Novel Anemia Therapies in CKD: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Elaine Ku,[1,2,3] Lucia Del Vecchio,[4] Kai-Uwe Eckardt,[5] Volker H. Haase,[6] Kirsten L. Johansen,[7] Masaomi Nangaku,[8] Navdeep Tangri,[9] Sushrut S. Waikar,[10] Andrzej Więcek,[11] Michael Cheung,[12] Michel Jadoul,[13] Wolfgang C. Winkelmayer,[14] and David C. Wheeler[15] for Conference Participants*

[1]Division of Nephrology, Department of Medicine, University of California San Francisco, San Francisco, California, USA;
[2]Division of Pediatric Nephrology, Department of Pediatrics, University of California San Francisco, San Francisco, California, USA;
[3]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA;
[4]Department of Nephrology and Dialysis, Sant'Anna Hospital, ASST Lariana, Como, Italy;
[5]Department of Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany;
[6]Department of Medicine, Vanderbilt University Medical Center; and Department of Molecular Physiology and Biophysics and Program in Cancer Biology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA;
[7]Division of Nephrology, Hennepin Healthcare, Minneapolis, Minnesota, USA; Division of Nephrology, University of Minnesota, Minneapolis, Minnesota, USA;
[8]Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan;
[9]Chronic Disease Innovation Centre, Seven Oaks General Hospital, Winnipeg, Manitoba, Canada; Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba. Winnipeg, Manitoba, Canada;
[10]Section of Nephrology, Boston University Chobanian & Avedisian School of Medicine and Boston Medical Center, Boston, USA;

[11]Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland;
[12]KDIGO, Brussels, Belgium;
[13]Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium;
[14]Selzman Institute for Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; and
[15]Department of Renal Medicine, University College London, London, UK

*Other conference participants: Baris Afsar, Turkey; Tadao Akizawa, Japan; Stefan D. Anker, Germany; Mustafa Arici, Turkey; Jodie L. Babitt, USA; Jonathan Barratt, UK; Jeffrey S. Berns, USA; Anatole Besarab, USA; Sunil Bhandari, UK; Christopher Brown, UK; Aleix Cases, Spain; Glenn M. Chertow, USA; Cynthia Delgado, USA; Tillman B. Drüeke, France; Steven Fishbane, USA; Rafael Gómez, Columbia; Morgan E. Grams, USA; Takayuki Hamano, Japan; Chuan-Ming Hao, China; Raymond K. Hsu, USA; Kunitoshi Iseki, Japan; Isabelle Jordans, Germany; Edgar V. Lerma, USA; Francesco Locatelli, Italy; Iain C. Macdougall, UK; Jolanta Małyszko, Poland; Patrick Maxwell, UK; Lawrence P. McMahon, Australia; Gregorio T. Obrador, Mexico; Marlies Ostermann, UK; Roberto Pecoits-Filho, USA; Farzana Perwad, USA; Simon D. Roger, Australia; Ajay K. Singh, USA; Laura Solá, Uruguay; Bruce S. Spinowitz, USA; Mai Sugahara, Japan; Toshiyuki Takahashi, Japan; Mototsugu Tanaka, Japan; Tetsuhiro Tanaka, Japan; Der-Cherng Tarng, Taiwan; Marcello Tonelli, Canada; Yusuke Tsukamoto, Japan; Carl P. Walther, USA; Angela Yee-Moon Wang, Hong Kong, China; Bradley A. Warady, USA; Angela C. Webster, Australia; Matthew R. Weir, USA; Jay B. Wish, USA, Muh Geot Wong, Australia.

Running title: Novel anemia therapies in CKD: A KDIGO Conference Report

Word count: 4917

Correspondence:

Elaine Ku
Division of Nephrology
University of California, San Francisco
533 Parnassus Avenue, U404
San Francisco, CA, USA 94143-0532
Email: elaine.ku@ucsf.edu

David C. Wheeler
Department of Renal Medicine
University College London
Royal Free Campus, Rowland Hill Street
London NW3 2NB, UK
Email: d.wheeler@ucl.ac.uk

Keywords: anemia; chronic kidney disease; dialysis; erythropoiesis stimulating agents; erythropoietin; hepcidin; hemoglobin; hyporesponsiveness; hypoxia-inducible factor-prolyl hydroxylase inhibitors; iron; iron deficiency; major adverse cardiovascular events

ABSTRACT

Anemia is common in patients with chronic kidney disease (CKD) and is associated with a high burden of morbidity and adverse clinical outcomes. In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) published a guideline for the diagnosis and management of anemia in CKD. Since then, new data from studies assessing established and emerging therapies for the treatment of anemia and iron deficiency have become available. Beginning in 2019, KDIGO planned two Controversies Conferences to review the new evidence and its potential impact on the management of anemia in clinical practice. Here we report on the second of these conferences held virtually in December 2021 which focused on a new class of agents, the hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs). This report provides a review of the consensus points and controversies from this second conference and highlights areas that warrant prioritization for future research.

INTRODUCTION

Anemia is common in patients with chronic kidney disease (CKD) and results from inadequate erythropoietin (EPO) production, abnormal iron metabolism, blood loss, inflammation, nutritional deficiencies, and oxidative stress.[1] The 2012 Kidney Disease: Improving Global Outcomes (anemia) guideline provided recommendations for the diagnosis and treatment of anemia related to CKD, including the use of iron, recombinant human EPO and its derivatives (collectively termed erythropoiesis-stimulating agents [ESAs]), and blood transfusions.[2] Since the publication of this guideline, new therapies for the treatment of anemia have emerged and a reevaluation of the 2012 KDIGO guideline is required. In December 2019, KDIGO held the first of two Controversies Conferences on CKD anemia, which focused on iron.[3] The second conference, held virtually in December 2021, focused primarily on hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) following the release of extensive efficacy and safety data. Given the historical nomenclature, we will continue to refer to epoetins, i.e., recombinant human EPO and its derivatives, but not HIF-PHIs as ESAs throughout even though HIF-PHIs also stimulate erythropoiesis.

Hypoxia-inducible factors (HIFs) are oxygen-regulated heterodimeric transcription factors that regulate multiple cellular processes.[4] HIFs coordinate the response to hypoxia by increasing EPO production in the kidneys and liver and by upregulating the expression of genes involved in iron transport, enhancing its uptake and absorption.[4-6] Hepcidin regulates ferroportin, an iron channel on the surface of enterocytes, hepatocytes, and macrophages, and inhibits iron absorption from the gut and its release from macrophages.[7] Systemic HIF activation leads to an increase in EPO production and use of iron by erythroblasts, which in turn results in suppression of hepcidin production in the liver and enhanced intestinal iron absorption and iron mobilization.[8-11] In the presence of oxygen, prolyl hydroxylase enzymes hydroxylate the oxygen-regulated HIF-α subunit, thereby targeting it for proteasomal degradation.[12] When oxygen levels decrease, prolyl hydroxylation and degradation of HIF-α are inhibited, resulting in its cellular accumulation and formation of the HIF heterodimeric transcription factor.[1, 13]

Prolyl hydroxylation can be pharmacologically inhibited by oral HIF-PHIs,[14, 15] which stimulates erythropoiesis, largely by increasing EPO production. Potential benefits of HIF-PHIs in addition to their oral route of administration (particular for patients who are not treated with hemodialysis) include the theoretical advantage of reduced exposure to high peak serum EPO concentrations, as substantially lower peak serum EPO levels have been found in patients treated with HIF-PHIs compared with those receiving epoetin injections.[16] Due to their mechanism of action, HIF-PHIs may enhance enteric iron absorption and iron utilization (unlike ESAs) and may be more efficacious in correcting anemia despite chronic inflammation, though this remains an area of controversy. Other possible advantages of HIF-PHIs over ESAs include their stability at room temperature. Eliminating the need for subcutaneous injections, although these may be infrequently for longer-acting ESAs, may be important for those with non-dialysis dependent CKD (ND-CKD) or treated with peritoneal dialysis (**Table 1**).

Because of HIF's pleiotropic functions, the pharmacologic activation of HIF in patients with anemia of CKD is also likely to have effects beyond erythropoiesis and iron metabolism, depending on the pharmacokinetic and pharmacodynamic properties of the administered compound, drug dosing, and drug exposure.[9] HIF-mediated effects on cellular differentiation and growth, vascular homeostasis and hemodynamics, inflammation, and cellular metabolism are well documented in preclinical studies and could modify the risk of cardiovascular disease, thrombosis, and malignancy. To what extent non-erythropoietic signaling pathways are activated in patients receiving HIF-PHIs is difficult to predict and to measure, and the advantages of HIF-PHIs must therefore be balanced against potential risks. Thus, controversy persists surrounding the role of HIF-PHIs in the treatment of anemia of CKD.[17, 18]

Overview of the available HIF-PHIs and clinical trial programs

To date, more than 50 randomized studies of HIF-PHIs have been published.[19] There are currently six HIF-PHIs in clinical development including daprodustat, desidustat, enarodustat, molidustat, roxadustat, and vadadustat (**Tables 2-3**).[20-51]

Most published Phase 2 and 3 trials have focused on the efficacy of HIF-PHIs compared with placebo or ESAs in treating anemia.[19] Because of concerns that became apparent during clinical trials of ESAs, particularly with respect to cardiovascular safety, regulators have required large-scale trials to establish the cardiovascular safety of these agents. Three large phase 3 programs (roxadustat, vadadustat, and daprodustat) have published data on cardiovascular outcomes in ND-CKD and dialysis-dependent CKD (DD-CKD) (**Tables 2-3**).[21, 26, 34, 37, 42, 51] Conference participants felt that because most of the experience with these agents has been in the context of trials, regulatory agencies should continue to gather data on adverse events in routine clinical practice as usage grows. Currently, different HIF-PHIs have been approved for clinical use in various countries and regions (**Supplemental Table 1**).

