Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
October 26, 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: The committee discussed new drug application (NDA) 216951, for the hypoxia inducible factor prolyl hydroxylase inhibitor (HIF-PHI), daprodustat tablets, submitted by GlaxoSmithKline, LLC, for the treatment of anemia due to chronic kidney disease (CKD) in adult patients not on dialysis (NDD) and on dialysis (DD).

These summary minutes for the October 26, 2022 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on ___11/19/22____.

I certify that I attended the October 26, 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/	**/s/**
Jessica Seo, PharmD, MPH	Julia B. Lewis, MD
Acting Designated Federal Officer, CRDAC	Chairperson, CRDAC

Final Summary Minutes of the Cardiovascular and Renal Drugs Advisory Committee Meeting
October 26, 2022

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on October 26, 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 GlaxoSmithKline, LLC. The meeting was called to order by Julia B. Lewis, MD (Chairperson). The conflict-of-interest statement was read into the record by Jessica Seo, PharmD, MPH (Acting Designated Federal Officer). There were approximately 803 people online. There were a total of ten 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) 216951, for the hypoxia inducible factor prolyl hydroxylase inhibitor (HIF-PHI), daprodustat tablets, submitted by GlaxoSmithKline, LLC, for the treatment of anemia due to chronic kidney disease (CKD) in adult patients not on dialysis (NDD) and on dialysis (DD).

Attendance:
Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting): Julia B. Lewis, MD, (*Chairperson*); 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; Christopher M. O'Connor, MD, MACC, FESC, FHFA, FHFSA; Ravi I. Thadhani, MD, MPH

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): Kevin C. Abbott, MD, MPH; Emilia Bagiella, PhD; Leslie S. Cho, MD; Paul T. Conway (*Patient Representative*); Patrick H. Nachman, MD, FASN; Milton Packer, MD; Afshin Parsa, MD, MPH; Thomas Wang, MD

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

FDA Participants (Non-Voting): Hylton V. Joffe, MD, MMSc; Ann Farrell, MD; Tanya Wroblewski, MD; Justin Penzenstadler, PharmD; Van Tran, PhD

Acting Designated Federal Officer (Non-Voting): Jessica Seo, PharmD, MPH

Open Public Hearing Speakers Present: Nina Zeldes, PhD (Public Citizen); Arnold L. Silva, MD, PhD; Kathleen Arntsen (Lupus and Allied Diseases Association, Inc); Carly Harrison; Michael Spigler (American Kidney Fund); Martin C. Stedtnitz; David H. Henry, MD; Volker H. Haase, MD; Jessica Coleman, MD; Erich Ditschman (Home Dialyzors United)

The agenda was as follows:

Call to Order	***Julia B. Lewis, MD*** *Chairperson, CRDAC*
Introduction of Committee and Conflict of Interest Statement	***Jessica Seo, PharmD, MPH*** *Acting Designated Federal Officer, CRDAC*
FDA Opening Remarks	***Ann Farrell, MD*** *Director* *Division of Non-Malignant Hematology (DNH)* *Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)* *Office of New Drugs (OND), CDER, FDA*
APPLICANT PRESENTATIONS	***GlaxoSmithKline, LLC (GSK)***
Introduction	***Janet van Adelsberg, MD*** *Medicines Development Leader, Daprodustat* *Vice President, GSK*
Unmet Need	***Kirsten Johansen, MD*** *Professor of Medicine, University of Minnesota* *Nephrology Division Director* *Co-Director, Chronic Disease Research Group* *Hennepin County Medical Center*
Clinical Trial Results	***Alexander Cobitz, MD, PhD*** *Clinical Development Lead, Daprodustat* *Senior Medical Director, GSK*
Cardiovascular Safety	***Kaivan Khavandi, MBChB, PhD, MCRP*** *Vice President* *Clinical Development, GSK*
Differential Dosing Frequency & On-Treatment Analysis Bias	***Kevin Carroll, PhD*** *Biostatistics Consultant* *Chief Statistician, KJC Statistics Ltd*

APPLICANT PRESENTATIONS (CONT.)

