

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting  
July 15, 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 213805, for the hypoxia inducible factor prolyl hydroxylase inhibitor, roxadustat tablets, submitted by FibroGen, Inc., for the treatment of anemia due to chronic kidney disease in adult patients not on dialysis and on dialysis.

These summary minutes for the July 15, 2021 meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration were approved on August 10, 2021.

I certify that I attended the July 15, 2021 CRDAC meeting of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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/s/  
Joyce Yu, PharmD  
Designated Federal Officer, CRDAC

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/s/  
Julia Lewis, MD  
Chairperson, CRDAC

## **Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting July 15, 2021**

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 15, 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 FibroGen, Inc. 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 1610 people online. There were 15 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 213805, for the hypoxia inducible factor prolyl hydroxylase inhibitor, roxadustat tablets, submitted by FibroGen, Inc., for the treatment of anemia due to chronic kidney disease in adult patients not on dialysis and on dialysis.

### **Attendance:**

#### **Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):**

Jacqueline D. Alikhaani, BA (Consumer Representative); C. Noel Bairey Merz, MD, FACC, FAHA, FESC; 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; Ravi I. Thadhani, MD, MPH

#### **Cardiovascular and Renal Drugs Advisory Committee Members Not Present (Voting):**

Javed Butler, MD, MPH, MBA; Peter E. Carson, MD; Csaba P. Kovesdy, MD, FASN

#### **Cardiovascular and Renal Drugs Advisory Committee Member Not Present (Non-Voting):**

Jerome A. Rossert, MD, PhD

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

**Temporary Members (Voting):** Leslie S. Cho, MD, FACC, FSCAI, FESC; Paul T. Conway (Patient Representative); Susan T. Crowley, MD, MBA, FASN; Milton Packer, MD; Afshin Parsa, MD, MPH; Thomas J. Wang, MD

**FDA Participants (Non-Voting):** Ellis F. Unger, MD; Ann T. Farrell, MD; Saleh Ayache, MD; Jae Joon Song, PhD

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

**Open Public Hearing Speakers:** Jayant Kumar, MD; Melissa Baker; S. Wyatt Carr; Arnold L. Silva, MD, PhD; Bridget Luebbers; Subir Paul, MD, FASN; Jessica Coleman, MD; Alice Wei,

MD; Roberto Manllo-Karim; Amanda Dilger; Liz Griffith; Louard Crumbaugh Jr.; Anjay Rastogi MD, PhD; Leigh-Ann Williams; Michael Douglas Spigler (American Kidney Fund)

*The agenda was as follows:*

Call to Order and Introduction of Committee	<b>Julia B. Lewis, MD</b> Chairperson, CRDAC
Conflict of Interest Statement	<b>Joyce Yu, PharmD</b> Designated Federal Officer, CRDAC
FDA Opening Remarks	<b>Ellis F. Unger, MD</b> Director Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN) Office of New Drugs (OND), CDER, FDA
<b>APPLICANT PRESENTATIONS</b>	<b>FibroGen, Inc.</b>
Introduction	<b>R. Wayne Frost, PharmD, JD</b> Senior Vice President Regulatory Affairs FibroGen, Inc.
Unmet Need	<b>Roberto Pecoits-Filho, MD, PhD</b> Nephrologist and Senior Research Scientist Arbor Research Collaborative for Health
Efficacy Results	<b>Lynda Szczech, MD</b> Vice President Clinical Development and Medical Affairs FibroGen, Inc.
Safety Results	<b>Dustin Little, MD</b> Global Clinical Head AstraZeneca LP
Clinical Perspective	<b>Steven Fishbane, MD</b> Professor of Medicine Chief, Division of Nephrology Donald and Barbara Zucker School of Medicine
Clarifying Questions	
<b>BREAK</b>	

**FDA PRESENTATIONS**

Roxadustat for the Treatment of Anemia Due to Chronic Kidney Disease in Adult Patients not on Dialysis and on Dialysis

**Saleh Ayache, MD**  
Clinical Reviewer  
Division of Non-Malignant Hematology (DNH)  
OCHEN, OND, CDER, FDA

**Jae Joon Song, PhD**  
Statistical Reviewer  
Division of Biometrics VII (DB-VII)  
Office of Biostatistics (OB)  
Office of Translational Sciences (OTS)  
CDER, FDA

Clarifying Questions

**LUNCH**

**OPEN PUBLIC HEARING**

Questions to the Committee/Committee Discussion

**BREAK**

Questions to the Committee/Committee Discussion (cont.)

**ADJOURNMENT**

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***Questions to the Committee:***

**Non-dialysis-dependent population:**

1. **DISCUSSION:** Discuss the benefits and risks of roxadustat in the non-dialysis-dependent (NDD) population.

