Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting

November 16, 2022

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

Topic: The committee discussed new drug application 213931, for tenapanor hydrochloride tablets, submitted by Ardelyx, Inc., for the control of serum phosphorus levels in adults with chronic kidney disease on dialysis. The committee was asked to comment on whether the size of the treatment effect on serum phosphorus is clinically meaningful and whether tenapanor's benefits outweigh its risks.

These summary minutes for the November 16, 2022 meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) meeting of the Food and Drug Administration were approved on January 17, 2023.

I certify that I attended the November 16, 2022 meeting of the Cardiovascular and Drugs Advisory Committee (CRDAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/

LaToya Bonner, PharmD
Acting Designated Federal Officer, CRDAC

/s/

Julia Lewis, MD
Chairperson, CRDAC

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
November 16, 2022

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on November 16, 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 Ardelyx, Inc. The meeting was called to order by Julia B. Lewis, MD (Chairperson). The conflict-of-interest statement was read into the record by LaToya Bonner, PharmD (Acting Designated Federal Officer). There were approximately 1106 people online. There was a total of 17 Open Public Hearing (OPH) speaker presentations.

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

Agenda:
The committee discussed new drug application 213931, for tenapanor hydrochloride tablets, submitted by Ardelyx, Inc., for the control of serum phosphorus levels in adults with chronic kidney disease on dialysis. The committee was asked to comment on whether the size of the treatment effect on serum phosphorus is clinically meaningful and whether tenapanor's benefits outweigh its risks.

Attendance:
Cardiovascular and Renal Drugs 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*); 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; David J. Moliterno, MD

Cardiovascular and Renal Drugs Advisory Committee Member Not Present (Non-Voting): Jerome Rossert, MD, PhD (*Industry Representative*)

Temporary Members (Voting): Paul T. Conway (*Patient Representative*); Ian de Boer, MD, MS; Scott S. Emerson, MD, PhD; Linda F. Fried, MD; Susan R. Mendley, MD; Patrick H. Nachman, MD, FASN.

Acting Industry Representative to the Committee (Non-Voting): David Soergel, MD (*Acting Industry Representative*)

FDA Participants (Non-Voting): Hylton V. Joffe, MD, MMSc; Norman Stockbridge, MD, PhD; Aliza Thompson, MD, MS; Selena DeConti, PharmD, MPH; Ling-Wan Chen, PhD, MS.
Acting Designated Federal Officer (Non-Voting): LaToya Bonner, PharmD

Open Public Hearing Speakers Present: Alex, Barrios; LaVarne A. Burton; Ealena Callender, MD, MPH (National Center for Health Research); Dawn P. Edwards; Lisa Evans; Derek Forfang; Mike Gillani, MD; Lori Hartwell; John Manley; Sharon M. Moe, MD; Sagar Nigwekar, MD; Rory C. Pace, MPH; Pablo E. Pergola; Arnold Silva; Alex Solis; David P. Tietjen, MD; Jay Wish, MD

The agenda was as follows:

Call to Order	**Julia B. Lewis, MD** Chairperson, CRDAC
Introduction of Committee and Conflict of Interest Statement	**LaToya Bonner, 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	**Ardelyx, Inc.**
Introduction	**Laura A. Williams, MD, MPH** Chief Medical Officer, Ardelyx
Unmet Need	**Glenn Chertow, MD** Norman S. Coplon Satellite Healthcare Professor of Medicine Professor of Epidemiology and Population Health Stanford University School of Medicine
Study Design Considerations	**Jason Conner, PhD** President and Lead Statistical Scientist Confluence Stat LLC
Efficacy and Clinical Meaningfulness	**David Spiegel, MD** Vice President, Nephrology Ardelyx
Safety	**Laura A. Williams, MD, MPH**

APPLICANT PRESENTATIONS (CONT.)

Clinical Perspective	**Stuart Sprague, DO** Clinical Professor of Medicine University of Chicago, Pritzker School of Medicine Chief, Division of Nephrology and Hypertension NorthShore University Health System

Clarifying Questions

BREAK

FDA PRESENTATIONS

Tenapanor's Efficacy and Safety	**Aliza Thompson, MD, MS** **Ling-Wan Chen, PhD** Biometrics Reviewer Division of Biometrics II, Office of Biostatistics Office of Translational Sciences, CDER, FDA **Selena DeConti, PharmD, MPH** Safety Analyst DCN, OCHEN, OND, CDER, FDA

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Clarifying Questions

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

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the magnitude and clinical meaningfulness of tenapanor's treatment effect on serum phosphorus when administered as monotherapy.

