Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
December 8, 2021

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 new drug application 215484, for the Nrf2 activator, bardoxolone methyl capsules, submitted by Reata Pharmaceuticals, Inc. The proposed indication is to slow the progression of chronic kidney disease caused by Alport syndrome in patients 12 years of age and older.

These summary minutes for the December 8, 2021 meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration were approved on January 5, 2022.

I certify that I attended the December 8, 2021 CRDAC meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Moon Hee V. Choi, PharmD	Julia Lewis, MD
Acting Designated Federal Officer, CRDAC	Chairperson, CRDAC

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
December 8, 2021

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on December 8, 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 Reata Pharmaceuticals, Inc. The meeting was called to order by Julia B. Lewis, 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 664 people online. There were a total of 23 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) 215484, for the Nrf2 activator, bardoxolone methyl capsules, submitted by Reata Pharmaceuticals, Inc. The proposed indication is to slow the progression of chronic kidney disease caused by Alport syndrome in patients 12 years of age and older.

Attendance:

Cardiovascular and Renal Drug Advisory Committee Members Present (Voting): Jacqueline D. Alikhaani, BA *(Consumer Representative);* C. Noel Bairey Merz, MD, FACC, FAHA, FESC; Javed Butler, MD, MPH, MBA; Thomas D. Cook, PhD, MS, MA; Edward K. Kasper, MD, FACC, FAHA; Julia B. Lewis, MD (*Chairperson);* David J. Moliterno, MD; Christopher M. O'Connor, MD, MACC, FESC, FHFA, FHFSA

Cardiovascular and Renal Drugs Advisory Committee Members Not Present (Voting): Peter E. Carson, MD**;** Csaba P. Kovesdy, MD, FASN**;** Ravi I. Thadhani, MD, MPH

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

Temporary Members (Voting): Paul T. Conway *(Patient Representative);* Gregory H. Gorman, MD, MHS; Susan R. Mendley, MD; Patrick H. Nachman, MD, FASN; Paul M. Palevsky, MD

FDA Participants (Non-Voting): Hylton Joffe, MD; Norman Stockbridge, MD, PhD; Aliza Thompson, MD, MS; Lars Johannesen, PhD; Dali Zhou, PhD

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

Open Public Hearing Speakers Present: Afton DeLucca; Lisa Bonebrake; Charri Lara; Philip Seymour; Cassandra Smith; Ryan Landwehr; Sharon Lagas; Janine Reed; Maddison Martin; Clifford E. Kashtan, MD, FASN; John Dunlap; Christopher Pak; Stuart M. Sprague, DO, FACP, FASN, FNKF; Kerry Willis, PhD; James F. Simon, MD, MBA; December West; Pablo E. Pergola, MD, PhD; Meg Seymour, PhD; Linda Klind; Arnold L. Silva, MD, PhD; Michael A. Carome, MD; Anthony Albert; Clint Kingsbery

The agenda was as follows:

Call to Order	**Julia B. Lewis, MD** Chairperson, CRDAC
Introduction of Committee and Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Acting Designated Federal Officer, CRDAC
FDA Opening Remarks	**Aliza Thompson, MD, MS** Deputy Director Division of Cardiology and Nephrology (DCN) Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**Reata Pharmaceuticals, Inc.**
Bardoxolone Methyl Capsules for Treatment of Alport Syndrome	**Melanie Chin, PhD** Vice President, Product Strategy Reata Pharmaceuticals
Alport Syndrome and Need for Therapies	**Bradley Warady, MD** Director, Division of Nephrology, Director of Dialysis and Transplantation Children's Mercy Kansas City Professor of Pediatrics University of Missouri Kansas City School of Medicine
Alport Syndrome Phase 3 Study Design	**Colin Meyer, MD** Chief Research and Development Officer Reata Pharmaceuticals
	Nathan Teuscher, PhD Vice President Integrated Drug Development Consulting Certara

APPLICANT PRESENTATIONS (CONT.)

Clinical Efficacy of Bardoxolone Methyl	**Colin Meyer, MD**
Clinical Safety of Bardoxolone Methyl	**Colin Meyer, MD**
Benefit/Risk Assessment	**Glenn Chertow, MD, MPH** Professor of Medicine (Nephrology) and (by courtesy) Professor of Epidemiology and Population Health Stanford University School of Medicine
Conclusion	**Colin Meyer, MD**

Clarifying Questions

BREAK

FDA PRESENTATIONS

Bardoxolone Efficacy and Safety	**Lars Johannesen, PhD** Clinical Analyst DCN, OCHEN, OND, CDER, FDA **Dali Zhou, PhD** Biometrics Reviewer Division of Biometrics II, Office of Biostatistics Office of Translational Sciences, CDER, FDA

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee	**Aliza Thompson, MD, MS**

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

The Applicant is seeking approval of bardoxolone methyl to slow the progression of chronic kidney disease caused by Alport syndrome in patients 12 years of age and older.

