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Division of Dockets Management
Food and Drug Administration
(HFA-305) Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Citizen Petition for FDA to Require Adequate Cardiovascular Safety and All-Cause Mortality Data Be Submitted to FDA for Review Before Approving Roxadustat (FG-4592) for the Treatment of Anemia in Patients with Chronic Kidney Disease (CKD), and Require a Boxed Warning

Dear Sir/Madam:

The undersigned submits this petition, on behalf of a client, pursuant to the Federal Food, Drug, and Cosmetic Act and 21 C.F.R. § 10.30, requesting that the Commissioner decline to approve any New Drug Application (NDA) for roxadustat (FG-4592) unless and until the applicant submits additional data demonstrating that the potential safety risks of roxadustat do not outweigh its therapeutic benefit, *i.e.,* when indicated for use in chronic kidney disease (CKD) patients who are not on dialysis (ND-CKD) and in dialysis-dependent CKD (DD-CKD) patients who are stable on dialysis.

Phase III clinical program data released by the roxadustat NDA applicant demonstrate that roxadustat poses an increased risk of adverse cardiovascular outcomes and mortality in comparison to the current standard of care, in particular, for patients who are stable on dialysis. Moreover, data released to date fail to demonstrate that roxadustat provides a meaningful treatment benefit over the existing standard of care for ND-CKD patients. Roxadustat has only been demonstrated to be non-inferior to placebo in this population, however, any meaningful correction of anemia would be expected to produce better cardiovascular safety and all-cause mortality outcomes than no anemia correction at all.

FDA has required similarly situated applicants to provide additional evidence of safety when the applicants' Phase III clinical program data, or post-marketing data, demonstrated the applicants' products posed an increased risk of adverse cardiovascular outcomes and/or mortality in certain

patient subpopulations. FDA has also used its other authorities to ensure patients are adequately protected against the cardiovascular and all-cause mortality risks potentially posed by these products, including by imposing Risk Evaluation and Mitigation Strategies (REMS), convening Advisory Committees, requiring the product to be approved only as an alternative to other treatments, and requiring the drug product's label to bear a boxed warning. The undersigned respectfully requests that FDA apply the same level of scrutiny and rigor to its review and approval of the roxadustat NDA that it has applied to these similarly situated products, to avoid arbitrary and capricious regulatory action under the Administrative Procedure Act.[1]

Specifically, to ensure both consistency and protection of the public health, the undersigned respectfully requests that FDA require the roxadustat NDA applicant to submit additional data and analysis to FDA for review before FDA approves the roxadustat NDA for use in ND-CKD patients or DD-CKD patients who are stable on dialysis. Also, if roxadustat poses risks for all-cause mortality or major adverse cardiovascular events that are similar to, or greater than, those posed by the current standard of care, the undersigned requests that FDA require roxadustat's label bear a boxed warning to appropriately alert consumers and healthcare professionals to the drug's potential safety risks.

I. Actions Requested

The undersigned hereby requests that FDA:

1. Decline to approve the roxadustat NDA unless and until the applicant submits additional data demonstrating that the drug's safety risks do not outweigh its potential therapeutic benefit, *i.e.*, when indicated for use in ND-CKD patients and DD-CKD patients who are stable on dialysis.

    a. To demonstrate roxadustat is adequately safe for use in ND-CKD patients, we request FDA require the applicant to conduct a head-to-head clinical trial that is adequately powered to demonstrate non-inferiority of roxadustat to the current standard of care on major adverse cardiovascular events and all-cause mortality.

    b. FDA should also require the applicant to submit for FDA's review a sub-analysis of all available data from the applicant's Phase III clinical program that evaluates all-cause mortality outcomes in DD-CKD patients who are stable on dialysis to ensure roxadustat is non-inferior to the standard of care.

2. Require roxadustat's approved label to bear a boxed warning if the risk for all-cause mortality, or major adverse cardiovascular events, is similar or worse in comparison to the current standard of care.

[1] *See Bracco Diagnostics, Inc. v. Shalala,* 963 F. Supp. 20 (D.D.C. 1997) ("Government is at its most arbitrary when it treats similarly situated people differently.").

II. Statement of Grounds

A. Background

1. Anemia in Patients with Chronic Kidney Disease (CKD)

According to Centers for Disease Control and Prevention (CDC) data, an estimated 15% of U.S. adults aged 18 years or older (approximately 37 million people) have CKD.[2] Anemia, a condition which results from a lack of healthy red blood cells (RBCs) (and is typically detected by low blood hemoglobin (Hb) concentration),[3] is a common complication in CKD patients, and its prevalence increases with CKD progression.[4]

One major cause of anemia in CKD patients is erythropoietin production deficiency due to kidney deterioration; however, other factors may contribute as well, including decreased RBC survival, iron and folate deficiencies, and the accumulation of toxic inhibitors of erythropoiesis.[5] CKD anemia can be associated with an increased risk of hospitalization, cardiovascular complications, and death,[6] and also frequently causes significant fatigue, cognitive dysfunction, and a reduced quality of life.[7]

2. Current Standard of Care

The current standard of care for the treatment of anemia in CKD patients is iron and erythropoiesis stimulating agents (ESAs).[8] Although life-threatening severe anemia in CKD patients can be treated with blood transfusions,[9] such transfusions reduce a patient's opportunity for kidney transplant, increase risk of infections, and carry the risk of complications such as heart failure and allergic reactions.[10] Therefore, transfusions should be avoided where clinically possible.[11]

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[2] CDC, *Chronic Kidney Disease in the United States, 2019* (2019), https://www.cdc.gov/kidneydisease/pdf/2019_National-Chronic-Kidney-Disease-Fact-Sheet.pdf **(Exhibit 1)**.

[3] Blood Hb serves as the key indicator for anemia because it can be directly measured and has an international standard. National Institute for Health and Care Excellence (NICE) National Clinical Guideline Centre, *Anaemia Management in Chronic Kidney Disease: Partial Update 2015* (2015), https://www.nice.org.uk/guidance/ng8/evidence/full-guideline-pdf-70545136 **(Exhibit 2)**.