HIF-PHIs have been studied in the context of either a superiority (compared with placebo) or non-inferiority (compared with ESAs) trial design. Non-inferiority trials formally test, within a statistical framework, whether a new treatment is not worse than the comparator by a pre-specified margin. This margin should ideally be based on the observed adverse event rate of the standard therapy versus placebo in randomized controlled trials (RCTs), or reflect a margin deemed acceptable to clinicians and patients.[52] The null hypothesis in a non-inferiority trial states that a novel therapy is worse than the standard therapy (comparator) on the outcome by the pre-specified margin. Therefore, interpretation of the results of non-inferiority trials of HIF-PHIs should take into consideration the non-inferiority margins incorporated into the design as well as the rates of dropout and crossover in both arms.[52] If multiple participants assigned to the new treatment switch to the comparator, non-inferiority will be more difficult to assess and erroneous rejection of the null hypothesis (i.e., a conclusion of non-inferiority) may occur. The three major phase 3 programs which have examined the cardiovascular safety of HIF-PHIs have all used non-inferiority trial designs.

Efficacy of HIF-PHIs in the correction of anemia

There was general consensus among the attendees that HIF-PHIs are superior to placebo and non-inferior to ESAs in increasing and maintaining hemoglobin (Hb) concentration among patients with ND-CKD and DD-CKD.[21, 26, 31, 34, 37, 42, 51] Large, randomized trials have demonstrated that roxadustat,[26, 42] vadadustat,[34, 51] and daprodustat[21, 37] are superior to placebo and/or non-inferior to ESAs in correcting and/or maintaining Hb at target levels in ND-CKD and incident and prevalent DD-CKD patients (**Tables 2-3**). Similar findings have been noted with molidustat, enarodustat, and desidustat.[22-25, 39, 40, 53-55] The Hb response with HIF-PHIs is dose-dependent and varies by agent and protocol, and at the starting doses applied according to protocol at trial entry, some agents increased the Hb more rapidly than others. Rates of blood transfusion are similar among patients receiving HIF-PHIs versus ESAs and generally lower than among those receiving placebo.[19]

Based on the results of trials that included patients treated with hemodialysis (HD) and peritoneal dialysis (PD) and single-arm trials among patients treated with PD,[56] HIF-PHIs appear to be at least as effective among those receiving PD versus HD.

Optimal hemoglobin targets for the correction of anemia

Current targets which aim for partial correction of Hb are based on clinical trials conducted several years ago.[57-59] These trials compared higher versus lower Hb targets achieved using ESAs, in which major adverse cardiovascular events (MACE), mortality, and thrombotic events were more common among patients assigned to the higher of the Hb targets.[57-59] In addition, one trial comparing a high Hb target with placebo (and a conservative rescue strategy) in ND-CKD patients with diabetes found an increased rate of strokes.[60] However, no HIF-PHI trials to date have compared Hb normalization or near-normalization with the currently recommended lower Hb targets for CKD patients. A few Japanese trials using daprodustat and molidustat have targeted Hb values exceeding 12 g/dl.[20, 24, 25] Because phase 3 trials of HIF-PHIs were designed primarily for efficacy and safety evaluation and to meet criteria set forth by regulatory agencies in different geographic regions, guideline-recommended Hb targets

were used resulting in some regional differences (**Tables 2-3**). Overall, the attendees felt that the available data do not provide a rationale for targeting higher Hb levels with HIF-PHIs than the currently recommended targets established using ESAs.

Implications for iron management during the correction of anemia

Iron therapy is a critical cornerstone of anemia management, and iron availability is impaired in patients with CKD.[3, 61] Although data from clinical trials suggest that HIF-PHIs may modulate iron metabolism,[62] iron parameters and iron utilization were not primary outcomes in these studies. The conference participants generally felt that the interpretation of iron-related data from these trials is impeded by significant limitations in trial design. Many aspects of iron management were not appropriately specified and were left to the discretion of the investigator and/or were based on local clinical practice patterns.[9] In some trials, iron protocols differed between treatment and comparator groups within a trial.[32, 47] Other design limitations included differences in Hb targets and achieved Hb between treatment arms, differences in the proportion of patients with baseline iron deficiency, and baseline imbalances in iron and hepcidin status and relevant co-morbidities.

Notwithstanding the limitations in trials thus far, higher serum transferrin levels in HIF-PHI treated patients, either measured directly [20, 26-28, 35, 42-45, 63-65] or indirectly by calculating total iron binding capacity (TIBC), were reported across different compounds. In contrast, the effects on serum iron, hepcidin, transferrin saturation (TSAT) and ferritin were more variable among individual trials and between compounds.[62] A summary of iron use and changes in iron parameters is shown in **Tables 4-5**.[21, 29-32,34,36-38,46-49,51]

Although there is potential for a reduction in intravenous (IV) iron treatment, there was general consensus that HIF-PHI therapy will not eliminate the need for iron replacement in DD-CKD patients. The conference participants agreed that iron parameters should be monitored during treatment with HIF-PHIs, and iron deficiency should be avoided because it is associated with thromboembolic events, impaired red blood cell production,[43] lower HRQoL, higher rates of cardiovascular events, and higher mortality.[66, 67]

In summary, conference participants agreed that clinically meaningful differences in iron utilization have not so far been demonstrated using HIF-PHIs. There will likely be a continued role of iron therapy in patients with ND- and DD-CKD treated with HIF-PHIs.

Effect of HIF-PHIs on Health-Related Quality of Life (HRQoL)

Several large Phase 3 HIF-PHI trials have included assessments of QoL as exploratory or secondary endpoints.[29-31, 47] These trials have used different scoring systems which may limit comparability across trials.[29-31, 47] Numerical improvements, in particular for the SF-36 Physical Functioning subscore, were reported in the OLYMPUS trial which compared roxadustat to placebo.[31] Data from the smaller dedicated ASCEND-NHQ study in ND-CKD patients, which evaluated the effects of daprodustat versus placebo on QoL using the SF-36 Vitality score, suggested higher vitality score (fatigue) in those receiving daprodustat.[68] In general, assessment of differences in HRQoL is difficult in trials that do not have a double-blinded design.

The patient representatives in attendance felt that although HRQoL was important, a new treatment should ideally be superior to the current standard of care for both safety and efficacy. However, some patients who were not treated with hemodialysis would prefer an oral option over an injection if safety and efficacy were similar.

Safety of HIF-PHIs

Cardiovascular outcomes

Cardiovascular safety signals from clinical trials of ESAs targeting normal or near-normal Hb concentrations led to labelling changes by the US Food and Drug Administration (FDA) beginning in 2007.[69] The current FDA labels for ESAs include warnings on increased risk of death, serious adverse cardiovascular events, and stroke when ESAs are administered to target Hb levels >11 g/dl. No trial has identified an ideal target Hb level, ESA dose, or dosing strategy that does not increase these risks. Thus, for HIF-PHI approval, regulatory agencies asked manufacturers to demonstrate non-inferiority or superiority of HIF-PHIs in terms of the risk for MACE in both dialysis and non-dialysis populations within target ranges recommended for ESAs.

*CKD not requiring dialysis (non-dialysis dependent, ND-CKD) (**Table 6**)*[21,29-31,34]

Roxadustat was the first HIF-PHI to be reviewed by the FDA. Data submitted in support of the New Drug Application included 3 separate trials comparing roxadustat with placebo that were pooled for meta-analyses in the ND-CKD (n = 4270) population.[70, 71] A fourth study comparing roxadustat to darbepoetin alfa was analyzed separately.[28] The pooled analyses for roxadustat did not have prespecified non-inferiority margins that were agreed upon by the FDA.[71, 72] Comparing the upper limits of the 95% CI against the pre-specified non-inferiority margin of daprodustat and vadadustat trials (HR 1.25), roxadustat would not have met the criteria for non-inferiority in pooled analyses of MACE in the ND-CKD population when compared with placebo: HR 1.10; 95% CI: 0.96-1.27. In further on-treatment sensitivity analyses (as opposed to intention-to-treat analysis) requested by the FDA to minimize the effect of including unexposed person-times or events that may not be affected by the intervention, this risk was heightened.[72] When assessing events occurring while patients were on treatment and for one week after discontinuation (on-treatment + 7 days analyses), 277 (7.2%) events were recorded in the roxadustat arm compared with 131 (5.6%) events in the placebo arm (HR 1.38; 95% CI: 1.11-1.70). A caveat in these analyses is the higher dropout rates in the placebo compared to roxadustat arms, with potential for bias that may have disadvantaged roxadustat.

