December 14, 2022

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Ann Farrell, M.D.
Director, Division of Non-Malignant Hematology
Office of Cardiology, Hematology, Endocrinology and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: New Drug Application (NDA) 216951 for daprodustat and the worrying class effects of this and other hypoxia-inducible factor prolyl hydroxylase inhibitors

Dear Dr. Cavazzoni and Dr. Farrell:

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, is writing to strongly urge the Food and Drug Administration (FDA) not to approve new drug application (NDA) 216951 submitted by GlaxoSmithKline for daprodustat, an oral hypoxia-inducible factor prolyl hydroxylase (HIF-PHD) inhibitor for the treatment of anemia due to chronic kidney disease (CKD) in adult patients not on dialysis and on dialysis. Daprodustat was the subject of the October 26, 2022, meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC).[1] This letter supplements Public Citizen's testimony presented at that meeting during the open public hearing.

However, because our concerns about daprodustat's safety profile are also relevant to the safety risks of other HIF-PHD inhibitors, such as roxadustat, which was the subject of the July 2021 CRDAC meeting[2] and was subsequently rejected by the FDA, and vadadustat, for which the

[1] Food and Drug Administration. FDA briefing document, NDA 216951, drug name: daprodustat; Cardiovascular and Renal Drugs Advisory Committee meeting. October 26, 2022. https://www.fda.gov/media/162521/download. Accessed December 14, 2022.
[2] Food and Drug Administration. FDA briefing document, Cardiovascular and Renal Drugs Advisory Committee meeting, July 15, 2021, Roxadustat. https://www.fda.gov/media/150728/download. Accessed on December 14, 2022.

FDA highlighted safety concerns in a complete response letter (CRL),[3] Public Citizen urges the FDA not to approve any NDA for drugs in this class for the treatment of anemia due to CKD in adult patients not on dialysis and on dialysis. The available information on HIF-PHD inhibitors, including the data presented at the two CRDAC meetings, discussed in more detail below, indicate that this new class of drugs does not offer patients any truly unique benefits and puts them at additional risk of serious adverse effects compared with currently available FDA-approved treatments.

Context and regulatory background

Current FDA-approved treatments for anemia in patients with CKD include erythropoiesis-stimulating agents (ESAs), which carry a black-box warning for increased mortality and serious cardiovascular and thromboembolic events, including stroke and myocardial infarction, as well as warnings for hypertension, seizures and thrombotic events.[4] Due to these serious safety concerns, there is an unmet need for new treatment options that are safe and effective for treating anemia in patients with CKD.

However, the available data on HIF-PHD inhibitors indicate that their safety profile, compared with placebo (and, more importantly, compared with ESAs), is concerning and that this new class of drugs is not a safe treatment alternative for patients. The serious additional safety risks present in HIF-PHD inhibitors were repeatedly acknowledged by the FDA, including the following examples:

- On July 15, 2021, CRDAC met to discuss the HIF-PHD inhibitor roxadustat (NDA 213805).[5] Due to concerns about the serious additional safety issues posed by roxadustat for patients on dialysis and those not on dialysis, Public Citizen sent written comments to the FDA on July 14, 2021, strongly opposing the approval of this drug.[6] The advisory committee shared our concerns over the drug's safety and, because of these safety concerns, voted 13-1 against approval for the non–dialysis-dependent patient population and 12-2 against approval for patients on dialysis.[7] On August 11, 2021, the sponsor,