General Safety	***Heather Stein, MD*** *Vice President* *Safety Evaluation and Risk Management* *Global Safety, GSK*
Clinical Perspective	***Ajay Singh, MBBS, FRCP*** *Senior Associate Dean for Postgraduate Medical Education* *Director, Master in Medical Sciences in Clinical Investigation (MMSCI) Program* *Harvard Medical School* *Renal Physician, Brigham and Women's Hospital*

Clarifying Questions

BREAK

FDA PRESENTATIONS

Background and Efficacy of Daprodustat	***Justin Penzenstadler, PharmD*** *Clinical Reviewer* *DNH, OCHEN, OND, CDER, FDA*
Daprodustat's Cardiovascular Safety	***Van Tran, PhD*** *Statistical Reviewer* *Division of Biometrics VII, Office of Biostatistics* *Office of Translational Sciences, CDER, FDA*
Daprodustat's General Safety and Summary	***Justin Penzenstadler, PharmD***

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion (cont.)

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss the benefits of daprodustat in adults with non-dialysis dependent (NDD) chronic kidney disease (CKD).

   Committee Discussion*: The Committee members generally agreed that the co-primary outcomes of the ASCEND-ND trial demonstrated non-inferiority of daprodustat to erythropoiesis stimulating agents (ESAs). One member noted that granting daprodustat approval would provide patients with NDD CKD another choice of therapies and highlighted the advantages of daprodustat such as its oral formulation and the convenience of patients not having to travel to a medical setting for treatment. Another member acknowledged these advantages but stated that the population the drug benefits is only a minority of patients with NDD CKD (e.g., those who live far from a medical center). Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION:** Discuss the benefits of daprodustat in adults with dialysis-dependent (DD) CKD.

   Several members agreed that the previously discussed benefits of an oral formulation may not necessarily be considered an advantage for the DD CKD population as this population is already going into a medical center three times a week for dialysis. One member added that an oral drug may have adherence concerns for this population, who are often patients on multiple medications due to multiple comorbidities. However, another member expressed the view that an oral medication would benefit the DD CKD population, pointing to the stress and burdens of current staffing shortages in dialysis units and suggested that offering an oral medication would enable staff to have more time to provide education and patient engagement. It was also noted that potential adverse effects of daprodustat, such as heart failure and gastric erosions, could be more easily managed in the DD population as they are being monitored on a routine basis. Another member again emphasized the importance of patient choice. Please see the transcript for details of the Committee's discussion.

3. **DISCUSSION:** Discuss the risks of daprodustat in adults with NDD CKD, including cardiovascular harm, gastrointestinal erosions/hemorrhage, and acute kidney injury.

   The Committee members agreed that non-inferiority was established for daprodustat compared to ESAs on the co-primary outcome of Major Adverse Cardiac Events (MACE), with several members acknowledging the difficulty in drawing definitive conclusions about the risks of gastrointestinal erosions and acute kidney injury (AKI) from the limited data presented. One member was not convinced by the data suggesting an increased risk of vascular access thrombosis due to the complexity of measuring such an outcome in a pre-dialysis population. Another member noted more sophisticated statistical methods would be needed to affirm a causal relationship on any of the secondary cardiovascular (CV) safety endpoints. A few members voiced concerns that the data presented may be underestimating the CV risk in this population, as the majority of patients with NDD CKD are not already on an ESA and daprodustat was compared against an ESA in the trial instead of placebo. In addition, it was noted that application of daprodustat in a real-world setting (where patients

with NDD CKD are not pre-selected trial participants who have scheduled monitoring of their hemoglobin levels) could potentially make CV risks significant in this population. A couple of members cited similar risks with other HIF-PHIs as a consideration, indicating the potential of a class effect and prior probability of these secondary CV safety signals as real risks in the NDD CKD population. However, another member countered that similar effects observed in other drugs of the same class does not necessarily imply a causal relationship and may have alternate explanations. Several members agreed that the data on risk of heart failure in the NDD CKD population is compelling, with a couple of members adding that heart failure can be managed with careful physician and patient involvement, and patients should have the choice to make an informed decision with their physicians. Please see the transcript for details of the Committee's discussion.