Vadadustat ND-CKD Phase 3 trials of ESA-treated (n = 1725) and ESA-untreated (n = 1751) patients were pooled, as pre-specified, with darbepoetin alfa as the comparator arm in both trials.[34] The primary MACE analysis did not meet the pre-specified HR=1.30 non-inferiority margin (HR 1.17; 95% CI: 1.01-1.36), and showed a higher risk of MACE in the vadadustat arm. The excess risk was accounted for by nonfatal MI and death from non-cardiovascular causes. Subgroup analyses found a regional difference in the study results, with the increased MACE risk observed in non-U.S. study sites (HR 1.30; 95% CI 1.05-1.62) but no difference in risk in the U.S. study sites (HR 1.06; 95% CI 0.87-1.29).[34]

Daprodustat non-inferiority trials met the pre-specified non-inferiority margins of a HR of 1.25 in primary analyses of the ND-CKD population in a mixed population of previously ESA-treated and untreated patients (HR: 1.03; 95% CI: 0.89-1.19) in comparison to darbepoetin alfa.[21] However, in the sensitivity on-treatment MACE analysis, which censored patients at 28 days after the last dose, participants randomized to daprodustat had a higher incidence of MACE than those randomized to ESA in the ND-CKD study (14.1% vs. 10.5%, HR 1.40; 95% CI: 1.17-1.68).[21] However, differences in the dosing frequency of daprodustat versus ESAs in this trial and differences in definitions of treatment periods may have led to potential bias that disadvantaged daprodustat.[21]

There was a general view among conference participants that major clinical trials have failed to conclusively demonstrate that HIF-PHIs are non-inferior to placebo or conventional ESAs in ND-CKD patients for cardiovascular outcomes. In fact, variable results have been reported for different HIF-PHIs and in different study settings, depending on the type of analyses being performed (e.g., intention-to-treat versus on-treatment analyses). Potential explanations for the differential effects on MACE outcomes between different trials and different agents may result from imbalances in patent characteristics or geographic location at baseline, or from non-matching intervals of follow-up assessment after the last study drug dose in different randomized groups.[73]

Dialysis-dependent (DD-CKD) population

In contrast to the ND-CKD trial results, there was consensus that HIF-PHIs in general met non-inferiority criteria for MACE in cardiovascular outcome trials in DD-CKD populations (**Table 7**)[36-38, 42-51] although controversies surrounding interpretation of the data were discussed. Moreover, in most clinical trials, efficacy and safety of HIF-PHIs was similar in incident and prevalent dialysis populations.

Three studies of roxadustat involving dialysis patients (N=3880) were meta-analyzed in a report submitted to the FDA.[70] All trials included in this report compared roxadustat to ESA. The analyses of the effect of roxadustat for MACE were discordant based on the analytical approach: in the primary, on-treatment + 7 day analyses, the risk of MACE was similar in the roxadustat and ESA groups: HR 1.02; 95% CI: 0.88-1.20. In the sensitivity, on-treatment analysis, the HR for the risk of MACE in patients treated with roxadustat versus ESA was 1.14; 95% CI: 1.00-1.30, a difference that just missed statistical significance for non-inferiority. A fourth trial conducted in Europe and not included in the pooled meta-analysis due to differences in study design demonstrated a higher risk of death in roxadustat vs. ESA-treated patients (8.9 per 100 patient years (PY) vs. 6.3 per 100 PY; HR 1.54, 95% CI 1.04-2.28).[70] In a published analysis of the four roxadustat trials in the DD-CKD population,[74] MACE and MACE+ (a composite of MACE plus unstable angina or congestive heart failure requiring hospitalization) in the on-treatment plus 7 day analyses showed different results in incident vs. prevalent dialysis patients, with the hazard ratio suggesting benefit in incident patients but harm in prevalent patients. In contrast to the ND-CKD studies, treatment duration was longer for the ESA group.

Vadadustat DD-CKD Phase 3 trials pooled two studies of prevalent (n = 3554) and incident (n = 369) patients, with darbepoetin alfa as the comparator group (**Table 3**).[51] Pooled results showed similar MACE rates in the two arms and met non-inferiority (HR 0.96; 95% CI: 0.83-1.11).[51] Sensitivity analyses were not available at the time of this conference.

Daprodustat trials met the pre-specified non-inferiority margin of 1.25 in primary analyses of the DD-CKD populations (DD: 0.93; 95% CI: 0.81-1.07).[21, 37] The sensitivity on-treatment analysis of the DD-CKD population was similar to the primary analysis (**Table 7**).

In most clinical trials, efficacy and safety of HIF-PHI were similar in incident and prevalent dialysis populations (**Tables 3 and 7**). A pooled analysis of roxadustat studies noted similar risk of MACE (HR 0.83; 95% CI: 0.61-1.13) and nominally lower risk of MACE+ (HR 0.76; 95% CI: 0.57-1.00) among incident dialysis patients treated with roxadustat, whereas roxadustat was less favorable for MACE (HR 1.18; 95% CI: 1.00-1.38) and all-cause mortality (HR 1.23; 95% CI: 1.02-1.49) in prevalent dialysis patients.[74] However, the statistical significance of this difference between incident and prevalent dialysis patients was not reported.

Despite overall consensus that HIF-PHI met non-inferiority criteria for MACE in cardiovascular outcome trials involving DD-CKD populations, it was recognized that controversy has surrounded interpretation of the relevant data for roxadustat in this context. This has been fueled by retraction of a published pooled analysis because of post-publication recognition of deviation from the prespecified analytical plan.[75]

Thromboembolic events, including vascular access thrombosis

Administration of HIF-PHIs has been associated with a higher risk of thrombotic events compared with ESAs or placebo.[76, 77] Although the underlying mechanisms are not understood and appear to be complex, they may be related to the steeper rate of rise in Hb as suggested by a recent FDA safety review for roxadustat.[76] In addition, HIF-PHI interactions with iron metabolism, i.e., upregulation of transferrin,[78] or the interference of HIF with the coagulation system, e.g., through increased expression of plasminogen activator inhibitor may contribute to thrombotic risk.[79]

Roxadustat showed an excess risk of thrombosis in both ND- (versus ESA) and DD-CKD (versus placebo) trials.[70] A pooled analysis of roxadustat trials showed higher risks of thromboembolic events that were associated with the rate of Hb rise.[71] It is

unclear, however, whether lower doses of roxadustat, which would be expected to lead to a slower rate of Hb rise, would ameliorate thrombosis risk while maintaining efficacy. Concerns surrounding the thrombotic risk with vadadustat were raised by the FDA although these concerns were not initially noted in published data.[80] Daprodustat trials have not reported excess risk of thrombosis compared with active comparator.[21, 37]

Hypertension

Pre-clinical studies in healthy rats and rats with CKD demonstrated that HIF-PHIs generate significant dose-dependent blood-pressure lowering effects.[81-83] However, so far, no significant blood pressure effects have been reported in any HIF-PHI phase 3 programs. The results from a dedicated blood pressure study with daprodustat (ASCEND-BP) have not yet been published (NCT03029247).

Lipid metabolism

Theoretically, HIF-dependent increases in lipoprotein uptake and reductions in cholesterol synthesis via enhanced degradation of 3-hydroxy-3-methyl-glutaryl-CoA reductase may lead to lower blood cholesterol levels with HIF-PHI treatment.[84, 85] Although dedicated clinical studies specifically focused on the interactions between HIF-PHIs and lipid metabolism have not yet been conducted, significant and consistent reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were reported in patients treated with roxadustat or daprodustat (ND- and DD-CKD).[20, 26, 29, 32, 42, 46, 47, 49, 63, 65] These reductions were not seen in patients treated with enarodustat, molidustat or vadadustat,[23, 24, 40, 53, 55, 86, 87] clearly indicating that different compounds may have different properties. To what degree cholesterol-lowering effects of daprodustat and roxadustat might impact cardiovascular risk in patients with CKD anemia is not clear. Given the lack of clear cardiovascular benefits with the initiation of statin therapy in dialysis patients,[88] HIF-PHI-mediated interactions with lipid metabolism may not necessarily translate into clinical benefits, even when considering long-term effects beyond the exposure in studies conducted so far.

Kidney disease progression

Pharmacologic HIF activation has been studied in multiple kidney disease models using pharmacologic and genetic approaches.[4] Experimental studies have consistently demonstrated renoprotective effects of HIF activation in acute kidney injury models, whereas the effects of HIF activation in models of chronic kidney injury appeared to be context-dependent and less consistent.[4] This has raised concerns that anemia therapy with HIF-PHIs may worsen CKD in certain subgroups of patients. In one trial of molidustat versus ESA, the risk of CKD progression was higher with molidustat, though whether this finding is specific to molidustat is unclear.[25]

Prespecified secondary analyses of Phase 3 trials of daprodustat and vadadustat in ND-CKD patients showed no beneficial or harmful effects of either drug on CKD outcomes, including the need for dialysis, kidney transplantation, or >40% decline in eGFR.[21, 34] A Phase 3 trial of roxadustat[31] suggested greater decline in kidney function compared with placebo. The annual rate of change in eGFR was -3.70 ml/min per 1.73 m^2 with roxadustat and -3.19 ml/min per 1.73 m^2 with placebo (difference -0.51 ml/min per 1.73 m^2; 95% CI: −1.00 - −0.01; nominal P = 0.046). Conference participants agreed that data from CKD anemia trials reported so far do not suggest any clinically relevant impact of HIF-PHIs on kidney disease progression, but also pointed out that these trials were not specifically designed to evaluate such effects.

Malignancy risk

Adaptation to regional hypoxia mediated by the HIF-pathway plays an important role in tumor progression.[89] Moreover, genetic HIF activation is a central mechanism of tumorigenesis in patients with the von Hippel-Lindau (VHL) disease and clear cell renal carcinomas.[90] This and other evidence implies that cancer initiation and/or progression could be an adverse event associated with HIF-PHI use.