[4] McClellan, W., Aronoff, S. L., Bolton, W. K., Hood, S., Lorber, D. L., Tang, K. L., Tse, T. F., Wasserman, B., & Leiserowitz, M. (2004). The prevalence of anemia in patients with chronic kidney disease. *Current Medical Research and Opinion*, *20*(9), 1501–1510. https://doi.org/10.1185/030079904X2763.

[5] *Id.*

[6] Babitt, J. L. & Lin, H. Y. (2012). Mechanisms of anemia in CKD. *Journal of the American Society of Nephrology: JASN*, *23*(10), 1631–1634. https://doi.org/10.1681/ASN.2011111078.

[7] KDOQI, & National Kidney Foundation. (2006). KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. *American Journal of Kidney Diseases*, *47*(5 Suppl 3), S11–S145. https://www.ajkd.org/issue/S0272-6386(06)X0211-1.

[8] Kidney Disease Improving Global Outcomes (KDIGO). (2012). KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney International Supplements*, *2*(4), 279-335. https://doi.org/10.1038/kisup.2012.37 (hereinafter, "KDIGO 2012 Guidelines").

[9] Begum, S. & Latunde-Dada, G. O. (2019). Anemia of inflammation with an emphasis on chronic kidney disease. *Nutrients*, *11*(10), 2424. https://doi.org/10.3390/nu11102424.

[10] Fox, K. M., Yee, J., Cong, Z., Brooks, J. M., Petersen, J., Lamerato, L., & Gandra, S. R. (2012). Transfusion burden in non-dialysis chronic kidney disease patients with persistent anemia treated in routine clinical practice: A retrospective observational study. *BMC Nephrology*, *13*, 5. https://doi.org/10.1186/1471-2369-13-5.

[11] *See* KDIGO 2012 Guidelines, *supra* note 8, at 299 ("avoidance of transfusions is important . . .").

In general, the treatment of anemia in CKD patients is driven by a desire to improve clinical outcomes and not just improve patients' Hb levels, the latter being simply a laboratory parameter.[12] Specifically, anemia correction in CKD patients should translate to improved cardiovascular outcomes[13] and decreased need for blood transfusions (and avoidance of the clinical risks associated with those transfusions).[14]

a) Iron Supplementation

Iron deficiency is a common cause of chronic or worsening anemia in CKD patients.[15] As such, iron therapy has been used for many years to manage anemia in this population (with or without concomitant ESA treatment, as discussed further below). According to the widely accepted Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in Chronic Kidney Disease, published in 2012, iron (administered intravenously for all adult anemic CKD patients or alternatively orally for ND-CKD patients) is recommended in the treatment of anemia in CKD patients to increase Hb levels without the use of ESAs, to increase iron stores prior to starting ESA treatment (or to enhance the response to ESA treatment once started), or to correct iron deficiency resulting from ESA treatment.[16] Several trials confirm the benefit of intravenous (IV) iron for anemia correction in ND-CKD and DD-CKD patients.[17] In the U.S., FDA has approved a number of IV iron products as first line treatments for ND-CKD patients with iron deficiency anemia.[18]

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[12] Manns, B. J. & Tonelli, M. (2012). The new FDA labeling for ESA–Implications for patients and providers. *Clinical Journal of the American Society of Nephrology: CJASN*, *7*(2), 348–353. https://doi.org/10.2215/CJN.09960911 ("Farther down the hierarchy of outcomes are those outcomes that are less relevant to patients (but on which the nephrology community has traditionally based much of our clinical decision making), including unvalidated surrogate endpoints such as achieved hemoglobin level.").

[13] Locatelli, F., de Francisco, A., Deray, G., Fliser, D., Armstrong, G., Dougherty, F. C., & Ehrhard, P. (2014). Mortality and cardiovascular morbidity associated with haemoglobin levels: A pooled analysis of randomised controlled trials. *Nephron Clinical Practice*, *128*(3-4), 323–332. https://doi.org/10.1159/000366478 (All-cause mortality was associated with Hb below 10 g/dl, decrease from stable baseline Hb by more than 1 g/dl, Hb decline >1.5 g/dl/4 weeks and increased Hb variability. The greatest risk for cerebrovascular events and myocardial infarction was found with a decrease from baseline >1 g/dl in the month preceding the event as well as with a last Hb value <10 g/dl before the event); Kovesdy, C. P., Trivedi, B. K., Kalantar-Zadeh, K., & Anderson, J. E. (2006). Association of anemia with outcomes in men with moderate and severe chronic kidney disease. *Kidney International*, *69*(3), 560–564. https://doi.org/10.1038/sj.ki.5000105 ("Anemia (especially time-averaged Hgb <120 g/l) is associated with both higher mortality and increased risk of ESRD in male patients with CKD not yet on dialysis."); Jurkovitz, C. T., Abramson, J. L., Vaccarino, L. V., Weintraub, W. S., & McClellan, W. M. (2003). Association of high serum creatinine and anemia increases the risk of coronary events: Results from the prospective community-based atherosclerosis risk in communities (ARIC) study. *Journal of the American Society of Nephrology: JASN*, *14*(11), 2919–2925. https://doi.org/10.1097/01.asn.0000092138.65211.71 (high serum creatinine (Scr) is associated with almost a threefold risk of coronary heart disease among middle-aged people with anemia, whereas no increased risk is found in people with high Scr in the absence of anemia).

[14] *See* KDIGO 2012 Clinical Guidelines, *supra* note 8.

[15] *See* KDIGO 2012 Clinical Guidelines, *supra* note 8, at 288.

[16] Roger, S. D. (2017). Practical considerations for iron therapy in the management of anaemia in patients with chronic kidney disease. *Clinical Kidney Journal*, *10* (Suppl 1), i9–i15. https://doi.org/10.1093/ckj/sfx100.