***Committee Discussion:*** *Committee members considered the convenience of roxadustat being an oral dosage form to be both a benefit and a risk. Committee members stated that while patients would no longer require an erythropoietin (EPO) injection, some members expressed concern that it would result in worse compliance with respect to monitoring of the patient's hemoglobin (Hb) levels. Committee members were also concerned about roxadustat's risks of thrombosis and mortality. Despite roxadustat's effect on Hb improvement and intravenous iron reduction, members noted a surprising lack of improvement in quality of life. There was discussion regarding the interpretability of on-study vs. on-treatment (OT) +7 pooled analyses results for analyses of major adverse*

*cardiovascular events (MACE) and mortality. Please see the transcript for details of the committee discussion.*

2. **DISCUSSION:** If you have concerns regarding these risks, discuss whether you believe they could be addressed through modification of the treatment algorithm, for example, changes in target hemoglobin, starting dose, titration scheme, monitoring paradigm.
  - a. If you favor changes to the treatment algorithm to enhance safety, discuss whether they should be tested (i) prior to approval, (ii) after approval, or (iii) not at all.

***Committee Discussion:** Committee members generally agreed that changes in the treatment algorithm with respect to Hb target and starting dose were reasonable proposals to address roxadustat's safety risks; however, several members commented that such modifications should be tested prior to roxadustat approval. Some committee members expressed uncertainty as to whether the risks were caused by the drug's mechanism of action (rapid Hb rise) or rather through an unknown off-target mechanism. There were various concerns with the post-marketing assessment proposed by the Applicant; none of the Committee members seemed convinced that a post-marketing real-world study would be adequate. A committee member also commented that a Risk Evaluation and Mitigation Strategy (REMS) program could potentially be considered as a way to reduce risk. Please see the transcript for details of the committee discussion.*

3. **VOTE:** Should roxadustat be approved for the treatment of anemia due to chronic kidney disease (CKD) in adult patients not on dialysis?
  - a. If not, provide your rationale, as well as recommendations for additional data and/or analyses that would support a favorable benefit-risk profile and approval of roxadustat.

**Vote Result:      Yes: 1                      No: 13                      Abstain: 0**

***Committee Discussion:** The majority of committee members voted against approval of roxadustat for the treatment of anemia due to CKD in adult patients not on dialysis. Committee members cited the following as their reasons for voting against approval: concerning safety risks, untested proposed mitigation dosing strategy with unknown efficacy, sicker patients with greater need to demonstrate safety, and difficulty in obtaining more definitive data in the post-marketing setting. One member commented that approval based on a mitigation dosing model would be non-traditional. The member who voted "Yes" commented that a REMS program could potentially be a fair strategy to mitigate the safety risks, and allow roxadustat to fulfill an unmet medical need. Please see the transcript for details of the committee discussion.*

Dialysis-dependent population:

4. **DISCUSSION:** Discuss the benefits and risks of roxadustat in the dialysis-dependent (DD) population.

*Committee Discussion:* Some committee members noted that roxadustat could have a benefit in EPO resistant patients. In addition, members expressed greater confidence in the risk mitigation for the DD population, as inadequate Hb monitoring would merit less concern in this setting. However, members remained concerned with the safety data given that on-study analyses of the three principal studies and Study 613 demonstrated increased mortality when compared to EPO. One committee member also commented that it was unclear whether the drug's benefit would be maintained with a lower roxadustat dose. Please see the transcript for details of the committee discussion.

5. **DISCUSSION:** If you have concerns regarding these risks, discuss whether you believe they could be addressed through modification of the treatment algorithm, for example, changes in target hemoglobin, starting dose, titration scheme, monitoring paradigm.
  - a. If you favor changes to the treatment algorithm to enhance safety, discuss whether they should be tested (i) prior to approval, (ii) after approval, or (iii) not at all.

*Committee Discussion:* Similarly to the NDD population, some committee members agreed that the changes to the treatment algorithm should be tested prior to approval of roxadustat in the DD population to provide clinical evidence of its efficacy and safety. Several committee members remained concerned that the Applicant's proposed dosing regimen to reduce thrombosis risks was not tested, and stated that modeling should not replace a clinical trial prior to approval. There were also comments made regarding the low percentage of African American patients studied. Please see the transcript for details of the committee discussion.

6. **VOTE:** Should roxadustat be approved for the treatment of anemia due to CKD in adult patients on dialysis?
  - a. If not, provide your rationale, as well as recommendations for additional data and/or analyses that would support a favorable benefit-risk profile and approval of roxadustat.

**Vote Result:      Yes: 2                      No: 12                      Abstain: 0**

*Committee Discussion:* The majority of committee members voted against approval of roxadustat for the treatment of anemia due to CKD in the DD population. The majority of members stated that more information was needed on both the efficacy and safety of the proposed dosing strategy prior to approval. Some members who voted "No" recommended additional testing of the lower dose in EPO resistant patients, while other members stated they would favor initial approval for that subpopulation. Other recommendations were to include more African American patients. One member commented that an additional trial

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*studying EPO hyporesponders should not be the “stand-alone” trial to support roxadustat approval. Committee members who voted “Yes” agreed with comments made by other members in regards to EPO resistant patients. These members also commented that providers would have more control in the DD setting and could therefore potentially better mitigate safety risks. Please see the transcript for details of the committee discussion.*

The meeting was adjourned at approximately 5:32 p.m.