, 2020.

I certify that I attended the December 10, 2019 CRDAC meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Yinghua S. Wang, PharmD, MPH, RAC Acting Designated Federal Officer, CRDAC	Julia Lewis, MD Chairperson, CRDAC

Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting December 10, 2019

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on December 10, 2019, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Correvio International Sàrl. The meeting was called to order by Julia B. Lewis, MD (Chairperson). The conflict of interest statement was read into the record by Yinghua S. Wang, PharmD, MPH, RAC (Acting Designated Federal Officer). There were approximately 70 people in attendance. There were two Open Public Hearing (OPH) 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) 022034, for vernakalant HCl solution, for intravenous injection, submitted by Correvio International Sàrl, for the proposed indication of rapid conversion of recent onset atrial fibrillation to sinus rhythm for non-surgery patients: Atrial fibrillation ≤ 7 days duration, and for post-cardiac surgery patients: Atrial fibrillation ≤ 3 days duration.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
John H. Alexander, MD, MHSc; Jacqueline D. Alikhaani, BA (Consumer Representative); Barry R. Davis, MD, PhD; C. Michael Gibson, MD, MS; Julia B. Lewis, MD (Chairperson); John M. Mandrola, MD, FACC; David J. Moliterno, MD; Milton Packer, MD; Paul M. Ridker, MD, MPH, FACC, FAHA

Cardiovascular and Renal Drugs Advisory Committee Member Present (Non-voting):
David G. Soergel, MD (Industry Representative)

Cardiovascular and Renal Drugs Advisory Committee Members Not Present (Voting):
Peter E. Carson, MD; Patrick H. Nachman, MD

Temporary Members (Voting): James Floyd, MD, MS; Nedra Hazlett, MSN, CRNP (Patient Representative); Jenna M. Merandi, PharmD, MS, CPPS; Matthew Needleman, MD, FACC, FHRS

FDA Participants (Non-voting): Ellis F. Unger, MD; Norman Stockbridge, MD, PhD

Acting Designated Federal Officer (Non-voting): Yinghua S. Wang, PharmD, MPH, RAC

Open Public Hearing Speakers: Nina Zeldes, MS (National Center for Health Research); Susan L. Miller

The agenda was as follows:

Call to Order and Introduction of Committee	**Julia B. Lewis, MD** Chairperson, CRDAC
Conflict of Interest Statement	**Yinghua S. Wang, PharmD, MPH, RAC** Acting Designated Federal Officer, CRDAC
FDA Opening Remarks	**Norman Stockbridge, MD, PhD** Director Division of Cardiovascular and Renal Products (DCaRP), Office of Drug Evaluation I (ODE I) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Correvio International Sàrl**
Introduction	**Mark Corrigan, MD** Chief Executive Officer Correvio International Sàrl
Recent Onset AF: High Unmet Need for an Additional Pharmaceutical Treatment	**Peter R. Kowey, MD** Professor Lankenau Institute for Medical Research Lankenau Heart Institute Jefferson Medical College of Thomas Jefferson University
Nonclinical Pharmacology	**Peter K.S. Siegl, PhD** Nonclinical Pharmacologist Correvio International Sàrl
Clinical Efficacy	**Andrew Tershakovec, MD, MPH** Clinical Lead Correvio International Sàrl
Safety	**W. Douglas Weaver, MD** Cardiologist Correvio International Sàrl
A Clinical Assessment of Benefit/Risk	**Peter R. Kowey, MD**
Conclusion	**Mark Corrigan, MD**
Clarifying Questions	
BREAK	

FDA PRESENTATIONS	
FDA Overview of Cardiovascular Safety	**Preston M. Dunnmon, MD, MBA, FACP, FACC** Medical Officer DCaRP, ODE I, OND, CDER, FDA
Safety of Ibutilide and Electrical Cardioversion in Patients with Atrial Fibrillation or Flutter	**Daniel Woronow, MD, FACC** Medical Officer Division of Pharmacovigilance I Office of Pharmacovigilance and Epidemiology Office of Surveillance and Epidemiology CDER, FDA
FDA Conclusion	**Preston M. Dunnmon, MD, MBA, FACP, FACC**
Clarifying Questions	
LUNCH	
OPEN PUBLIC HEARING	
Charge to the Committee	**Norman Stockbridge, MD, PhD**
Questions to the Committee/Committee Discussion	
BREAK	
Questions to the Committee/Committee Discussion	
ADJOURNMENT	

Questions to the Committee:

1. **DISCUSSION:** Please discuss whether the safety profile of vernakalant for rapid conversion of recent onset atrial fibrillation has been adequately characterized. If so, please comment on the sources upon which you relied—randomized studies, SPECTRUM, others.

   Committee Discussion: *Some Committee members noted that the safety profile of vernakalant was not adequately characterized. The SPECTRUM study had selection bias and combined prospective and retrospective data; the proposed checklist may not identify the at-risk patients; and the clinical study population did not represent the U.S. patient population. Some Committee members commented that the SPECTRUM data are reassuring for use in patients without structural heart disease. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Please discuss whether the efficacy and safety profiles of alternative approaches to cardioversion are relevant to assessment of vernakalant's benefit-risk assessment. If so, given the indirect comparisons, how do vernakalant and alternatives compare…
    a. for effectiveness?
    b. for safety?

    Committee Discussion: *The Committee members had mixed views on assessing vernakalant in comparison to alternative treatment options. Some members commented that current cardioversion options are straightforward with well-understood risks. Some members noted that having an additional option for pharmacological cardioversion is valuable and converting patients in the emergency room may avoid prolonged hospital stays and general anesthesia. The Committee members opined on the use of an echocardiogram in identifying high-risk patients. Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** Do you recommend approval of vernakalant for the rapid conversion of recent onset atrial fibrillation?

    Vote Result: Yes: 2 No: 11 Abstain: 0

    Committee Discussion: *The majority of Committee members voted "No", that they did not recommend approval of vernakalant for the rapid conversion of recent onset atrial fibrillation. These members noted that the benefit of vernakalant does not outweigh the serious risk associated with it, considering the alternatives. Several members who voted "No" called for a clear understanding of which patients constitute the high-risk group. The Committee members who voted "Yes" argued that the study data showed that vernakalant can benefit patients at low risk for serious adverse events; thus, patient selection is the key. However, it was noted that more work is needed to clarify who are the "low risk" patients. Please see the transcript for details of the Committee's discussion.*

4. **DISCUSSION:** If vernakalant was approved, what restrictions would you place on patients or on the conditions of use?

    Committee Discussion: *The Committee members noted that vernakalant, if approved, should not be used in elderly patients, hypotensive patients, high risk patients who are constantly being cardioverted, and those with structural heart disease. The Committee members recommended that vernakalant be restricted to low risk patients, prescribed by electrophysiologists or cardiologists only, and that physicians and the multidisciplinary team caring for patients on vernakalant be required to undergo additional training or Risk Evaluation and Mitigation Strategies (REMS) certification. Several members suggested further clinical trials in low risk patients to confirm vernakalant's safety in this patient population. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 2:52 p.m.