[3] Akebia Therapeutics. Press Release. Akebia therapeutics receives complete response letter from the FDA for vadadustat for the treatment of anemia due to chronic kidney disease in adult patients. https://ir.akebia.com/news-releases/news-release-details/akebia-therapeutics-receives-complete-response-letter-fda. Accessed December 14, 2022.
[4] Food and Drug Administration. FDA briefing document, NDA 216951, drug name: daprodustat; Cardiovascular and Renal Drugs Advisory Committee meeting. October 26, 2022. https://www.fda.gov/media/162521/download. Accessed December 14, 2022.
[5] Food and Drug Administration. FDA briefing document, Cardiovascular and Renal Drugs Advisory Committee meeting, July 28, 2021, Roxadustat. https://www.fda.gov/media/150728/download. Accessed on December 14, 2022.
[6] Public Citizen. Comments submitted to Docket No. FDA-2021-N-0441 for the Cardiovascular and Renal Drugs Advisory Committee Meeting on July 15, 2021. https://www.citizen.org/wp-content/uploads/2595.pdf. Accessed December 14, 2022.
[7] Food and Drug Administration. Final summary minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting. July 15, 2021. https://www.fda.gov/media/151422/download. Accessed December 14, 2022.

FibroGen, announced that it had received a CRL from the FDA stating that the agency "will not approve the roxadustat NDA in its present form."[8]

- On March 30, 2022, the sponsor of another drug from the same class, vadadustat, announced that it had received a CRL stating that the FDA had expressed safety concerns and that the available data "do not support a favorable benefit-risk assessment."[9] For this NDA, no CRDAC meeting was convened.

- On October 26, 2022, the CRDAC was convened to discuss daprodustat (NDA 216951),[10] and because of the concerning safety profile of this drug compared with ESAs, Public Citizen testified during the open public hearing at this meeting against approval for patients on dialysis and those not on dialysis.[11] Although the advisory committee shared our concerns and voted 11-5 against approval for patients not on dialysis, the panel voted 13-3 in favor of approval for patients on dialysis.[12]

Safety concerns of HIF-PHD inhibitors

All clinical trials discussed below tested the efficacy and safety of the HIF-PHD inhibitors roxadustat, vadadustat, and daprodustat against either placebo or an ESA.[13,14,15,16] Although these drugs demonstrated efficacy, the safety profile of drugs in this class is concerning because subjects, both in the not-on-dialysis population (NDD) and in the on-dialysis population (DD), were exposed to substantial additional safety risks.

---

[8] FibroGen. Press Release. FibroGen receives complete response letter from the FDA for roxadustat for anemia of chronic kidney disease. https://fibrogen.gcs-web.com/news-releases/news-release-details/fibrogen-receives-complete-response-letter-fda-roxadustat-anemia. Accessed December 14, 2022.

[9] Akebia Therapeutics. Press Release. Akebia Therapeutics receives complete response letter from the FDA for vadadustat for the treatment of anemia due to chronic kidney disease in adult patients. https://ir.akebia.com/news-releases/news-release-details/akebia-therapeutics-receives-complete-response-letter-fda. Accessed December 14, 2022.

[10] Food and Drug Administration. FDA briefing document, NDA 216951, drug name: daprodustat; Cardiovascular and Renal Drugs Advisory Committee meeting. October 26, 2022. https://www.fda.gov/media/162521/download. Accessed December 14, 2022.

[11] Public Citizen. Testimony before the FDA's Cardiovascular and Renal Drugs Advisory Committee regarding daprodustat for the treatment of anemia due to chronic kidney disease. https://www.citizen.org/article/testimony-before-the-fdas-cardiovascular-and-renal-drugs-advisory-committee-regarding-daprodustat-for-the-treatment-of-anemia-due-to-chronic-kidney-disease/. Accessed on December 14, 2022.

[12] Food and Drug Administration. Final summary minutes of the Cardiovascular and Renal Drugs Advisory Committee meeting. October 26, 2022. https://www.fda.gov/media/163406/download. Accessed December 14, 2022.

[13] Food and Drug Administration. FDA briefing document, NDA 216951, drug name: daprodustat; Cardiovascular and Renal Drugs Advisory Committee meeting. October 26, 2022. https://www.fda.gov/media/162521/download. Accessed December 14, 2022.