While the HIF-PHI phase 3 studies have mostly not shown any signals supporting this assumption, in the ASCEND-ND trial, cancer-related death or tumor progression or recurrence was more commonly observed in those randomized to

daprodustat (72 of 1937, 3.7%) than in those randomized to darbepoetin alfa (49 of 1933, 2.5%), with relative risk of 1.47 (95% CI: 1.03- 2.10).[21] *Post hoc* analyses that accounted for differential dosing frequency attenuated this observed risk.[21] A clinical trial of molidustat also reported neoplasms in 9.8% of trial participants in the molidustat group compared with 5.3% in the darbepoetin group.[41] The conference participants agreed that there has been no consistent signal across the HIF-PHIs of an excess risk of malignancy-related adverse events, but the accrued exposure time in clinical trials and clinical practice has not been long enough to be confident of the absence of a clinically relevant risk compared with ESAs, and patients with a history of recent or active malignancy were excluded from trials. Post-marketing surveillance will be important to confirm the safety of HIF-PHIs from the standpoint of cancer risk and provide longer-term follow-up data, and avoidance of HIF-PHIs in patients with a history of malignancy is recommended.

Additional safety concerns

An approximate 2-fold increase in the risk for sepsis and septic shock was reported for roxadustat in ND-CKD patients (pooled studies).[76] No increased risk of infections has been noted in the serious adverse events of other trials.[21, 34, 37, 51]

Upregulation of vascular endothelial growth factor by the HIF pathway may increase angiogenesis and therefore in theory worsen diabetic retinopathy and age-related macular degeneration.[91, 92] All HIF-PHI trials have included individuals with diabetes at risk for diabetic retinopathy. However, to date, retinopathy has not been reported to worsen during treatment with HIF-PHIs.[93]

Although higher rates of hyperkalemia and low serum bicarbonate have been reported for HIF-PHIs in some studies,[26, 29, 42, 94-96] such data have not been reproduced by centralized laboratory analysis or in larger trials.[33, 34, 50, 51]

Central hypothyroidism has been reported in patients treated with roxadustat,[97-99] and the Japanese regulatory agency recently added central hypothyroidism as a potential complication of roxadustat in the package insert. This may be due to the

structure of roxadustat, which has a molecular structure similar to triiodothyronine (T3), so that its binding to thyroid hormone receptor β may lead to the down-regulation of thyrotropin releasing hormone (TRH). There has been no report of hypothyroidism as a complication in patients treated with other HIF-PHIs according to our knowledge.

Other clinically significant adverse events may become more apparent as we gain experience with the use of HIF-PHIs in clinical practice.

Practical considerations

Dosing considerations

There have been no head-to-head trials comparing different HIF-PHIs in patients with ND- or DD-CKD. However, marked differences exist in potency, dose requirements, and presumably pharmacokinetics. Phase 3 trials generally showed good efficacy in achieving and maintaining target Hb ranges overall and in subgroups based on age, sex, race, and dialysis modality. There was consensus among conference participants that the appropriate dose depends on the drug and should follow label recommendations. There was also general consensus that the starting HIF-PHI dose should be lower for those who are ESA-naïve versus those who are not. Based on the current Hb and the achieved change in Hb (typically over a 4-week period), the dosing in phase 3 trials was maintained or changed in stepwise fashion. Treatment was temporarily discontinued when Hb exceeded 12 or 13 g/dl in most studies.[21, 22, 24-26, 31, 34, 35, 37, 39, 42, 46, 51, 54-56, 100, 101] Conference participants generally felt that in clinical routine the HIF-PHI dose should be maintained or changed in similar stepwise fashion as in trial protocols based on the current Hb and its rate of change.

Use of HIF-PHIs in subpopulations of interest

Patients hyporesponsive to ESAs

By lowering hepcidin levels, HIF-PHIs may theoretically be more effective in treating patients who are hyporesponsive to ESAs because of chronic inflammation or functional iron deficiency. Preliminary data suggest that whereas higher doses of ESAs are needed for patients with high C-reactive protein (CRP) levels, this may not be true for HIF-PHIs.[16, 45] However, CRP concentrations that were considered high in trial participants were only slightly elevated, and sicker and more inflamed patients may have been less likely to have been enrolled in trials of HIF-PHIs. Conference participants also felt that data on the effect of HIF-PHIs in ESA-hyporesponsive patients are limited.

Although the use of HIF-PHIs in combination with ESAs might theoretically be advantageous for patients who are ESA hyporesponsive, there are no data available to support this strategy in clinical practice at present.[102] As with all drugs, there is a risk for drug-drug interactions with the use of HIF-PHIs, particularly in combination with other oral agents (**Supplemental Table 2**).

Children

Anemia is also a common complication of CKD in children and is associated with decreased quality of life, reduced neurocognitive ability, left ventricular hypertrophy, and increased risk of hospitalizations.[103] Pain has also been reported with subcutaneous injections of ESAs, making an oral formulation for anemia treatment especially attractive in the pediatric population.[104] However, participants felt that there are insufficient data supporting the use of HIF-PHIs in pediatric patients with anemia of CKD because patients under the age of 18 years were excluded from all Phase 3 trials.[105] Several new trials with roxadustat, daprodustat, and molidustat are planned in pediatric patients after completion of Phase 3 trials in adults.

Polycystic kidney disease

HIF activation occurs in polycystic kidneys in humans and rodents and activation of the HIF–pathway has been shown to enhance cyst expansion in preclinical models.[106] However, whether the use of HIF-PHIs to treat anemia may enhance cyst growth remains unclear. Nevertheless conference participants felt that these agents should not be used in patients with polycystic kidney disease until adequate safety data emerge.

Kidney transplantation

While kidney transplant recipients were excluded from Phase 3 trials of roxadustat and vadadustat, no formal exclusion of subjects with prior kidney transplant was stated in the Phase 3 trials of daprodustat.[21, 37, 107] However, whether subjects with a functioning kidney transplant at baseline were actually enrolled is currently unknown. HIF-PHIs play a role in immune cell function and therefore HIF-PHIs use could potentially promote graft rejection or increase the risk of malignancy.[108] There is limited experience of using HIF-PHIs in patients who are receiving immunosuppression, such as those with kidney allografts.

Other novel therapeutic agents

Several new agents have been introduced into clinical medicine that may be beneficial for patients with CKD anemia and might be used concurrently with ESAs or HIF-PHIs. Agents in clinical development have been discussed during the first KDIGO Controversies in Optimal Anemia Management Conference in 2019 and are not further discussed here.[3] In analogy with HIF-PHIs, SGLT2 inhibitors (SGLT2i) are also considered to stimulate endogenous EPO production.

SGLT2 inhibitors

In addition to their antidiabetic and beneficial cardiovascular and kidney effects, SGLT2i have been shown to increase Hb in patients with kidney disease and/or heart failure.[109-114] Because increased Hb in patients treated with SGLT2i appears to be independent of diuretic use and/or rate of intravascular volume depletion,[115] SGLT2i-

induced changes in Hb are no longer believed to simply reflect hemoconcentration due to diuresis.[116] In fact, SGLT2i administration was associated with transient increases in serum EPO concentrations (30-40%), an increase in reticulocyte counts, a decrease in ferritin and hepcidin, indicating erythropoietic stimulation.[117-120] It has been hypothesized that these pro-erythropoietic actions may have contributed to SGLT2i-mediated protective effects on heart failure outcomes and kidney disease progression.[109-111] Although current data suggest that SGLT2i may provide beneficial "anti-anemic" effects and delay or prevent the initiation of anemia therapy,[121] conference participants agreed that more information is needed to better understand the mechanisms of action underlying these effects and their clinical relevance.

Conclusions

In summary, HIF-PHIs are non-inferior to conventional ESAs in increasing and maintaining Hb concentrations in patients with NDD- and DD-CKD, and reduce transfusion requirements when compared with placebo. In terms of cardiovascular safety, HIF-PHIs are inferior, or at best similar to conventional ESAs. Different safety signals were observed for different HIF-PHIs across large phase 3 trial programs, and concerns surrounding cardiovascular and thrombotic risks persist. The data that are currently available do not support the concept that use of HIF-PHIs will reduce the need for IV or oral iron supplementation among patients with NDD- or DD-CKD nor have superior efficacy in the correction of anemia in states of chronic inflammation. However, published trials to date were not designed to address these questions, and iron was administered according to trial protocols which varied widely. Studies examining alternative iron dosing strategies in patients receiving HIF-PHIs are needed. Currently, there are insufficient data to determine whether use of HIF-PHIs improves quality of life in patients with ND-CKD. Further research recommendations are provided in **Table 8**.

DISCLOSURES

The conference was sponsored by KDIGO and was in part supported by unrestricted educational grants from 7 Elements Global, Akebia Therapeutics, Amgen, Astellas, AstraZeneca, GlaxoSmithKline, Mitsubishi Tanabe Pharma Group, Otsuka, Roche, Rockwell Medical, Torii Pharmaceutical Co., Ltd., US Renal Care, and Vifor Fresenius Medical Care Renal Pharma.

Tables

Table 1: Potential advantages and disadvantages of various CKD-anemia therapies

Table 2: Efficacy data from phase 3 HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Table 3: Efficacy data from phase 3 HIF-PHI clinical trials in patients with dialysis-dependent chronic kidney disease

Table 4: Iron parameters from phase 3 HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Table 5: Iron parameters from phase 3 HIF-PHI clinical trials in dialysis-dependent chronic kidney disease

Table 6: Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Table 7: Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in dialysis-dependent chronic kidney disease

Table 8: Research recommendations

Supplemental Table 1: Availability of HIF-PHIs (as of April 24, 2023)

Supplemental Table 2: Drug-drug interactions of HIF-PHIs

REFERENCES

1. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol* 2012; **23:** 1631-1634.

2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl*. 2012; 2: 279–335.

3. Babitt JL, Eisenga MF, Haase VH*, et al.* Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. *Kidney international* 2021; **99:** 1280-1295.

4. Schodel J, Ratcliffe PJ. Mechanisms of hypoxia signalling: new implications for nephrology. *Nat Rev Nephrol* 2019; **15:** 641-659.