1. **DISCUSSION:** Discuss whether CARDINAL Phase 3 was adequately designed to assess for an effect on the progression of chronic kidney disease in patients with Alport syndrome.

   Committee Discussion: *Overall, the Committee members did not agree that CARDINAL Phase 3 was adequately designed to assess for an effect on the progression of chronic kidney disease in patients with Alport syndrome. Several Committee members observed that the study may have been more informative if another marker had also been used to measure GFR, such as cystatin C, since such a marker would allow one to distinguish drug effects on serum creatinine from effects on GFR. One Committee member expressed that the study may have been able to demonstrate an effect on more relevant patient outcomes if it had enrolled more adolescent patients as these patients demonstrated greater eGFR loss in the trial as compared to adult patients. Other Committee members had concerns with the following aspects of study design: 1) outcome measures (e.g., choice of on-treatment as primary, lack of additional serum creatinine measurements during the off-treatment periods); 2) duration of washout periods, particularly after the 104-week visit; and 3) lack of information on findings in key genetic subgroups (i.e., male patients with X-linked Alport syndrome) and whether the design could have been optimized in this regard (e.g., by prespecifying such analyses or possibly by stratifying randomization). Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Discuss whether the available data indicate that bardoxolone methyl slows the progression of chronic kidney disease and whether it is reasonable to conclude, based on the available data, that bardoxolone methyl will reduce the risk of progression to kidney failure when used chronically in patients with Alport syndrome.

   Committee Discussion: *The Committee agreed that the available data did not indicate that bardoxolone methyl slows the progression of chronic kidney disease. The Committee also did not think that it was reasonable to conclude, based on the available data, that bardoxolone methyl will reduce the risk of progression to kidney failure when used chronically in patients with Alport syndrome. One Committee member highlighted the importance of the sensitivity analyses and explained that such analyses assess whether there's an alternative explanation for the proposed positive effect (i.e., an explanation other than an effect on disease progression), and that the data suggest that what was observed was not a change in the progression of the disease but simply an artifact of the pharmacodynamic effect on GFR. Another Committee member noted that the study used a surrogate endpoint to assess whether the long-term outcome would be improved with treatment; however, the difference in GFR between the control and the treatment group narrowed over time. Several Committee members agreed that it would be beneficial to incorporate patient reported outcomes in future studies. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** Discuss bardoxolone methyl's safety profile.

   a. Do bardoxolone methyl's effects on albuminuria, blood pressure or other parameters raise concerns about its long-term efficacy and/or safety in patients with Alport syndrome?

b. What are the implications of bardoxolone methyl's effect on body weight for pediatric patients?

Committee Discussion: *Overall, the Committee members agreed that bardoxolone methyl's safety profile raised concerns. One Committee member noted that albuminuria and proteinuria are markers of bad outcomes for both the kidney and heart. Several Committee members expressed concern that despite the trial population having a relatively high GFR, brain natriuretic peptide values increased. Another Committee member added that given the modest size of the CARDINAL trial, it was important to consider the data from the BEACON trial, in which there were safety signals for heart failure and cardiovascular events. In terms of bardoxolone methyl's effect on body weight and its implications for pediatric patients, one Committee member observed that there appeared to be a safety signal in adolescent patients, with a flattening of age expected weight gain and that this could translate into an effect on growth over time. This Committee member also noted that because treatment could be used starting at 12 years of age and into the final stages of growth and development, children should be studied further to assuage the concern of the impact on growth. Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Does the provided evidence demonstrate that bardoxolone methyl is effective in slowing the progression of chronic kidney disease in Alport syndrome and that its benefits outweigh its risks?

   a. If you voted yes, provide your rationale.

   b. If you voted no, provide your rationale and provide recommendations for additional data and/or analyses that are needed to support approval.

   Vote Result: Yes: 0 No: 13 Abstain: 0

   Committee Discussion: *The Committee unanimously agreed that the provided evidence did not demonstrate that bardoxolone methyl is effective in slowing the progression of chronic kidney disease in Alport syndrome and that its benefits outweigh its risks. The Committee members provided the following rationale for their vote: 1) low enrollment of patients from the adolescent population where more convincing outcomes may be possible; 2) questionable efficacy (excluded data, differential discontinuation, duration of off-treatment period, etc.); and 3) concerns with the safety profile (e.g., albuminuria, increases in blood pressure, increase in cardiovascular events and brain natriuretic peptide levels) in the CARDINAL and/or BEACON trials. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 5:12 p.m. ET.