[14] Food and Drug Administration. FDA briefing document, Cardiovascular and Renal Drugs Advisory Committee meeting, July 15, 2021, Roxadustat. https://www.fda.gov/media/150728/download. Accessed on December 14, 2022.

[15] Eckardt KU, Agarwal R, Aswad A, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. *N Engl J Med*. 2021;384(17):1601-1612.

[16] Chertow GM, Pergola PE, Farag YM, et al. Vadadustat in patients with anemia and non–dialysis-dependent CKD. *N Engl J Med*. 2021;384(17):1589-1600.

This was not only true compared with placebo, but much more concerningly also compared with ESAs. Due to these additional safety concerns, Public Citizen shares the FDA's assessment that the increase in the risks of these drugs "beyond that seen with the ESAs is concerning."[17]

Patients on dialysis (DD)

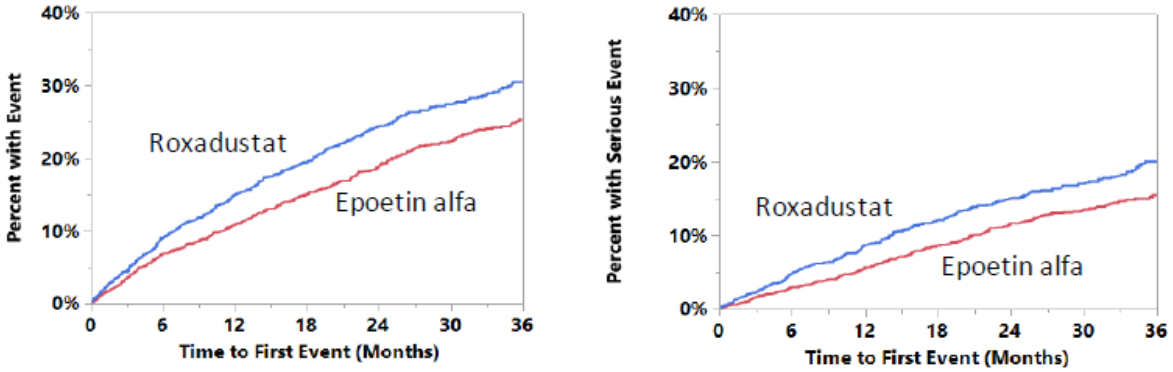
In the DD population, **roxadustat** was compared with an FDA-approved ESA in three randomized, open-label clinical trials, in which 18% of subjects for all three trials combined were Black, and in a fourth study (study 613), which was conducted only in Europe, using a comparator ESA in some subjects that is not licensed in the U.S., and in which only 1.4% of the subjects were Black.[18]

Across the three trials that compared roxadustat only with FDA-approved ESAs, the on-study sensitivity analysis showed that the hazard ratio (HR) for time to a first major adverse cardiovascular event (MACE; the composite of death from any cause, a nonfatal myocardial infarction, or a nonfatal stroke) in subjects in the roxadustat arms was 1.14 (95% confidence interval [CI] 1.00, 1.30).[19] The FDA also highlighted hypoglycemia, gastroenteritis, and pancreatitis as additional safety concerns in the briefing materials for the July 15, 2021, CRDAC meeting.[20]

The data from these three studies also demonstrated that subjects taking roxadustat were more likely to have thrombosis (7.27 events per 100 patient-years [PY]) than those in the ESA arms (5.37 events per PY), resulting in a relative risk of 1.4; in particular, the roxadustat subjects had a higher rate of deep vein thrombosis (0.72 events per 100 PY vs. 0.19 events per 100 PY, a relative risk of 3.9).[21] Because of the importance of these adverse effects, the FDA performed a Kaplan-Meier time-to-first-thrombotic-event analysis for these three studies for all (left panel) and serious (right panel) events (see Figure 22 below, excerpted from the FDA's briefing materials).[22] These analyses revealed that the excess risk of thrombotic events in roxadustat subjects accrued continuously throughout the three studies.