[17] *Id.*

[18] *See e.g.,* FDA, Label for Feraheme (ferumoxytol injection) (rev. Sept. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022180s024lbl.pdf ("Feraheme is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients with chronic kidney disease (CKD)."); FDA, Label for Venofer (iron sucrose) (rev. Sept. 2020), https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021135s036lbl.pdf

b) Erythropoiesis Stimulating Agents

Many CKD patients are deficient in erythropoietin (a hormone synthesized by the kidney that is responsible for RBC maturation), predisposing them to erythropoietin-deficient anemia.[19] The low erythropoietic activity that characterizes the anemia in patients with CKD is consistent with insufficient erythropoietin stimulation.[20]

The introduction of recombinant human erythropoietin into clinical practice in the 1980s was a major breakthrough in the treatment of anemia in patients with CKD.[21] Early on, administration was limited to dialysis patients with the most severe forms of anemia,[22] but, progressively, its use was extended to the majority of dialysis patients with renal anemia, and subsequently also to anemic patients with ND-CKD.[23]

Results of studies conducted in 1996 and 2006 showed that patients with CKD were at increased risk for serious cardiovascular complications when ESAs were administered to target higher, rather than lower, hemoglobin levels.[24] These complications included stroke, heart attack, heart failure, and death.[25] FDA's Cardiovascular and Renal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee met in September 2007 to discuss the risks and benefits of ESAs when used to treat anemia due to chronic kidney failure.[26] Although the committees did not reach a consensus recommendation on a specific target hemoglobin level, many members at the meeting recommended a target range of 10 to 12 g/dL or a specific target within that range.[27]

Based on the results of clinical trials and input from the FDA advisory committees, FDA undertook a number of regulatory actions to inform providers and patients about the cardiovascular risks associated with ESAs. FDA required ESA manufacturers to revise their product labeling to discuss these risks and include a boxed warning.[28] The current FDA-required boxed warning on ESAs' labels prominently warns practitioners and patients about the increased risk of death, myocardial infarction, stroke, venous thromboembolism, thromboembolism, thrombosis of vascular access and tumor progression or reoccurrence, and includes other warnings and precautions related to the cardiovascular risks associated with ESAs when used in patients with CKD.[29]

("Venofer is an iron replacement product indicated for the treatment of iron deficiency anemia (IDA) in patients with chronic kidney disease (CKD).").

[19] Hayat, A., Haria, D., & Salifu, M. O. (2008). Erythropoietin stimulating agents in the management of anemia of chronic kidney disease. *Patient Preference and Adherence*, *2*, 195–200. https://doi.org/10.2147/ppa.s2356.

[20] *See* KDIGO 2012 Guidelines, *supra* note 8, at 290.

[21] *See* KDIGO 2012 Guidelines, *supra* note 8, at 293.

[22] *Id*.

[23] *Id*.

[24] HHS, OIG, *Memorandum Report: "Renal Dialysis Facilities' Dosage Protocols for Administering Erythropoiesis-Stimulating Agents," OEI-03-09-00010* (Nov. 5, 2009), https://oig.hhs.gov/oei/reports/oei-03-09-00010.pdf **(Exhibit 3)**.

[25] *Id.*

[26] *Id.*

[27] *Id.*

[28] *Id.*

[29] *See e.g.,* FDA, Label for Aranesp (Rev. June 2011), https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103951orig1s5173_103951orig1s5258lbl.pdf.

FDA also imposed a Risk Evaluation and Mitigation Strategy (REMS) requirement on ESAs that was fully implemented in 2011.[30] The ESA REMS consisted of a Medication Guide, communication plan, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.[31] KDIGO updated its Guidelines in 2012 to, among other things, incorporate new insights on the safety of ESA (and iron) therapy. FDA released the ESA REMS in 2017 based on a finding that the risks could be adequately communicated by the current product prescribing information.[32]

FDA further required manufacturers of ESAs to conduct post-market clinical trials to assess the safety risks for ESAs,[33] and took steps to inform the public about its various actions related to ESAs through dissemination of a drug safety podcast and other drug safety communications.[34]

3. Hypoxia-Inducible Factor-Prolyl Hydroxylase (HIF-PH) Inhibitors as a Next Generation Therapy for Anemia in CKD Patients

HIF-PH inhibitors have emerged as a potential new class of small molecule drugs for the treatment of anemia in CKD patients. HIF-PH inhibitors work by mimicking the response to a cellular reduction in oxygen levels, thereby increasing HIF activity and stimulating erythropoiesis.[35] However, the relative safety of this new class of products is not well understood, and recent data from randomized controlled trials suggest that this class of products may pose greater safety risks, both cardiovascular-related and otherwise, than the current standard of care.

The undersigned recognizes the importance of advancing the treatment of CKD anemia, in particular, the need to reduce the potential cardiovascular risks associated with ESAs. However, the undersigned respectfully requests that FDA apply the same level of scrutiny and regulatory oversight to this newly emerging class of products that it has historically applied to ESAs, and other similarly situated products,[36] and ensure patients are protected from unnecessary cardiovascular and mortality risks.

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[30] FDA, *Information on Erythropoiesis-Stimulating Agents (ESA) Epoetin alfa (marketed as Procrit, Epogen), Darbepoetin alfa (marketed as Aranesp)*, https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-erythropoiesis-stimulating-agents-esa-epoetin-alfa-marketed-procrit-epogen-darbepoetin (last accessed Nov. 6, 2020).

[31] *Id.*

[32] *Id.*

[33] *See e.g.,* FDA, *Postmarket Requirements and Commitments Database*, https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm (last accessed Nov. 6, 2020).

[34] FDA, *Drug Safety Podcast on ESAs*, https://wayback.archive-it.org/7993/20170722153152/https://www.fda.gov/Drugs/DrugSafety/DrugSafetyPodcasts/ucm260913.htm (last accessed Nov. 6, 2020). In 2007, the Centers for Medicare and Medicaid Services (CMS) made a National Coverage Determination (NCD) to limit coverage of ESAs for non-renal disease indications. These actions coincided with: a decrease in the proportion of patients receiving chemotherapy using ESAs, an increase in the proportion of patients receiving chemotherapy who initiate ESAs at a hemoglobin level 10g>, and an increase in the proportion of patients who initiate ESAs at a dosage consistent with product prescribing information. FDA, *supra* note 30.

[35] Locatelli, F., Fishbane, S., Block, G. A., & Macdougall, I. C. (2017). Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease patients. *American Journal of Nephrology*, *45*(3), 187–199. https://doi.org/10.1159/000455166.

[36] *See Bracco Diagnostics, Inc., supra* note 1.