5. Barrett TD, Palomino HL, Brondstetter TI*, et al.* Prolyl hydroxylase inhibition corrects functional iron deficiency and inflammation-induced anaemia in rats. *Br J Pharmacol* 2015; **172:** 4078-4088.

6. Rankin EB, Biju MP, Liu Q*, et al.* Hypoxia-inducible factor-2 (HIF-2) regulates hepatic erythropoietin in vivo. *J Clin Invest* 2007; **117:** 1068-1077.

7. Sun CC, Vaja V, Chen S*, et al.* A hepcidin lowering agent mobilizes iron for incorporation into red blood cells in an adenine-induced kidney disease model of anemia in rats. *Nephrol Dial Transplant* 2013; **28:** 1733-1743.

8. Haase VH. Pathophysiological Consequences of HIF Activation: HIF as a modulator of fibrosis. *Ann N Y Acad Sci* 2009; **1177:** 57-65.

9. Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease. *Kidney Int Suppl (2011)* 2021; **11:** 8-25.

10. Hanudel MR, Wong S, Jung G*, et al.* Amelioration of chronic kidney disease-associated anemia by vadadustat in mice is not dependent on erythroferrone. *Kidney international* 2021; **100:** 79-89.

11. Nicolas G, Chauvet C, Viatte L*, et al.* The gene encoding the iron regulatory peptide hepcidin is regulated by anemia, hypoxia, and inflammation. *J Clin Invest* 2002; **110:** 1037-1044.

12. Bruick RK, McKnight SL. A conserved family of prolyl-4-hydroxylases that modify HIF. *Science* 2001; **294:** 1337-1340.

13. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: A potential new treatment for anemia in patients with CKD. *Am J Kidney Dis* 2017; **69:** 815-826.

14. Kurata Y, Tanaka T, Nangaku M. Hypoxia-inducible factor prolyl hydroxylase inhibitor in the treatment of anemia in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2020; **29:** 414-422.

15. Sugahara M, Tanaka T, Nangaku M. Prolyl hydroxylase domain inhibitors as a novel therapeutic approach against anemia in chronic kidney disease. *Kidney international* 2017; **92:** 306-312.

16. Provenzano R, Besarab A, Wright S*, et al.* Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study. *Am J Kidney Dis* 2016; **67:** 912-924.

17. Hill P, Shukla D, Tran MG*, et al.* Inhibition of hypoxia inducible factor hydroxylases protects against renal ischemia-reperfusion injury. *J Am Soc Nephrol* 2008; **19:** 39-46.

18. Kapitsinou PP, Jaffe J, Michael M*, et al.* Preischemic targeting of HIF prolyl hydroxylation inhibits fibrosis associated with acute kidney injury. *Am J Physiol Renal Physiol* 2012; **302:** F1172-1179.

19. Natale P, Palmer SC, Jaure A*, et al.* Hypoxia-inducible factor stabilisers for the anaemia of chronic kidney disease. *Cochrane Database Syst Rev* 2022; **8:** CD013751.

20. Nangaku M, Hamano T, Akizawa T*, et al.* Daprodustat Compared with Epoetin Beta Pegol for Anemia in Japanese Patients Not on Dialysis: A 52-Week Randomized Open-Label Phase 3 Trial. *Am J Nephrol* 2021; **52:** 26-35.

21. Singh AK, Carroll K, McMurray JJV*, et al.* Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis. *N Engl J Med* 2021; **385:** 2313-2324.

22. Agrawal D, Varade D, Shah H*, et al.* Desidustat in Anemia due to Non-Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-ND). *Am J Nephrol* 2022; **53:** 352-360.

23. Akizawa T, Nangaku M, Yamaguchi T*, et al.* A Phase 3 Study of Enarodustat in Anemic Patients with CKD not Requiring Dialysis: The SYMPHONY ND Study. *Kidney Int Rep* 2021; **6:** 1840-1849.

24. Yamamoto H, Nobori K, Matsuda Y*, et al.* Efficacy and Safety of Molidustat for Anemia in ESA-Naive Nondialysis Patients: A Randomized, Phase 3 Trial. *Am J Nephrol* 2021; **52:** 871-883.

25. Yamamoto H, Nobori K, Matsuda Y*, et al.* Molidustat for Renal Anemia in Nondialysis Patients Previously Treated with Erythropoiesis-Stimulating Agents: A Randomized, Open-Label, Phase 3 Study. *Am J Nephrol* 2021; **52:** 884-893.

26. Chen N, Hao C, Peng X*, et al.* Roxadustat for anemia in patients with kidney disease not receiving dialysis. *N Engl J Med* 2019; **381:** 1001-1010.

27. Akizawa T, Yamaguchi Y, Otsuka T*, et al.* A Phase 3, Multicenter, Randomized, Two-Arm, Open-Label Study of Intermittent Oral Dosing of Roxadustat for the Treatment of Anemia in Japanese Erythropoiesis-Stimulating Agent-Naive Chronic Kidney Disease Patients Not on Dialysis. *Nephron* 2020; **144:** 372-382.

28. Akizawa T, Iwasaki M, Otsuka T*, et al.* Phase 3 Study of Roxadustat to Treat Anemia in Non-Dialysis-Dependant CKD. *Kidney Int Rep* 2021; **6:** 1810-1828.

29. Shutov E, Sulowicz W, Esposito C*, et al.* Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, double-blind, placebo-controlled study (ALPS). *Nephrol Dial Transplant* 2021; **36:** 1629-1639.

30. Coyne DW, Roger SD, Shin SK*, et al.* Roxadustat for CKD-related Anemia in Non-dialysis Patients. *Kidney Int Rep* 2021; **6:** 624-635.

31. Fishbane S, El-Shahawy MA, Pecoits-Filho R*, et al.* Roxadustat for Treating Anemia in Patients with CKD Not on Dialysis: Results from a Randomized Phase 3 Study. *J Am Soc Nephrol* 2021; **32:** 737-755.

32. Barratt J, Andric B, Tataradze A*, et al.* Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, open-label, active-controlled study (DOLOMITES). *Nephrol Dial Transplant* 2021; **36:** 1616-1628.

33. Nangaku M, Kondo K, Kokado Y*, et al.* Phase 3 Randomized Study Comparing Vadadustat with Darbepoetin Alfa for Anemia in Japanese Patients with Nondialysis-Dependent CKD. *J Am Soc Nephrol* 2021; **32:** 1779-1790.

34. Chertow GM, Pergola PE, Farag YMK, *et al.* Vadadustat in Patients with Anemia and Non-Dialysis-Dependent CKD. *N Engl J Med* 2021; **384:** 1589-1600.

35. Akizawa T, Nangaku M, Yonekawa T, *et al.* Efficacy and Safety of Daprodustat Compared with Darbepoetin Alfa in Japanese Hemodialysis Patients with Anemia: A Randomized, Double-Blind, Phase 3 Trial. *Clin J Am Soc Nephrol* 2020; **15:** 1155-1165.

36. Singh AK, Cizman B, Carroll K, *et al.* Efficacy and Safety of Daprodustat for Treatment of Anemia of Chronic Kidney Disease in Incident Dialysis Patients: A Randomized Clinical Trial. *JAMA Intern Med* 2022; **182:** 592-602.

37. Singh AK, Carroll K, Perkovic V, *et al.* Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis. *N Engl J Med* 2021; **385:** 2325-2335.

38. Coyne DW, Singh AK, Lopes RD, *et al.* Three Times Weekly Dosing of Daprodustat versus Conventional Epoetin for Treatment of Anemia in Hemodialysis Patients: ASCEND-TD: A Phase 3 Randomized, Double-Blind, Noninferiority Trial. *Clin J Am Soc Nephrol* 2022; **17:** 1325-1336.

39. Gang S, Khetan P, Varade D, *et al.* Desidustat in Anemia due to Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-D). *Am J Nephrol* 2022; **53:** 343-351.

40. Akizawa T, Nangaku M, Yamaguchi T, *et al.* A Phase 3 Study of Enarodustat (JTZ-951) in Japanese Hemodialysis Patients for Treatment of Anemia in Chronic Kidney Disease: SYMPHONY HD Study. *Kidney Dis (Basel)* 2021; **7:** 494-502.

41. Akizawa T, Yamada T, Nobori K, *et al.* Molidustat for Japanese Patients With Renal Anemia Receiving Dialysis. *Kidney Int Rep* 2021; **6:** 2604-2616.

42. Chen N, Hao C, Liu BC, *et al.* Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis. *N Engl J Med* 2019; **381:** 1011-1022.

43. Akizawa T, Ueno M, Shiga T, *et al.* Oral roxadustat three times weekly in ESA-naive and ESA-converted patients with anemia of chronic kidney disease on hemodialysis: Results from two phase 3 studies. *Ther Apher Dial* 2020; **24:** 628-641.

44. Akizawa T, Otsuka T, Reusch M, *et al.* Intermittent Oral Dosing of Roxadustat in Peritoneal Dialysis Chronic Kidney Disease Patients with Anemia: A Randomized, Phase 3, Multicenter, Open-Label Study. *Ther Apher Dial* 2020; **24:** 115-125.

45. Akizawa T, Iwasaki M, Yamaguchi Y*, et al.* Phase 3, Randomized, Double-Blind, Active-Comparator (Darbepoetin Alfa) Study of Oral Roxadustat in CKD Patients with Anemia on Hemodialysis in Japan. *J Am Soc Nephrol* 2020; **31:** 1628-1639.

46. Provenzano R, Shutov E, Eremeeva L*, et al.* Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. *Nephrol Dial Transplant* 2021; **36:** 1717-1730.