[17] Food and Drug Administration. FDA briefing document, NDA 216951, drug name: daprodustat; Cardiovascular and Renal Drugs Advisory Committee meeting. October 26, 2022. https://www.fda.gov/media/162521/download. Accessed December 14, 2022.
[18] Food and Drug Administration. FDA briefing document, Cardiovascular and Renal Drugs Advisory Committee meeting, July 15, 2021, Roxadustat. https://www.fda.gov/media/150728/download. Accessed on December 14, 2022.
[19] *Ibid*.
[20] *Ibid*.
[21] *Ibid*.
[22] *Ibid*.

Figure 22: Time to First Thrombotic Event—All Events (Left); Serious Events (Right) for the DD Population (Studies 002, 063, and 064); OT+7 Ascertainment Window



Source: FDA analysis

According to the FDA, the safety signals from study 613 were also "quite concerning."[23] For example, subjects in the roxadustat arms had a relative risk of 2.0 for both congestive heart failure (7.5% vs. 3.8%) and arteriovenous fistula thrombosis (7% vs. 3.6%) and a relative risk of 1.2 (12.6% vs. 10.2%) for thrombosis compared with subjects in the ESA arms.[24]

For **vadadustat**, DD patients were enrolled in two open-label, randomized trials comparing the HIF-PHD inhibitor with an ESA, in which 24% of the subjects were Black.[25]Although the pooled data across the two trials showed that vadadustat was noninferior to the ESA in all DD subjects regarding cardiovascular safety, it is important to note that Black subjects had a higher risk of a first MACE occurring, with an HR of 1.17 (95% CI 0.88, 1.56).

For **daprodustat**'s NDA for DD patients, the FDA considered one open-label trial that randomized subjects, 15% of whom were Black, to either the HIF-PHD inhibitor or an ESA.[26] Subjects on dialysis taking daprodustat had a higher risk of hospitalization for heart failure, with 3.3 events per 100 PY, compared with 3.0 events per 100 PY in subjects in the ESA arm, an HR of 1.10 (95% CI 0.84, 1.45). This risk was even higher for those subjects who had a history of heart failure, with an HR of 1.44 (95% CI 0.97, 2.14).[27] Daprodustat subjects also had a higher risk of serious gastric erosions than the ESA subjects, with an HR of 1.16 (95% CI 0.78, 1.73).[28]

[23] *Ibid*.
[24] *Ibid*.
[25] Eckardt KU, Agarwal R, Aswad A, et al. Safety and efficacy of vadadustat for anemia in patients undergoing dialysis. *N Engl J Med*. 2021;384(17):1601-1612.
[26] Food and Drug Administration. FDA briefing document, NDA 216951, drug name: daprodustat; Cardiovascular and Renal Drugs Advisory Committee meeting. October 26, 2022. https://www.fda.gov/media/162521/download. Accessed December 14, 2022.
[27] *Ibid*.
[28] *Ibid*.

Although the data across these trials in the DD population consistently show serious additional safety risks for subjects taking an HIF-PHD inhibitor as compared with those taking placebo or an ESA, the safety risks for the NDD population are even more worrisome.

Patients not on dialysis (NDD)

In the NDD patient population, the HIF-PHD inhibitor **roxadustat** was compared with placebo in three randomized, double-blind trials and to an ESA in one randomized, open-label trial (study 610). Across the three placebo-controlled trials, 8% of subjects were Black, and in the active comparator trial, which was conducted entirely in Europe, only 1.6% of subjects were Black.[29]

As pointed out in the FDA briefing materials for the for the July 15, 2021, CRDAC meeting, compared with placebo-arm subjects, roxadustat-arm subjects had a higher incidence of MACE, at least in some analyses. For example, in the on-treatment plus seven days analysis, the HR for MACE was 1.38 (95% CI 1.11, 1.70).[30]