B. Substantial Evidence Does Not Support Approval of Roxadustat for Use in Certain CKD Patients.

To approve an NDA, FDA must determine there is "substantial evidence" of drug safety and effectiveness.[37] Among the key questions considered by FDA in its review of an NDA are: (1) "[w]hether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks;" and (2) "whether the drug's proposed labeling (package insert) is appropriate, and what it should contain."[38]

FDA must deny marketing approval if, among other things: (1) there is a lack of substantial evidence that the drug is effective for use under the conditions prescribed, recommend, or suggested in the proposed labeling; (2) the results of safety testing fail to show that the drug is safe for use under such conditions; or (3) if on the basis of any other information before the Agency, there is insufficient evidence to determine whether or not the drug is safe for use under such conditions.[39] Moreover, FDA may not approve an NDA for a product with an unfavorable risk-benefit profile.[40]

When assessing the risk-benefit profile for a drug, FDA conducts an analysis of: (1) the relevant condition, including the context of drug's use for the proposed indication; (2) current treatment options, including the efficacy and safety of available therapies, and any unmet medical needs; (3) the potential benefit of the drug, including the clinical relevance of the study endpoints and generalizability of the clinical trial evidence to the intended patient population; and (4) drug risk and risk management, including serious adverse events or safety signals, and how prescribers and real-world use in the post-market setting may differ from the clinical trial setting.[41]

As detailed below, recently published data fail to demonstrate that the treatment benefits of roxadustat outweigh its safety risks, particularly if the drug is indicated for patients who are non-dialysis dependent, or who have been on dialysis for four months or longer. Close evaluation of the clinical trial data from roxadustat's pivotal Phase III program suggests that roxadustat may present greater cardiovascular and all-cause mortality risks than the current standard of care for these patients.

1. The Currently Published Roxadustat Pooled MACE Analysis for Dialysis-Dependent Patients Disguises an Important Safety Concern.

In November 2019, Fibrogen, Inc. (Fibrogen) and AstraZeneca presented data from seven Phase III randomized clinical trials (comprising over 9,000 patients) comparing the safety and efficacy

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[37] 21 U.S.C. §§ 355(c) & (d).
[38] FDA, *New Drug Application (NDA)*, https://www.fda.gov/drugs/types-applications/new-drug-application-nda (last accessed Nov. 6, 2020).
[39] 21 U.S.C. § 355(d).
[40] *See* FDA, *Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision Making: Draft 40 Implementation Plan – February 2013, Fiscal Years 2013-2017*, at 6, https://www.fda.gov/media/84831/download.
[41] Lackey, L., Thompson, G., & Eggers, S. (2020). FDA's benefit-risk framework for human drugs and biologics: role in benefit-risk assessment and analysis of use for drug approvals. *Therapeutic Innovation & Regulatory Science*, https://doi.org/10.1007/s43441-020-00203-6 (advance online publication).

of (1) roxadustat versus ESA treatment in DD-CKD patients (including incident to dialysis (ID) patients), and (2) roxadustat versus placebo in ND-CKD patients.[42]

The applicant conducted four Phase III global clinical trials evaluating roxadustat versus ESA therapy in DD-CKD patients: ROCKIES, HIMALAYAS, SIERRAS and PYRENEES. Each trial evaluated patients from various subpopulations of the broader dialysis-dependent population. In particular, HIMALAYAS evaluated ID patients (*i.e.*, those on dialysis for ≤ 4 months), while the ROCKIES and SIERRAS trials evaluated both ID patients and patients who were stable on dialysis (*i.e.*, on dialysis for > 4 months).[43] The PYRENEES trial only evaluated patients who were stable on dialysis. ROCKIES, HIMALAYAS, and SIERRAS used epoetin alfa as the ESA comparator while PYRENEES included both epoetin alfa and darbepoetin alfa as treatment comparators.[44]

At the American Society of Nephrology Kidney Week 2019 conference, a speaker who received funding from Fibrogen[45] presented pooled safety data from three of these four global trials – ROCKIES, SIERRAS, and HIMALAYAS – in an attempt to show that roxadustat did not increase the risk of MACE (Major Adverse Cardiovascular Event; defined as a composite of all-cause mortality, stroke, and heart attack), and all-cause mortality in DD-CKD patients compared to epoetin alfa.[46] The speaker also presented this pooled safety analysis in an attempt to show superiority of roxadustat versus ESA on MACE+ (defined as a composite of MACE, hospitalization stemming from unstable angina, and hospitalization stemming from congestive heart failure).

However, this pooled safety analysis *excluded* data from the PYRENEES trial, which presented a less favorable safety profile for roxadustat as compared to ESAs, in particular to epoetin alfa.[47] Specifically, in the PYRENEES trial, although roxadustat was found to be non-inferior to ESAs and placebo on the primary efficacy endpoint of change in baseline Hb, safety data were unfavourable for roxadustat:

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[42] AstraZeneca, *Roxadustat Phase III Programme Pooled Analyses Showed Positive Efficacy and No Increased Cardiovascular Risk in Patients with Anaemia from Chronic Kidney Disease* (Nov. 8, 2019), https://www.astrazeneca.com/media-centre/press-releases/2019/roxadustat-phase-iii-programme-pooled-analyses-showed-positive-efficacy-and-no-increased-cv-risk-in-patients-with-anaemia-from-chronic-kidney-disease.html **(Exhibit 4)**.

[43] The enrollment criteria for the ROCKIES trial were later amended to limit recruitment for ID patients only. *See* Clinicaltrials.gov, *History of Changes for Study: NCT02174731 (ROCKIES)*, https://clinicaltrials.gov/ct2/history/NCT02174731?V_49=View#StudyPageTop **(Exhibit 5)**.

[44] Clinicaltrials.gov, *Study Results: NCT02278341 (PYRENEES)*, https://clinicaltrials.gov/ct2/show/results/NCT02278341 **(Exhibit 6)**.

[45] *See* Renal & Urology News, *Expert Perspective: Novel Agent May Improve Renal Anemia Management*, https://www.renalandurologynews.com/home/expert-perspectives/robert-provenzano-md/ (last accessed Nov. 6, 2020) **(Exhibit 7)**.