47. Csiky B, Schomig M, Esposito C*, et al.* Roxadustat for the Maintenance Treatment of Anemia in Patients with End-Stage Kidney Disease on Stable Dialysis: A European Phase 3, Randomized, Open-Label, Active-Controlled Study (PYRENEES). *Adv Ther* 2021; **38:** 5361-5380.

48. Fishbane S, Pollock CA, El-Shahawy M*, et al.* Roxadustat Versus Epoetin Alfa for Treating Anemia in Patients with Chronic Kidney Disease on Dialysis: Results from the Randomized Phase 3 ROCKIES Study. *J Am Soc Nephrol* 2022; **33:** 850-866.

49. Charytan C, Manllo-Karim R, Martin ER*, et al.* A Randomized Trial of Roxadustat in Anemia of Kidney Failure: SIERRAS Study. *Kidney Int Rep* 2021; **6:** 1829-1839.

50. Nangaku M, Kondo K, Ueta K*, et al.* Efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese anemic patients on hemodialysis: a Phase 3, multicenter, randomized, double-blind study. *Nephrol Dial Transplant* 2021; **36:** 1731-1741.

51. 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:** 1601-1612.

52. Mauri L, D'Agostino RB, Sr. Challenges in the Design and Interpretation of Noninferiority Trials. *N Engl J Med* 2017; **377:** 1357-1367.

53. Akizawa T, Nangaku M, Yamaguchi T*, et al.* A Placebo-Controlled, Randomized Trial of Enarodustat in Patients with Chronic Kidney Disease Followed by Long-Term Trial. *Am J Nephrol* 2019; **49:** 165-174.

54. Akizawa T, Nobori K, Matsuda Y*, et al.* Molidustat for anemia correction in Japanese patients undergoing hemodialysis: a single-arm, phase 3 study. *Ther Apher Dial* 2021; **25:** 917-925.

55. Macdougall IC, Akizawa T, Berns JS*, et al.* Effects of Molidustat in the Treatment of Anemia in CKD. *Clin J Am Soc Nephrol* 2019; **14:** 28-39.

56. Kanai H, Nangaku M, Nagai R*, et al.* Efficacy and safety of daprodustat in Japanese peritoneal dialysis patients. *Ther Apher Dial* 2021; **25:** 979-987.

57. Besarab A, Bolton WK, Browne JK, *et al.* The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; **339:** 584-590.

58. Drüeke TB, Locatelli F, Clyne N, *et al.* Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia. *New England Journal of Medicine* 2006; **355:** 2071-2084.

59. Singh AK, Szczech L, Tang KL, *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355:** 2085-2098.

60. Pfeffer MA, Burdmann EA, Chen CY, *et al.* A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; **361:** 2019-2032.

61. Macdougall IC, White C, Anker SD, *et al.* Intravenous Iron in Patients Undergoing Maintenance Hemodialysis. *N Engl J Med* 2019; **380:** 447-458.

62. Agarwal AK. Iron metabolism and management: focus on chronic kidney disease. *Kidney Int Suppl (2011)* 2021; **11:** 46-58.

63. Akizawa T, Tsubakihara Y, Nangaku M, *et al.* Effects of Daprodustat, a Novel Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor on Anemia Management in Japanese Hemodialysis Subjects. *Am J Nephrol* 2017; **45:** 127-135.

64. Besarab A, Chernyavskaya E, Motylev I, *et al.* Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients. *J Am Soc Nephrol* 2016; **27:** 1225-1233.

65. Holdstock L, Meadowcroft AM, Maier R, *et al.* Four-Week Studies of Oral Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor GSK1278863 for Treatment of Anemia. *J Am Soc Nephrol* 2016; **27:** 1234-1244.

66. Guedes M, Muenz D, Zee J, *et al.* Serum biomarkers of iron stores are associated with worse physical health-related quality of life in nondialysis-dependent chronic kidney disease patients with or without anemia. *Nephrol Dial Transplant* 2021; **36:** 1694-1703.

67. Guedes M, Muenz DG, Zee J, *et al.* Serum Biomarkers of Iron Stores Are Associated with Increased Risk of All-Cause Mortality and Cardiovascular Events in Nondialysis CKD Patients, with or without Anemia. *J Am Soc Nephrol* 2021; **32:** 2020-2030.

68. Johansen KL, Cobitz AR, Singh AK, *et al*. The ASCEND-NHQ trial found positive effects of daprodustat on hemoglobin and quality of life in patients with non-dialysis-dependent

chronic kidney disease. *Kidney Int* (in press). DOI: https://doi.org/10.1016/j.kint.2023.02.019.

69. FDA. FDA Drug Safety Communication: Modified Dosing Recommendations to Improve the Safe Use of Erythropoiesis-Stimulating Agents in Chronic Kidney Disease. (http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm).

70. FDA. Cardiovascular and Renal Drugs Advisory Committee Meeting - Roxadustat. https://www.fda.gov/media/150728/download.

71. Provenzano R, Szczech L, Leong R*, et al.* Efficacy and Cardiovascular Safety of Roxadustat for Treatment of Anemia in Patients with Non-Dialysis-Dependent CKD: Pooled Results of Three Randomized Clinical Trials. *Clin J Am Soc Nephrol* 2021; **16:** 1190-1200.

72. Winkelmayer WC, Walther CP. Cardiovascular Safety of Roxadustat in CKD Anemia: A Fig Leaf Named Noninferiority. *Clin J Am Soc Nephrol* 2021; **16:** 1155-1157.

73. Mc Causland FR, Singh AK, Claggett BL*, et al.* Daprodustat and On-Treatment Cardiovascular Events in Chronic Kidney Disease. Reply. *N Engl J Med* 2022; **387:** 2482-2485.

74. Barratt J, Sulowicz W, Schomig M*, et al.* Efficacy and Cardiovascular Safety of Roxadustat in Dialysis-Dependent Chronic Kidney Disease: Pooled Analysis of Four Phase 3 Studies. *Adv Ther* 2021; **38:** 5345-5360.

75. Provenzano R, Fishbane S, Szczech L*, et al.* Retraction notice to "Pooled Analysis of Roxadustat for Anemia in Patients With Kidney Failure Incident to Dialysis." Kidney Int Rep. 2021;6:613-623. *Kidney Int Rep* 2022; **7:** 665.

76. FDA. Roxadustat for the Treatment of Anemia Due to Chronic Kidney Disease in Adult Patients not on Dialysis and on Dialysis. FDA Presentation: Cardiovascular and Renal Drugs Advisory Committee Meeting. 2021. Available at: https://www.fda.gov/media/150756/download. Accessed January 27, 2023.

77. Yap DYH, McMahon LP, Hao CM*, et al.* Recommendations by the Asian Pacific society of nephrology (APSN) on the appropriate use of HIF-PH inhibitors. *Nephrology (Carlton)* 2021; **26:** 105-118.

78. Tang X, Fang M, Cheng R*, et al.* Iron-Deficiency and Estrogen Are Associated With Ischemic Stroke by Up-Regulating Transferrin to Induce Hypercoagulability. *Circ Res* 2020; **127:** 651-663.

79. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. *Thromb Res* 2019; **181:** 77-83.

80. Akebia Therapeutics Receives Complete Response Letter from the FDA for Vadadustat for the Treatment of Anemia due to Chronic Kidney Disease in Adult Patients. Press release, March 30, 2022. https://ir.akebia.com/news-releases/news-release-details/akebia-therapeutics-receives-complete-response-letter-fda.

81. Burmakin M, Fasching A, Kobayashi H*, et al.* Pharmacological HIF-PHD inhibition reduces renovascular resistance and increases glomerular filtration by stimulating nitric oxide generation. *Acta Physiol (Oxf)* 2021; **233:** e13668.

82. Flamme I, Oehme F, Ellinghaus P*, et al.* Mimicking hypoxia to treat anemia: HIF-stabilizer BAY 85-3934 (Molidustat) stimulates erythropoietin production without hypertensive effects. *PLoS One* 2014; **9:** e111838.

83. Yu J, Wang S, Shi W*, et al.* Roxadustat prevents Ang II hypertension by targeting angiotensin receptors and eNOS. *JCI Insight* 2021; **6:** e133690.

84. Hwang S, Nguyen AD, Jo Y*, et al.* Hypoxia-inducible factor 1alpha activates insulin-induced gene 2 (Insig-2) transcription for degradation of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase in the liver. *J Biol Chem* 2017; **292:** 9382-9393.

85. Shen GM, Zhao YZ, Chen MT*, et al.* Hypoxia-inducible factor-1 (HIF-1) promotes LDL and VLDL uptake through inducing VLDLR under hypoxia. *Biochem J* 2012; **441:** 675-683.

86. Akizawa T, Nangaku M, Yamaguchi T*, et al.* Two long-term phase 3 studies of enarodustat (JTZ-951) in Japanese anemic patients with chronic kidney disease not on dialysis or on maintenance hemodialysis: SYMPHONY ND-Long and HD-Long studies. *Ther Apher Dial* 2022; **26:** 345-356.

87. Nangaku M, Farag YMK, deGoma E*, et al.* Vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, for treatment of anemia of chronic kidney disease: two randomized Phase 2 trials in Japanese patients. *Nephrol Dial Transplant* 2020**:** gfaa060.

88. Ku E, Campese V. Is lipid management effective for all stages of CKD? *Blood Purif* 2013; **35:** 26-30.

89. Rashid M, Zadeh LR, Baradaran B*, et al.* Up-down regulation of HIF-1α in cancer progression. *Gene* 2021; **798:** 145796.