There were also several other serious safety concerns for roxadustat compared with placebo: with 3.62 events per 100 PY and 2.50 events per 100 PY, respectively, subjects taking the HIF-PHD inhibitor had a relative risk of serious thrombotic events of 1.45.[31] The relative risks of 6.0 for deep vein thrombosis and 4.8 for pulmonary embolism for roxadustat compared with placebo were especially troubling. Compared with placebo, subjects in the roxadustat arm also had higher risks of acute kidney injury and infections.[32]

In the active comparator study 610, subjects taking roxadustat also had a higher incidence of several adverse events compared with those taking an ESA. For example, the relative risk of serious thrombosis events was 1.41 in the HIF-PHD inhibitor arm subjects (6.2%) compared with subjects in the ESA group (4.4%).[33] Subjects in the roxadustat also had higher relative risks of many adverse events than those in the ESA arm, including hyperphosphatemia, muscle spasms, arrhythmia, headache, and hypotension, which, according to the FDA, were "not heretofore observed" for ESAs.[34]

The safety concerns for **vadadustat** in the NDD population were even more concerning, as this HIF-PHD inhibitor did not meet the noninferiority margin for a first MACE compared with an ESA.[35] Vadadustat was compared with an ESA in two randomized, open-label trials, in which 17% of enrolled subjects were Black.[36] A first MACE occurred in 22% of subjects taking vadadustat, compared with 19.9% of subjects in the ESA arm, an HR of 1.17 (95% CI 1.01,

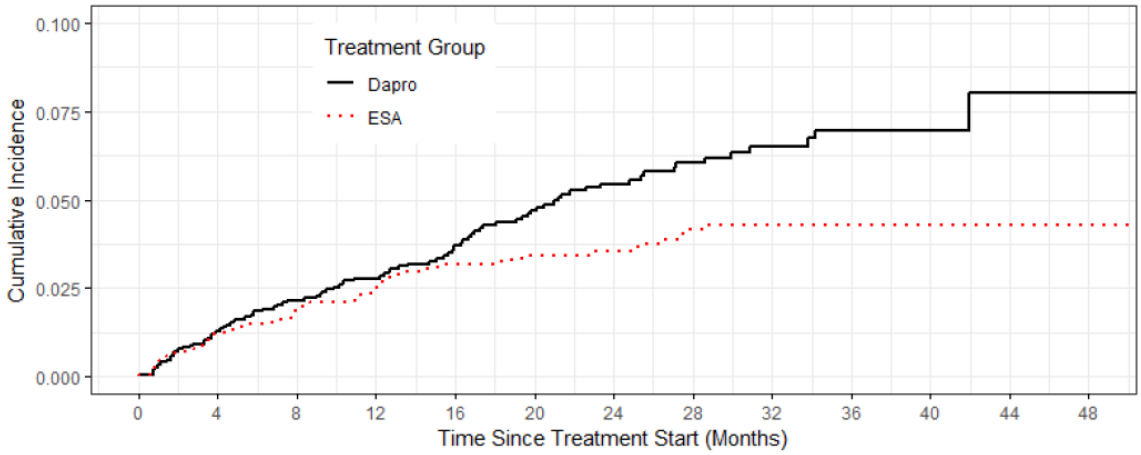
[29] Food and Drug Administration. FDA briefing document, Cardiovascular and Renal Drugs Advisory Committee meeting, July 15, 2021, Roxadustat. https://www.fda.gov/media/150728/download. Accessed on December 14, 2022.
[30] *Ibid*.
[31] *Ibid*.
[32] *Ibid*.
[33] *Ibid*.
[34] *Ibid*.
[35] Chertow GM, Pergola PE, Farag YM, et al. Vadadustat in patients with anemia and non–dialysis-dependent CKD. *N Engl J Med*. 2021;384(17):1589-1600.
[36] *Ibid*.