[46] Fibrogen, *Roxadustat Global Phase 3 Results for Treatment of Chronic Kidney Disease (CKD) Anemia to be Presented at American Society of Nephrology Kidney Week 2019* (Oct. 11, 2019), https://investor.fibrogen.com/news-releases/news-release-details/roxadustat-global-phase-3-results-treatment-chronic-kidney **(Exhibit 8)**; A. Inserro, *Pooled Cardiovascular Data on Roxadustat Show No Increased Risk to Patients With CKD*, American Journal of Managed Care (Nov. 8, 2019), https://www.ajmc.com/view/pooled-cardiovascular-data-on-roxadustat-shows-no-increased-risk-to-patients-with-ckd **(Exhibit 9)**; & AstraZeneca, *supra* note 42. We note that additional roxadustat sub-analysis data was presented at the recent 2020 ASN Kidney Week Conference, though none of these data resolve the concerns raised by this petition.

[47] Astellas, *Clinical Study Result, PYRENEES*, https://astellasclinicalstudyresults.com/study.aspx?ID=364 (last accessed Nov. 6, 2020) **(Exhibit 10)**.

- 78 (18.8%) roxadustat-treated patients died; in contrast 59 (14.0%) patients treated with ESA died;
- Five patient deaths in the roxadustat group (n=414) could have been related to roxadustat, while two patient deaths in the slightly larger ESA treatment group (n=420) could have been related to the ESAs; and
- 33 roxadustat patients (8%) experienced serious adverse reactions, while 10 ESA patients (2.4%) experienced such reactions.[48]

The incidence of serious treatment-emergent adverse events ("TEAEs") leading to withdrawal was higher in the roxadustat treatment group compared with the ESA treatment group, with hazard ratios favoring the ESA treatment group.[49] There was also an increased incidence of serious TEAEs and TEAEs leading to patient death in the roxadustat treatment group, and the cumulative incidence of serious TEAEs and deaths over time was greater in the roxadustat treatment group compared with the ESA treatment group, as indicated above.[50] Baseline disease factors associated with mortality (including age, cardiovascular history, and diabetes) did not appear to affect mortality or account for the mortality difference seen between treatment groups.[51] Given the similarities in the enrollment criteria for the PYRENEES, ROCKIES, and SIERRAS trials, and the fact that MACE for patients on epoetin alfa treatment can be easily extracted from the PYRENEES trial, it is mystifying that the PYRENEES trial was excluded from Fibrogen's pooled safety analysis.

The decision to exclude this troubling PYRENEES safety data becomes even more confusing when taken in context with the statistical analysis plan for the PYRENEES trial that states the "pre-specified adjudicated cardiovascular and thrombo-embolic events will be analyzed in meta-analyses across ***multiple phase 3 studies*** and compared between treatment groups."[52]

This selective pooling disguises a potential safety concern regarding the use of roxadustat in the broader DD-CKD population. Pooling of safety data from all ***four*** DD-CKD roxadustat trials (including PYRENEES) for the intent to treat (ITT) population (*i.e.*, all patients randomized into the trial(s)) actually suggests a higher incidence of all-cause mortality for patients on roxadustat versus ESA treatment (450 deaths vs. 407 deaths, respectively).[53] These more inclusive pooled

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[48] *Id.*
[49] *Id.*
[50] *Id.*
[51] *Id.*
[52] Clinicaltrials.gov, *Statistical Analysis Plan for PYRENEES*, at 96, https://clinicaltrials.gov/ProvidedDocs/41/NCT02278341/SAP_001.pdf (emphasis added) **(Exhibit 11)**. Although pooling data from different studies can be useful in conducting an integrated safety analysis (by enlarging the sample size and thus narrowing the confidence intervals), such pooling must be done consistently, and incorporate data from all sufficiently similar studies. FDA, Reviewer Guidance: Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (2005), https://www.fda.gov/media/71665/download.
[53] *See* EU Clinical Trials Register, *Eudra CT No. 2014-000780-40 (ROCKIES)*, at 17, https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-000780-40/results#trialInformationSection (roxadustat = 247; ESA = 231) **(Exhibit 12)**; Clinicaltrials.gov, *supra* note 44 (roxadustat = 78; ESA =59) **(Exhibit 6)**; Clinicaltrials.gov, *Study Results: NCT02273726 (SIERRAS)*, https://clinicaltrials.gov/ct2/show/NCT02273726 (results not published) **(Exhibit 13)**; C. Charytan et al., *SIERRAS: A Phase 3, Open-Label, Randomized, Active-Controlled Study of the Efficacy and Safety of Roxadustat in the Maintenance Treatment of Anemia in Subjects with ESRD on Stable* Dialysis, Poster SA_PO_227_Sierras, Presented at the ASN Kidney Week 2019 Conference (Nov. 2019) (serious treatment adverse effects leading to death for roxadustat = 62; ESAs = 58) **(Exhibit 14)**; Fibrogen, *HIMALAYAS: A Phase 3, Randomized, Open-Label, Active-Controlled Study of the Efficacy and Safety of*

data confirm, in part, the potential safety risk seen in the PYRENEES clinical trial when examining serious adverse events across treatment arms. This inclusive analysis also underscores the need for additional data demonstrating adequate safety of roxadustat before concluding that the benefits of roxadustat outweigh its potential risks.[54]

FDA requires NDA reviewers to include an analysis of overall mortality for all Phase II and III exposures across treatment groups precisely because such comprehensive assessment may uncover safety signals not apparent when data are selectively considered.[55] In response to petitions similar to this one, FDA has explicitly held that "comparison of mortality rates between the active and comparator group provides a particularly informative method of assessing the potential for a safety signal related to death."[56] FDA must consider this broader pooled analysis in determining whether there is substantial evidence of safety for roxadustat use in the DD-CKD population, and in so doing, should require the applicant to provide additional evidence demonstrating a favorable risk-benefit profile for roxadustat in this population.