   Committee Discussion*: The Committee agreed that the data indicate that tenapanor has a measurable effect on serum phosphorus but also noted that tenapanor appeared to be less effective than approved phosphate binders. Several members noted the pill burden associated with existing treatments and opined there may be a role for tenapanor as monotherapy in a subset of patients, for example, for those who do not appear to tolerate existing treatment and who respond to tenapanor. However, one member noted that he had not seen any data indicating that patients who do not tolerate existing treatments can tolerate tenapanor and also achieve adequate control with tenapanor as monotherapy. Several members voiced concern about the limitations of the data supporting the use of serum phosphorus as a surrogate for clinical outcomes, and specifically the absence of data from randomized controlled trials supporting its use as a surrogate. Members also noted that the community did not have strong evidence to know what target phosphorus levels should be, however a trial was underway to address the issue. Given the existing data, members indicated that it was difficult to comment on the clinical meaningfulness of the magnitude of tenapanor's effect. Several members highlighted the importance of patient choice and shared decision making and also noted that dialysis patients were highly monitored. Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Discuss the magnitude and clinical meaningfulness of tenapanor's treatment effect on serum phosphorus when administered in combination with phosphate binder treatment.

   Committee Discussion*: One member of the committee noted the short timeframe of Study 202 and that the trial did not require optimization of background phosphate binder treatment, but also commented that using tenapanor on top of phosphate binders increased the proportion of patients reaching the serum phosphorus threshold of less than 5.5 mg/dL, and opined that, assuming the findings generalized beyond the 4-week period, this was the way tenapanor should be used. During discussion of this question and the prior question, other members of the committee also noted that tenapanor was a "tool" that could be used on top of phosphate binders to get patients to goal. Concern was again voiced about the state of the evidence supporting use of serum phosphorus as a surrogate endpoint and particular serum phosphorus targets and it was noted that more data were needed. The importance of patient choice and shared decision making was discussed, with one member indicating that the data from Study 402 were important to consider. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** Diarrhea was the most common adverse reaction in clinical trials of tenapanor in adults with CKD on dialysis. Discuss this risk from a safety and tolerability perspective.

***Committee Discussion**: Members noted that the adverse events shown (diarrhea and loose stools) may be welcomed by some patients who are experiencing chronic constipation, that patients who do not tolerate tenapanor will discontinue the drug, and that dialysis patients are carefully monitored. One member commented that FDA had approved tenapanor for irritable bowel syndrome with constipation (IBS-C) in adults, indicating that the product is safe enough in IBS-C patients, and that tenapanor also appeared to be safe enough in dialysis patients. Members generally viewed diarrhea as a tolerability issue, though a few members voiced concerns about the severity of diarrhea in a vulnerable population, potential adverse cardiovascular consequences of diarrhea particularly in older patients, and/or that down titration of the drug in response to diarrhea would result in further attenuation of the treatment effect on serum phosphorus. Some members also noted that based on what was presented, they did not have a clear understanding of the findings as relates to the duration and severity of diarrhea. Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Do tenapanor's benefits outweigh its risks for the control of serum phosphorus in adults with CKD on dialysis when administered as monotherapy?

    a. Provide your rationale.
    b. If you voted no, provide recommendations for additional data and/or analyses that may support a positive benefit/risk assessment for tenapanor as monotherapy.

    Vote Result: Yes: 9 No: 4 Abstain: 0

***Committee Discussion:** The majority of the committee members voted "Yes," agreeing that tenapanor's benefits outweigh its risks for the control of serum phosphorus in adults with CKD on dialysis when administered as monotherapy. These committee members recognized an underserved sub-population who are unable to tolerate current treatments and noted that tenapanor will provide additional options for the subgroup of patients who can tolerate tenapanor and achieve adequate response. Members also noted the importance of patient choice and preference in a setting where data are limited as relates to clinical benefit. Those who voted "No" voiced concern about clinical benefit, noting that the surrogate endpoint had not been adequately validated with clinical outcomes, the modest treatment effect on serum phosphorus, and that it didn't seem likely that a sizeable population would achieve adequate control with monotherapy given the size of the treatment effect. Please see the transcript for details of the Committee's discussion.*

5. **VOTE:** Do tenapanor's benefits outweigh its risks for the control of serum phosphorus in adults with CKD on dialysis when administered in combination with phosphate binder treatment?

    a. Provide your rationale.
    b. If you voted no, provide recommendations for additional data and/or analyses that may support a positive benefit/risk assessment for tenapanor in combination with phosphate binder treatment.

    Vote Result: Yes: 10 No: 2 Abstain: 1

Committee Discussion: *The majority of the committee members voted "Yes", indicating that tenapanor's benefits outweigh its risks for the control of serum phosphorus in adults with CKD on dialysis when administered in combination with phosphate binder treatment. These committee members generally thought there was likely to be greater use in this setting and that there was more support for use in this setting, particularly in patients with more severe hyperphosphatemia. These members also noted the importance of having tools to individualize care. The members who voted "No", voiced concern about the nature of the data supporting serum phosphorus as a surrogate endpoint, the modest treatment effect, and the need for better data to guide the management of hyperphosphatemia in clinical practice. One member who abstained stated that it was challenging to compare benefits versus risks without reliable data to make a well-informed decision. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 5:00 p.m. EST.