1.36). The incidence of first expanded MACE (MACE plus hospitalization for either heart failure or a thromboembolic event) was also higher for subjects in the vadadustat group than those in the ESA group (HR 1.11; 95% CI 0.97, 1.27). Nonfatal myocardial infarction occurred in 3.9% of subjects taking the HIF-PHD inhibitor, compared with 2.8% of subjects in the ESA arm, and nonfatal stroke also occurred more often in subjects taking vadadustat (2% vs. 1.6%).[37]

The FDA briefing materials for the October 26, 2022, CRDAC meeting regarding **daprodustat** assessed one randomized, open-label trial comparing the HIF-PHD inhibitor to an ESA in the NDD patient population.[38] Black subjects made up 9.5% of the enrolled subjects.[39] As with roxadustat and vadadustat, the data showed serious additional safety signals for this HIF-PHD inhibitor.

For example, subjects in the daprodustat arm had a higher risk of hospitalization for heart failure than those receiving an ESA (HR 1.22; 95% CI 0.95, 1.56), a risk that was even higher for subjects with a history of heart failure (HR 1.51; 95% CI 1.01, 2.25).[40] There were also higher incidence rates of serious esophageal and gastric erosions in subjects taking daprodustat than in those in the ESA arm, with an HR of 1.96 (95% CI 1.24, 3.09), the risk of which appeared to accumulate constantly over time.[41] Subjects taking daprodustat also had an increased risk of acute kidney injury than those in the ESA group, regardless of subjects' history of heart failure, with a relative risk of 1.47 (95% CI 1.07, 2.00). The cumulative incidences over 48 months are shown in Figure 8 below, excerpted from the FDA review.[42]

Figure 8. Time to First TESAE of Acute Kidney Injury (Narrow FMQ), (On-Study Analysis)



[37] *Ibid.*
[38] Food and Drug Administration. FDA briefing document, NDA 216951, drug name: daprodustat; Cardiovascular and Renal Drugs Advisory Committee meeting. October 26, 2022. https://www.fda.gov/media/162521/download. Accessed December 14, 2022.
[39] *Ibid.*
[40] *Ibid.*
[41] *Ibid.*
[42] *Ibid.*

Subjects taking daprodustat also had a higher risk of MACE in some analyses. For example, an on-treatment + 28 days analysis showed that compared with subjects in the ESA group, those taking the HIF-PHD inhibitor had a higher incidence of MACE, with an HR of 1.40 (95% CI 1.17, 1.68), with "consistently increased risk estimates across different CV endpoints," including for stroke (HR 1.33; 95% CI 0.85,2.07), thromboembolic events (HR 1.27; 95% CI 0.88, 1.84), and vascular access thrombosis (HR 1.49; 95% CI 0.94, 2.35).[43]

The trend of increased risk estimates was particularly pronounced in the U.S. subgroup, where subjects taking daprodustat had elevated HRs for several cardiovascular outcomes, including cardiovascular mortality, myocardial infarction, and thromboembolic events.[44]

Additional data on safety risks of HIF-PHD inhibitors

The safety risks of this class of drugs, which have been demonstrated for both the NDD and DD patient populations, also have been shown to be of concern in a meta-analysis with a total of over 13,000 patients across 30 trials with a total of 38 comparisons.[45] Of note, most trials in the DD patient population included in this meta-analysis were ESA-controlled, whereas most trials in the NDD patient population compared an HIF-PHD inhibitor with a placebo.

The meta-analysis showed that HIF-PHD inhibitors increased the risks for patients not only compared with placebo, but also compared with ESAs. For example, patients taking HIF-PHD inhibitors have been shown to have a higher risk of thrombosis, with a risk ratio of 1.31 (95% CI 1.05, 1.63, $p = 0.02$) compared with ESAs.

That the safety concerns are a class effect is further demonstrated by the fact that this meta-analysis included studies on a variety of HIF-PHD inhibitors, such as those discussed above (roxadustat, vadadustat, and daprodustat) as well as molidustat, desidustat, and enarodustat.