90. Haase VH. The VHL tumor suppressor: master regulator of HIF. *Curr Pharm Des* 2009; **15:** 3895-3903.

91. Barben M, Samardzija M, Grimm C. The Role of Hypoxia, Hypoxia-Inducible Factor (HIF), and VEGF in Retinal Angiomatous Proliferation. *Adv Exp Med Biol* 2018; **1074:** 177-183.

92. Zhang D, Lv FL, Wang GH. Effects of HIF-1alpha on diabetic retinopathy angiogenesis and VEGF expression. *Eur Rev Med Pharmacol Sci* 2018; **22:** 5071-5076.

93. Sepah YJ, Nguyen QD, Yamaguchi Y*, et al.* Two Phase 3 Studies on Ophthalmologic Effects of Roxadustat Versus Darbepoetin. *Kidney Int Rep* 2022; **7:** 763-775.

94. Besarab A, Provenzano R, Hertel J*, et al.* Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. *Nephrol Dial Transplant* 2015; **30:** 1665-1673.

95. Meadowcroft AM, Cizman B, Holdstock L*, et al.* Daprodustat for anemia: a 24-week, open-label, randomized controlled trial in participants on hemodialysis. *Clin Kidney J* 2019; **12:** 139-148.

96. Pergola PE, Spinowitz BS, Hartman CS*, et al.* Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. *Kidney international* 2016; **90:** 1115-1122.

97. Ichii M, Mori K, Miyaoka D*, et al.* Suppression of thyrotropin secretion during roxadustat treatment for renal anemia in a patient undergoing hemodialysis. *BMC Nephrol* 2021; **22:** 104.

98. Tokuyama A, Kadoya H, Obata A*, et al.* Roxadustat and thyroid-stimulating hormone suppression. *Clin Kidney J* 2021; **14:** 1472-1474.

99. Cheng Y, Xiang Q, Cao T*, et al.* Suppression of thyroid profile during roxadustat treatment in chronic kidney disease patients. *Nephrol Dial Transplant* 2023.

100. Nangaku M, Kondo K, Takabe S*, et al.* Vadadustat for anemia in chronic kidney disease patients on peritoneal dialysis: A phase 3 open-label study in Japan. *Ther Apher Dial* 2021; **25:** 642-653.

101. Nangaku M, Kondo K, Takabe S*, et al.* A phase 3, open-label, single-arm study of vadadustat for anemia in chronic kidney disease for Japanese patients on hemodialysis not receiving erythropoiesis-stimulating agents. *Ther Apher Dial* 2022; **26:** 45-54.

102. Joharapurkar AA, Patel VJ, Kshirsagar SG*, et al.* Prolyl hydroxylase inhibitor desidustat improves anemia in erythropoietin hyporesponsive state. *Curr Res Pharmacol Drug Discov* 2022; **3:** 100102.

103. Atkinson MA, Martz K, Warady BA*, et al.* Risk for anemia in pediatric chronic kidney disease patients: a report of NAPRTCS. *Pediatr Nephrol* 2010; **25:** 1699-1706.

104. Schmitt CP, Nau B, Brummer C*, et al.* Increased injection pain with darbepoetin-alpha compared to epoetin-beta in paediatric dialysis patients. *Nephrol Dial Transplant* 2006; **21:** 3520-3524.

105. Kular D, Macdougall IC. HIF stabilizers in the management of renal anemia: from bench to bedside to pediatrics. *Pediatr Nephrol* 2019; **34:** 365-378.

106. Buchholz B, Eckardt KU. Role of oxygen and the HIF-pathway in polycystic kidney disease. *Cell Signal* 2020; **69:** 109524.

107. Perkovic V, Blackorby A, Cizman B*, et al.* The ASCEND-ND trial: study design and participant characteristics. *Nephrol Dial Transplant* 2022; **37:** 2157-2170.

108. Taylor CT, Doherty G, Fallon PG*, et al.* Hypoxia-dependent regulation of inflammatory pathways in immune cells. *J Clin Invest* 2016; **126:** 3716-3724.

109. Inzucchi SE, Zinman B, Fitchett D*, et al.* How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. *Diabetes Care* 2018; **41:** 356-363.

110. Li J, Neal B, Perkovic V*, et al.* Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. *Kidney international* 2020; **98:** 769-777.

111. Li J, Woodward M, Perkovic V*, et al.* Mediators of the Effects of Canagliflozin on Heart Failure in Patients With Type 2 Diabetes. *JACC Heart Fail* 2020; **8:** 57-66.

112. Marathias KP, Lambadiari VA, Markakis KP*, et al.* Competing Effects of Renin Angiotensin System Blockade and Sodium-Glucose Cotransporter-2 Inhibitors on Erythropoietin Secretion in Diabetes. *Am J Nephrol* 2020; **51:** 349-356.

113. Stefansson BV, Heerspink HJL, Wheeler DC*, et al.* Correction of anemia by dapagliflozin in patients with type 2 diabetes. *J Diabetes Complications* 2020; **34:** 107729.

114. Zinman B, Wanner C, Lachin JM*, et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373:** 2117-2128.

115. Jackson AM, Dewan P, Anand IS*, et al.* Dapagliflozin and Diuretic Use in Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF. *Circulation* 2020; **142:** 1040-1054.

116. Docherty KF, Curtain JP, Anand IS*, et al.* Effect of dapagliflozin on anaemia in DAPA-HF. *Eur J Heart Fail* 2021; **23:** 617-628.

117. Ferrannini E, Baldi S, Frascerra S*, et al.* Renal Handling of Ketones in Response to Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 2 Diabetes. *Diabetes Care* 2017; **40:** 771-776.

118. Ghanim H, Abuaysheh S, Hejna J*, et al.* Dapagliflozin Suppresses Hepcidin And Increases Erythropoiesis. *J Clin Endocrinol Metab* 2020; **105**.

119. Lambers Heerspink HJ, de Zeeuw D, Wie L*, et al.* Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab* 2013; **15:** 853-862.

120. Maruyama T, Takashima H, Oguma H*, et al.* Canagliflozin Improves Erythropoiesis in Diabetes Patients with Anemia of Chronic Kidney Disease. *Diabetes Technol Ther* 2019; **21:** 713-720.

121. Oshima M, Neuen BL, Jardine MJ*, et al.* Effects of canagliflozin on anaemia in patients with type 2 diabetes and chronic kidney disease: a post-hoc analysis from the CREDENCE trial. *Lancet Diabetes Endocrinol* 2020; **8:** 903-914.

Novel Anemia Therapies in CKD: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

Elaine Ku,[1,2,3] Lucia Del Vecchio,[4] Kai-Uwe Eckardt,[5] Volker H. Haase,[6] Kirsten L. Johansen,[7] Masaomi Nangaku,[8] Navdeep Tangri,[9] Sushrut S. Waikar,[10] Andrzej Więcek,[11] Michael Cheung,[12] Michel Jadoul,[13] Wolfgang C. Winkelmayer,[14] and David C. Wheeler[15] for Conference Participants*

[1]Division of Nephrology, Department of Medicine, University of California San Francisco, San Francisco, California, USA;
[2]Division of Pediatric Nephrology, Department of Pediatrics, University of California San Francisco, San Francisco, California, USA;
[3]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA;
[4]Department of Nephrology and Dialysis, Sant'Anna Hospital, ASST Lariana, Como, Italy;
[5]Department of Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany;
[6]Department of Medicine, Vanderbilt University Medical Center; and Department of Molecular Physiology and Biophysics and Program in Cancer Biology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA;
[7]Division of Nephrology, Hennepin Healthcare, Minneapolis, Minnesota, USA; Division of Nephrology, University of Minnesota, Minneapolis, Minnesota, USA;
[8]Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan;
[9]Chronic Disease Innovation Centre, Seven Oaks General Hospital, Winnipeg, Manitoba, Canada; Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba. Winnipeg, Manitoba, Canada;
[10]Section of Nephrology, Boston University Chobanian & Avedisian School of Medicine and Boston Medical Center, Boston, USA;

[11]Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland;

[12]KDIGO, Brussels, Belgium;

[13]Cliniques Universitaires Saint Luc, Université Catholique de Louvain, Brussels, Belgium;

[14]Selzman Institute for Kidney Health, Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; and

[15]Department of Renal Medicine, University College London, London, UK

[*]Other conference participants: Baris Afsar, Turkey; Tadao Akizawa, Japan; Stefan D. Anker, Germany; Mustafa Arici, Turkey; Jodie L. Babitt, USA; Jonathan Barratt, UK; Jeffrey S. Berns, USA; Anatole Besarab, USA; Sunil Bhandari, UK; Christopher Brown, UK; Aleix Cases, Spain; Glenn M. Chertow, USA; Cynthia Delgado, USA; Tillman B. Drüeke, France; Steven Fishbane, USA; Rafael Gómez, Columbia; Morgan E. Grams, USA; Takayuki Hamano, Japan; Chuan-Ming Hao, China; Raymond K. Hsu, USA; Kunitoshi Iseki, Japan; Isabelle Jordans, Germany; Edgar V. Lerma, USA; Francesco Locatelli, Italy; Iain C. Macdougall, UK; Jolanta Małyszko, Poland; Patrick Maxwell, UK; Lawrence P. McMahon, Australia; Gregorio T. Obrador, Mexico; Marlies Ostermann, UK; Roberto Pecoits-Filho, USA; Farzana Perwad, USA; Simon D. Roger, Australia; Ajay K. Singh, USA; Laura Solá, Uruguay; Bruce S. Spinowitz, USA; Mai Sugahara, Japan; Toshiyuki Takahashi, Japan; Mototsugu Tanaka, Japan; Tetsuhiro Tanaka, Japan; Der-Cherng Tarng, Taiwan; Marcello Tonelli, Canada; Yusuke Tsukamoto, Japan; Carl P. Walther, USA; Angela Yee-Moon Wang, Hong Kong, China; Bradley A. Warady, USA; Angela C. Webster, Australia; Matthew R. Weir, USA; Jay B. Wish, USA, Muh Geot Wong, Australia.