2. *Lack of Key Sub-Analysis Data Raises Serious Safety Questions Around the Use of Roxadustat in Patients Stable on Dialysis, and, Therefore, Dialysis-Dependent Patients More Broadly.*

Pooled safety data from the roxadustat Phase III clinical trial program suggest that, for ID patients *only*, those taking roxadustat had a 30% lower risk of MACE, a 34% lower risk of MACE+, and a trend toward lower all-cause mortality compared to those receiving ESA therapy.[57] However, when the DD-CKD patient group is considered in its totality (*i.e.*, including both ID and stable-on-dialysis patients), risk of MACE and all-cause mortality for roxadustat is only non-inferior to ESA treatment (risk of MACE+, however, remained superior).[58] One conclusion that can be drawn from this is that for a subpopulation of patients stable on dialysis, risk of MACE and all-cause mortality is higher with roxadustat than with ESA treatment. Data around this critical patient population was however not isolated and presented at the American Society of Nephrology Kidney Week 2019 or 2020 conferences or, to our knowledge, to FDA.[59] Therefore, current data do not

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Roxadustat in the Treatment of Anemia in Incident-Dialysis Patients, https://investor.fibrogen.com/static-files/8720f26b-e86f-4770-bfb9-0fb1e45da3a1 (roxadustat = 63; ESAs = 59) **(Exhibit 15)**.

[54] *See* FDA, PDUFA V, Draft Implementation Plan at 7, https://www.fda.gov/media/84831/download (The risk-benefit assessment "draws on the key supporting evidence and uncertainties, accounts for the understanding of the condition, and considers the available therapies that establish the context in which benefits and risks are weighed.").

[55] FDA, *supra* note 52, at 13.

[56] *See* FDA, *Response to Citizen Petition filed on behalf of Luitpold Pharmaceuticals, Inc.*, Docket No. FDA-2008-P-0524 (2008) (finding that "[t]he ferumoxytol database did not show important differences in mortality rates between the active and comparator groups").

[57] UKidney, *Pooled Efficacy and Cardiovascular (CV) Analyses of Roxadustat in the Treatment of Anemia in CKD* (Nov. 9, 2019), https://ukidney.com/news/asn-2019/entry/pooled-efficacy-and-cardiovascular-cv-analyses-of-roxadustat-in-the-treatment-of-anemia-in-ckd-patients-on-and-not-on-dialysis **(Exhibit 16)**; AstraZeneca, *supra* note 42.

[58] *Id.*

[59] We note that while the roxadustat NDA Phase III program was completed several years ago, the results from that program have not, to our knowledge, been published by any peer-reviewed journal. We also note that the sponsor has not published the results of all of the Phase III clinical trials on clinicaltrials.gov. This has made it difficult for the public to understand the full scope of data that is being considered and reviewed by FDA in evaluating the safety and efficacy of roxadustat. While the undersigned was optimistic that a sub-analysis of MACE and all-cause mortality in DD-CKD patients, and the results of the PYRENEES trial, would be discussed at the most recent American Society for Nephrology Kidney Week 2020 conference, held just a few weeks ago, that data was not

appear to support the safe use of roxadustat in the stable-on-dialysis patient population. This potential safety concern is further supported by the PYRENEES trial data, which focused exclusively on patients stable on dialysis, and demonstrated a significantly greater risk of mortality and TEAEs for patients taking roxadustat versus ESAs.

These data suggest that even if ID patients may experience lower MACE or MACE+ risk when treated with roxadustat versus ESA treatment, improved risk profile may be lost or even negated (*i.e.*, replaced with increased risk) once they are no longer incident to dialysis, *i.e.* after the patient has been on dialysis for longer than four months. The differences in MACE between the ID and dialysis-dependent patient populations may also raise safety concerns about switching patients from ESA therapy to roxadustat. Indeed, it is reasonable to presume that some, if not most, stable-on-dialysis patients in the roxadustat treatment arms were stable on ESA treatment when enrolled in these clinical trials.

The lack of generalizability of improved MACE outcomes observed in the ID patient population to the broader DD-CKD population is important to consider in evaluating the risk-benefit profile of roxadustat for its proposed indications. From a clinical perspective, it is unlikely that a DD-CKD patient would be started on roxadustat and later switched to an ESA. Moreover, the potential risks of such switching have not, to our knowledge, been evaluated by the roxadustat NDA applicant or otherwise. In evaluating the roxadustat NDA, FDA should consider this real-world impact, in particular, the potential that patients will be maintained on a therapy that may provide greater cardiovascular and mortality risks over time than the existing standard of care.[60]

In conducting its risk-benefit assessment, FDA should also consider that the definition of ID used in the roxadustat clinical trials is not one that has been broadly adopted by the nephrology community. In some cases, physicians consider patients incident to dialysis when they have been on dialysis for six months or less, while in other contexts, they consider this population to mean three months or less.[61] To our knowledge, the sponsor has never publicly clarified why it chose this limited time period (patients on dialysis for less than four months), and why any benefits observed in this narrow population would translate to better clinical outcomes in CKD anemic patients.

In light of the safety concerns highlighted above, and to ensure that there is substantial evidence of adequate safety for roxadustat in the broader DD-CKD population, FDA should require the applicant to submit for its review a sub-analysis of all available data from the applicant's Phase III

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presented. Therefore, the undersigned believes that there is an urgent need to now raise the issues set forth in this petition to FDA to ensure that they are duly considered.

[60] *See* FDA, *Public Meeting on Benefit-Risk Framework Implementation Testimony of Dr. Rich Moscicki, CDER's Former Deputy Center Director for Science Operations*, Tr. at 14 (Sept. 18, 2017) ("We must also consider how people will actually use the drugs once they're marketed. So critically then, every decision must also be made in the context of the disease that is being treated, how severe is that disease and how well do available treatments currently meet the patient's needs.").

[61] *See* Lukowsky, L. R., Kheifets, L., Arah, O. A., Nissenson, A. R., & Kalantar-Zadeh, K. (2012). Patterns and predictors of early mortality in incident hemodialysis patients: new insights. *American Journal of Nephrology*, *35*(6), 548–558. https://doi.org/10.1159/000338673; Renal Physicians Association, *Incident ESRD Clinical Episode Payment Model* (May 2017), https://cdn.ymaws.com/www.renalmd.org/resource/resmgr/LegRegsComp/PTAC_Incident_ESRD_APM_Propo.pdf **(Exhibit 17)**.

clinical program that evaluates all-cause mortality outcomes in DD-CKD patients who are stable on dialysis to ensure roxadustat is non-inferior to the standard of care.