4. **DISCUSSION:** Discuss the risks of daprodustat in adults with DD CKD, including the risks of heart failure and gastrointestinal erosions/hemorrhage.

   Several committee members agreed that the data presented showed a more favorable safety profile for daprodustat in the DD CKD population, noting lower risk of CV harm among these patients in comparison to the NDD CKD population. A few members noted that frequent monitoring in the medical center may be contributing to their safety, thus reassuring them these safety concerns can be managed for the DD CKD population. However, one member commented that heart failure is a serious complication with high mortality rate, and while there are many therapies available to manage it as a chronic disease, none of those therapies have proven beneficial in the DD CKD population. Regarding the data on gastrointestinal erosions/hemorrhage, one member noted the curves separated quickly in the NDD CKD population in comparison to them separating after two years in the DD CKD population, with a smaller separation in the DD CKD population. Please see the transcript for details of the Committee's discussion.

5. **VOTE:** Do the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults not on dialysis?
   - Provide rationale for your vote.
   - If you voted No, provide recommendations for additional data and/or analyses that may support a positive benefit/risk assessment.

   Vote Result: Yes: 5 No: 11 Abstain: 0

   Committee Discussion: *The majority of the Committee members voted "No", indicating that the benefits of daprodustat do not outweigh its risks for the treatment of anemia due to CKD in adults not on dialysis. While the need and benefit of an oral treatment option for the NDD CKD population was acknowledged, committee members who voted "No" expressed discomfort with the uncertainty surrounding the risk of CV safety endpoints in this population, citing the increased risk of some CV outcomes in comparison to ESAs, and a potential heart failure safety signal as major concerns. Recommendations for additional data and/or analyses that may support a positive benefit/risk assessment included: conducting a metanalysis of all HIF-PHIs to determine if there are any class effects, studies comparing daily versus less frequent dosing (e.g. every other day), more data from the United States*

population (particularly in the African American subgroup), expanded patient-reported outcome (PRO) endpoints and analysis, comparison of daprodustat against placebo, development of risk mitigation strategies, identification of low risk populations, and additional studies to clarify heart failure risk with daprodustat in the NDD CKD population.

Committee members who voted "Yes" pointed to the need for an oral formulation and its potential to increase patient access to care. While several of these members acknowledged the potential safety concerns previously discussed, they were not convinced that the evidence presented adequately established the safety risks of daprodustat. A couple of members agreed that the potential risks of daprodustat could be managed by physicians with appropriate education and safety measures, including boxed warnings for individuals with a history of heart failure or gastrointestinal ulcers, restricting refills and requiring documentation of hemoglobin levels. Please see the transcript for details of the Committee's discussion.

6. **VOTE:** Do the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults on dialysis?
   - Provide rationale for your vote.
   - If you voted No, provide recommendations for additional data and/or analyses that may support a positive benefit/risk assessment.

   Vote Result: Yes: 13 No: 3 Abstain: 0

   Committee Discussion: *The majority of the committee members voted "Yes," reflecting agreement that the benefits of daprodustat outweigh its risks for the treatment of anemia due to CKD in adults on dialysis. Several members noted that the totality of evidence demonstrated that efficacy of daprodustat was met, and safety signals appeared more favorable in the DD CKD population compared to the NDD CKD population. Many members acknowledged the ability to carefully monitor this drug in dialysis centers as a consideration in their vote, and others voiced support for patient choice. Additional studies looking at heart failure in this population, as well as a pharmacovigilance plan for daprodustat were recommended.*

   Three members voted "No," voicing uncertainty with daprodustat's safety and cited the need for additional information, particularly an analysis of potential class effects and additional PRO data. Another member also noted the risk of heart failure hospitalizations and lack of effective heart failure therapy for the DD CKD population as a consideration in their vote, as well as the potential for less benefit of an oral drug in this population. Please see the transcript for details of the Committee's discussion.

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