Summary and conclusion

The approval of daprodustat or any other HIF-PHD inhibitor with a similarly concerning safety profile for patients on dialysis or not on dialysis would raise serious public health concerns.

(1) An FDA approval of daprodustat would mean that a drug would become widely available that has no truly unique benefits for patients. Even the potential benefit of the oral administration of HIF-PHD inhibitors was questioned by the FDA in their briefing materials on daprodustat. They noted that without adequate monitoring, the oral route could even have "potential downsides" [46] for this class of drugs, and that especially for patients who are already undergoing hemodialysis, any advantage may be lost. In fact, the

[43] *Ibid*.
[44] *Ibid*.
[45] Chen H, Cheng Q, Wang J, et al. Long-term efficacy and safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in anaemia of chronic kidney disease: A meta-analysis including 13,146 patients. *J Clin Pharm Ther*. 2021;46(4):999-1009.
[46] Food and Drug Administration. FDA briefing document, NDA 216951, drug name: daprodustat; Cardiovascular and Renal Drugs Advisory Committee meeting. October 26, 2022. https://www.fda.gov/media/162521/download. Accessed December 14, 2022.

FDA stated that this drug "did not demonstrate any other benefits… on how patients feel, function, or survive."[47]

(2) Approval of daprodustat (or any other HIF-PHD inhibitor) would mean that this drug could be used in unintended ways. Since this drug would be the first orally administered treatment option available, this is of particular concern. Unlike patients already on dialysis who are frequently monitored or patients who are part of a clinical trial, in practice patients who could be prescribed this drug will be followed much less often – bolstered by the myth that the FDA would not have approved the drug if it were not safe enough for them.

(3) There are also several general limitations across many of the trials discussed above that question the safety of this class of drugs. For instance, the low enrollment of Black patients in several of these trials is concerning, especially since CKD in the U.S. is more prevalent among Black adults.[48] Moreover, several trials were relatively short, thus not providing enough long-term data to monitor patients for potential oncogenic and other long-term adverse events.[49] In fact, several "theoretical concerns" for HIF-PHD inhibitors that have not been addressed in the clinical trials discussed above could have been missed due to the short follow-up. These concerns include worsening diabetic retinopathy, exacerbation of pulmonary arterial hypertension, enhanced progression of polycystic kidney disease, increased angiogenesis, and worsening renal progression due to kidney fibrosis.[50]

Public Citizen therefore urges the FDA not to approve daprodustat for patients on dialysis or patients not on dialysis for the treatment of anemia in CKD. Because the serious safety concerns seem to be a class effect for all HIF-PHD inhibitors, we also urge the FDA not to approve any other drugs of this class.

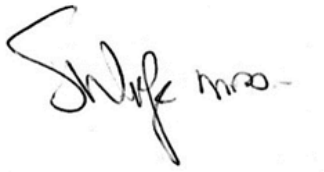
Thank you for considering our comments on this important matter.

Sincerely,

Nina Zeldes, Ph.D.
Health Researcher
Public Citizen's Health Research Group

[47] *Ibid.*
[48] Centers for Disease Control and Prevention. Chronic Kidney Disease in the United States, 2021. July 12, 2022.https://www.cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html. Accessed on December 14, 2022.
[49] Doggrell SA. Are there advantages of daprodustat over erythropoiesis-stimulating agents (ESAs) in treating anemia associated with chronic kidney disease (CKD)? *Expert Opin Pharmacother.* 2022;23(7):769-773.
[50] Macdougall IC. Hypoxia-inducible factor prolyl hydroxylase enzyme inhibitors: ready for primetime?. *Curr Opin Nephrol Hypertens.* 2022; 31(5):399-405.

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group



Sidney M. Wolfe, M.D.
Founder and Senior Adviser
Public Citizen's Health Research Group