3. For ND-CKD Patients, the Applicant's Finding that the Safety of Roxadustat is Non-Inferior to Placebo Should be Viewed with Caution.

The current standard of care for treating anemia in ND-CKD patients is iron (and ESAs, when needed). It has been shown that Hb correction for these patients can be very effectively achieved with iron supplementation alone; specifically, one large study found that over 76% of ND-CKD patients treated with IV iron would not require any additional anemia treatment to correct and maintain their Hb levels over a period of one year.[62] However, in studying roxadustat, the applicant's trials compared roxadustat to placebo (*i.e.*, no treatment) rather than an active comparator (*i.e.*, IV iron), making any conclusions about the relative safety of roxadustat treatment for ND-CKD patients much less clear.

At the American Society of Nephrology Kidney Week 2019 and 2020 conferences, Fibrogen presented pooled safety and efficacy data from three Phase III clinical trials evaluating roxadustat versus placebo in ND-CKD patients: (1) OLYMPUS, (2) ALPS, and (3) ANDES. The pooled efficacy analysis showed roxadustat was superior to placebo in increasing baseline Hb, while the pooled safety analysis showed that risk of MACE, MACE+, and all-cause mortality in roxadustat patients was numerically worse, but non-inferior to that of placebo in these patients.[63]

While the presenters framed these results positively, the implications of a non-inferiority judgement regarding the safety of roxadustat versus placebo should be reviewed more closely. It is well-accepted amongst clinicians that the goal of anemia correction is not simply to increase Hb levels, but a desire to improve cardiovascular outcomes and reduce the need for blood transfusions.[64] If anemia correction is expected to result in better cardiovascular outcomes, then any appropriate treatment should, by default, result in better MACE outcomes than placebo. Because roxadustat was merely shown to be non-inferior to placebo with regard to MACE, it stands to reason that any cardiovascular benefit driven by the anemia correction from roxadustat was offset by its cardiovascular risks, resulting in a net non-inferior outcome to placebo. Thus, roxadustat may, in fact, provide no benefit as compared to placebo, and potentially, less benefit or greater safety risk in comparison to other anemia-correction treatments (*e.g.*, iron or ESA treatment) for ND-CKD patients.

This potential efficacy concern is underscored by the fact that roxadustat was evaluated for efficacy based on improvement in Hb, which is considered a less than optimal surrogate endpoint for demonstrating improvement in anemia. According to an article from the *Journal of Clinical Nephrology*, "farther down the hierarchy of outcomes are those outcomes that are less relevant to patients (but on which the nephrology community has traditionally based much of our clinical

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[62] Clinicaltrials.gov, *Study Results: NCT00994318 (Ferric Carboxymaltose (FCM) Assessment in Subjects With Iron Deficiency Anaemia and Non-dialysis-dependent Chronic Kidney Disease (NDD-CKD) (FIND-CKD))*, https://clinicaltrials.gov/ct2/show/results/NCT00994318 **(Exhibit 18)**.

[63] UKidney, *supra* note 57.

[64] *See* Fox et al., *supra* note 10.

decision making), including unvalidated surrogate endpoints such as achieved hemoglobin level."[65]

To fully understand the risks and benefits associated with roxadustat treatment in ND-CKD patients, FDA should require a head-to-head clinical trial that is adequately powered to assess MACE outcomes for patients on roxadustat versus the current standard of care (e.g., IV iron, ESAs). This recommendation, and underlying concern, is shared by the broader scientific community. In September 2019, the *New England Journal of Medicine* published an article concluding, "Additional data are needed regarding the efficacy and safety of roxadustat for the treatment of anemia in patients with chronic kidney disease who are not undergoing dialysis."[66]

4. FDA Should Consider Safety Data from Studies of Other HIF-PH Inhibitor Products in Evaluating the Safety Risks of Roxadustat.

As indicated above, FDA must decline to approve an NDA if, on the basis of any information before the Agency, there is insufficient evidence to determine whether the drug is safe for use under the conditions prescribed, recommended, or suggested in the labeling. Recently released top-line results from the PRO_2TECT clinical trial, a randomized, open-label, active-controlled study evaluating the efficacy and safety of oral vadadustat (another HIF-PH inhibitor in development for the correction and/or control of anemia in subjects with ND-CKD), showed that vadadustat failed to demonstrate non-inferiority versus darbepoetin alfa in time to first occurrence of MACE, with a hazard ratio of 1.17 (95% CI 1.01, 1.36).[67] In addition to the other evidence presented in this petition, these results underscore that the MACE risks associated with HIF-PH inhibitor products compared to ESAs deserve further evaluation before FDA can approve roxadustat for the correction of anemia in CKD patients, especially ND-CKD patients.

C. FDA Should Require Roxadustat's Label Bear a Boxed Warning.

Based on the results of clinical trials and input from the FDA advisory committees, FDA required the manufacturer of ESAs to revise the labeling for ESAs and add a boxed warning. This warning, placed prominently at the top of the labeling, is used to highlight cautionary information that is especially important to the prescriber's risk-benefit assessment, including identification of an adverse reaction(s) so serious in proportion to the potential benefit from the drug (*e.g.*, a fatal, life-threatening, or permanently disabling adverse reaction) as to be essential in assessing the risks and benefits of using a drug.[68] It is also used to highlight a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug.[69]

FDA required the manufacturer of ESAs to add a boxed warning to their products in response to cardiovascular risks similar to – yet potentially less severe than – those identified in the Phase III clinical program for roxadustat. To ensure patients and healthcare providers are fully apprised of

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[65] Manns & Tonelli, *supra* note 12.
[66] Chen, N. et al. (2019). Roxadustat treatment for anemia in patients undergoing long-term dialysis. *The New England Journal of Medicine*, *381*(11), 1011–1022. https://doi.org/10.1056/NEJMoa1901713.
[67] *See* M. Dennis, *Akebia's Vadadustat Fails Safety Endpoint of Key Anaemia Study*, FirstWord Pharma (Sept. 3, 2020), https://www.firstwordpharma.com/node/1754576#:~:text=Top%2Dline%20results%20showed%20that,remarked%20Akebia%20CEO%20John%20Butler **(Exhibit 19)**.
[68] 21 C.F.R. § 201.57.
[69] *Id.*

these risks, if FDA approves roxadustat for use in any CKD patient population, we recommend FDA require the product's label bear a boxed warning.

Notably, at the American Society of Nephrology Kidney Week 2020 conference, Fibrogen presented that in Japan, where roxadustat is currently approved for the treatment of anemia in CKD patients, the health authority has imposed a boxed warning requirement on roxadustat because "it is necessary to give warning about thrombosis and embolism by roxadustat."[70] Japan has also imposed a post-marketing safety study requirement on the applicant to evaluate the incidence of thrombosis and embolism post-approval.[71] Further, in guidance, Japan stresses the importance of correcting iron deficiency before initiation of HIF-PH inhibitor treatment and states that HIF-PH inhibitors are considered an alternative to an ESA.[72] Japan's actions with respect to roxadustat underscore the need for FDA to impose similar warnings or limitations if FDA approves roxadustat for the treatment of anemia in patients with CKD.

D. Requiring the Roxadustat NDA Applicant to Provide Additional Safety Data And Analysis Prior to Approval and Imposing a Boxed Warning Requirement is Consistent with FDA Precedent.

FDA has required NDA applicants to further evaluate the safety of products, and taken other regulatory actions, where the Phase III clinical program data for the products raised safety concerns similar to those raised by the Phase III clinical program for roxadustat.

For example, in 2011, FDA issued a Complete Response Letter to Orexigen Therapeutics, Inc., regarding its NDA for Contrave (naltrexone HCl/bupropion HCl) due to "statistically significantly higher mean systolic and diastolic blood pressure and heart rate among naltrexone/bupropion-treated subjects compared with placebo-treated subjects."[73] In addition, more adverse events related to hypertension were observed in the naltrexone/bupropion groups, particularly among subjects with type 2 diabetes. FDA found that this collective data raised concern about the cardiovascular safety profile of naltrexone/bupropion when used long-term in a population of overweight and obese individuals.[74] Therefore, FDA found that before the NDA could be approved, "the sponsor must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events in overweight and obese subjects treated with naltrexone/bupropion does not adversely affect the drug's benefit-risk profile."[75]

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[70] M. Nangaku, *New Era of Anemia of CKD After the Nobel Prize*, Slide Deck Presented at the ASN Kidney Week 2020 Conference (Oct. 2020) **(Exhibit 20)**.

[71] While FDA may be considering imposing a similar post-marketing safety study requirement for roxadustat to assuage the safety concerns raised by Phase III clinical trial data for roxadustat, we recommend against FDA doing so. Historically, applicants have delayed completion of those trials; indeed, it is our understanding that none of the post-marketing study requirements for ESAs have been completed to date. Therefore, we recommend that FDA decline to impose a post-marketing study requirement on roxadustat and instead require a demonstration of adequate safety and efficacy before the drug is approved to ensure the drug is safe for use before it is commercially available in the U.S.

[72] *See* Nangaku, *supra* note 70.

[73] FDA, Summary Review, NDA 200063, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/200063Orig1s000SumR.pdf.

[74] *Id.*

[75] *Id.*

Likewise, in 2013, FDA issued Complete Response Letters to Novo Nordisk related to its NDAs for Tresiba (insulin degludec injection) and Ryzodeg 70/30 (insulin degludec and insulin apart injection).[76] FDA did so "because results of a meta-analysis comparing cardiovascular risk (CV-risk) between insulin degludec and comparators (mostly other insulins and predominantly insulin glargine) suggested CV-risk was higher in patients randomized to insulin degludec."[77] FDA thus, asked the applicant to exclude the possibility that insulin degludec was associated with excess CV-risk by comparing degludec to glargine in a dedicated, double-blind, cardiovascular outcomes trial, focused on MACE.[78] Only after the applicant conducted that trial and provided an updated integrated safety analysis with safety data accrued from ongoing extensions of previously reviewed Phase III trials, and certain newly completed short-term trials, did FDA approve the applicant's NDAs in 2015.[79]

In addition, in 2011, FDA issued a Complete Response Letter to the NDA applicant for telavancin, finding that telavancin treated patients who had acute renal failure or renal impairment at baseline were more likely to die compared to vancomycin-treated subjects.[80] While FDA later approved the NDA for telavancin, it did so only after convening an FDA Advisory Committee Meeting, where the Committee voted in favor of the drug's approval. FDA also imposed a REMS for this product that required surveys assessing healthcare professionals' understanding of the increased risk of mortality in telavancin-treated patients with preexisting creatinine clearance of $\leq$ 50 mL/min being treated for hospital acquired bacterial pneumonia (HABP)/ventilator-associated bacterial pneumonia (VABP).[81] FDA further imposed a boxed warning requirement, and limited the approved indication for use only when other alternative treatments are unavailable.[82]

E. Conclusion

For the reasons set forth above, the undersigned requests that FDA: (1) decline to approve the roxadustat NDA until the applicant submits additional data and analysis demonstrating the safety risks do not outweigh the therapeutic benefit of the drug, *i.e.*, for use in ND-CKD patients and the DD-CKD patients stable on dialysis; and (2) require roxadustat's label bear a boxed warning if the risk for all-cause mortality or major adverse cardiovascular events is similar or worse in comparison to the current standard of care.

III. Environmental Impact

Petitioner believes that under 21 C.F.R. § 25.31, this petition does not require an environmental impact analysis report.

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[76] FDA, Summary Review, NDAs 203314 & 203313, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/203313Orig1s000_203314Orig1s000SumR.pdf.
[77] *Id.*
[78] *Id.*
[79] *Id.*
[80] FDA, Medical Review, NDA 022407, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022407Orig1s000MedR.pdf.
[81] *Id.*
[82] Vibativ, Full Prescribing Information (Rev. June 2013), https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022407s000,022110s003lbl.pdf.

IV. Economic Impact

Under 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition. Petitioner hereby commits to promptly provide this information, if so requested.

V. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Sincerely,

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Attachments