Running title: Novel anemia therapies in CKD: A KDIGO Conference Report

Word count: 4917

Correspondence:

Elaine Ku
Division of Nephrology
University of California, San Francisco
533 Parnassus Avenue, U404
San Francisco, CA, USA 94143-0532
Email: elaine.ku@ucsf.edu

David C. Wheeler
Department of Renal Medicine
University College London
Royal Free Campus, Rowland Hill Street
London NW3 2NB, UK
Email: d.wheeler@ucl.ac.uk

Keywords: anemia; chronic kidney disease; dialysis; erythropoiesis stimulating agents; erythropoietin; hepcidin; hemoglobin; hyporesponsiveness; hypoxia-inducible factor-prolyl hydroxylase inhibitors; iron; iron deficiency; major adverse cardiovascular events

ABSTRACT

Anemia is common in patients with chronic kidney disease (CKD) and is associated with a high burden of morbidity and adverse clinical outcomes. In 2012, Kidney Disease: Improving Global Outcomes (KDIGO) published a guideline for the diagnosis and management of anemia in CKD. Since then, new data from studies assessing established and emerging therapies for the treatment of anemia and iron deficiency have become available. Beginning in 2019, KDIGO planned two Controversies Conferences to review the new evidence and its potential impact on the management of anemia in clinical practice. Here we report on the second of these conferences held virtually in December 2021 which focused on a new class of agents, the hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs). This report provides a review of the consensus points and controversies from this second conference and highlights areas that warrant prioritization for future research.

INTRODUCTION

Anemia is common in patients with chronic kidney disease (CKD) and results from inadequate erythropoietin (EPO) production, abnormal iron metabolism, blood loss, inflammation, nutritional deficiencies, and oxidative stress.[1] The 2012 Kidney Disease: Improving Global Outcomes (anemia) guideline provided recommendations for the diagnosis and treatment of anemia related to CKD, including the use of iron, recombinant human EPO and its derivatives (collectively termed erythropoiesis-stimulating agents [ESAs]), and blood transfusions.[2] Since the publication of this guideline, new therapies for the treatment of anemia have emerged and a reevaluation of the 2012 KDIGO guideline is required. In December 2019, KDIGO held the first of two Controversies Conferences on CKD anemia, which focused on iron.[3] The second conference, held virtually in December 2021, focused primarily on hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs) following the release of extensive efficacy and safety data. Given the historical nomenclature, we will continue to refer to epoetins, i.e., recombinant human EPO and its derivatives, but not HIF-PHIs as ESAs throughout even though HIF-PHIs also stimulate erythropoiesis.

Hypoxia-inducible factors (HIFs) are oxygen-regulated heterodimeric transcription factors that regulate multiple cellular processes.[4] HIFs coordinate the response to hypoxia by increasing EPO production in the kidneys and liver ~~liver and kidneys~~ and by upregulating the expression of genes involved in iron transport, enhancing its uptake and absorption.[4-6] Hepcidin regulates ferroportin, an iron channel on the surface of enterocytes, hepatocytes, and macrophages, and inhibits iron absorption from the gut and its release from macrophages.[7] Systemic HIF activation leads to an increase in EPO production and use of iron by erythroblasts, which in turn results in~~leads to~~~~indirectly~~ suppression of ~~es~~ hepcidin production in the liver and ~~, which leads to~~ enhanced intestinal iron absorption and iron mobilization.[8-11] In the presence of oxygen, prolyl hydroxylase enzymes hydroxylate the oxygen-regulated HIF-α subunit, thereby targeting it for proteasomal degradation.[12] When oxygen levels decrease, prolyl hydroxylation and degradation of HIF-α are inhibited, resulting in its cellular accumulation and formation of the HIF heterodimeric transcription factor.[1, 13]

Prolyl hydroxylation can be pharmacologically inhibited by oral HIF-PHIs,[14, 15] which stimulates erythropoiesis, largely by increasing EPO production. Potential benefits of HIF-PHIs in addition to their oral route of administration (particular for patients who are not treated with hemodialysis) include the theoretical advantage of reduced exposure to high peak serum EPO concentrations, as substantially lower peak serum EPO levels have been found in patients treated with HIF-PHIs compared with those receiving intravenous epoetin injections.[16] Due to their mechanism of action, HIF-PHIs may enhance enteric iron absorption and iron utilization (unlike ESAs) and may be more efficacious in correcting anemia despite chronic inflammation, though this remains an area of controversy. Other possible advantages of HIF-PHIs over ESAs include their oral route of administration and stability at room temperature. Eliminating the need for frequent subcutaneous injections, although these may be infrequently for longer-acting ESAs, may be important for those with non-dialysis dependent CKD (ND-CKD) or treated with peritoneal dialysis (**Table 1**).

Because of HIF's pleiotropic functions, the pharmacologic activation of HIF in patients with anemia of CKD is also likely to have effects beyond erythropoiesis and iron metabolism, depending on the pharmacokinetic and pharmacodynamic properties of the administered compound, drug dosing, and drug exposure.[9] HIF-mediated effects on cellular differentiation and growth, vascular homeostasis and hemodynamics, inflammation, and cellular metabolism are well documented in preclinical studies and could modify the risk of cardiovascular disease, thrombosis, and malignancy. To what extent non-erythropoietic signaling pathways are activated in patients receiving HIF-PHIs is difficult to predict and to measure, and the advantages of HIF-PHIs must therefore be balanced against potential risks. Thus, controversy persists surrounding the role of HIF-PHIs in the treatment of anemia of CKD.[17, 18]

Overview of the available HIF-PHIs and clinical trial programs

To date, more than 50 randomized studies of HIF-PHIs have been published.[19] There are currently six available HIF-PHIs agents in clinical development including

daprodustat, desidustat, enarodustat, molidustat, roxadustat, and vadadustat (**Tables 2-3**).[20-51]

Most published Phase 2 and 3 trials have focused on the efficacy of HIF-PHIs compared with placebo or ESAs in treating anemia.[19] Because of concerns that became apparent during clinical trials of ESAs, particularly with respect to cardiovascular safety, regulators have required large-scale trials to establish the cardiovascular safety of these agents. Three large phase 3 programs (roxadustat, vadadustat, and daprodustat) have published data on cardiovascular outcomes in ND-CKD and dialysis-dependent CKD (DD-CKD) (**Tables 2-3**).[21, 26, 34, 37, 42, 51] Conference participants felt that because most of the experience with these agents has been in the context of trials, regulatory agencies should continue to gather data on adverse events in routine clinical practice as usage grows. Currently, different HIF-PHIs have been approved for clinical use in various countries and regions (**Supplemental Table 1**).

~~Mos~~Ht ~~H~~IF-PHIs have been studied in the context of either a superiority (compared with placebo) or non-inferiority (compared with ESAs) ~~or superiority (compared with placebo)~~ trial design. Non-inferiority trials formally test, within a statistical framework, whether a new treatment is not worse than the comparator by a pre-specified margin. This margin should ideally be based on the observed adverse event rate of the standard therapy versus placebo in randomized controlled trials (RCTs), or reflect a margin deemed acceptable to clinicians and patients.[52] The null hypothesis in a non-inferiority trial states that a novel therapy is worse than the standard therapy (comparator) on the outcome by the pre-specified margin. Therefore, interpretation of the results of non-inferiority trials of HIF-PHIs should take into consideration the non-inferiority margins incorporated into the design as well as the rates of dropout and crossover in both arms.[52] If multiple participants assigned to the new treatment switch to the comparator, non-inferiority will be more difficult to assess and erroneous rejection of the null hypothesis (i.e., a conclusion of non-inferiority) may occur. The three major phase 3 programs which have examined the cardiovascular safety of HIF-PHIs have all used non-inferiority trial designs. ~~and two have also used superiority designs~~.

Efficacy of HIF-PHIs in the correction of anemia

There was general consensus among the attendees that HIF-PHIs are superior to placebo and non-inferior to ESAs in increasing and maintaining hemoglobin (Hb) concentration among patients with ND-CKD and DD-CKD.[21, 26, 31, 34, 37, 42, 51] Large, randomized trials have demonstrated that roxadustat,[26, 42] vadadustat,[34, 51] and daprodustat[21, 37] are superior to placebo and/or non-inferior to ESAs in correcting and/or maintaining Hb at target levels in ND-CKD and incident and prevalent DD-CKD patients (**Tables 2-3**). Similar findings have been noted with molidustat, enarodustat, and desidustat.[22-25, 39, 40, 53-55] The Hb response with HIF-PHIs is dose-dependent and varies by agent and protocol, and at the ~~recommended~~starting doses applied according to protocol at trial entry, some agents ~~may~~increased the Hb more rapidly than others. Rates of blood transfusion are similar among patients receiving HIF-PHIs versus ESAs and generally lower than among those receiving placebo.[19]

Based on the results of trials that included patients treated with hemodialysis (HD) and peritoneal dialysis (PD) and single-arm trials among patients treated with PD,[56] HIF-PHIs appear to be at least as effective among those receiving PD versus HD. ~~A detailed comparison of Japanese HD and PD patients receiving daprodustat or vadadustat indicated that patients treated with HD required a higher dose to achieve the same Hb as patients treated with PD.[37-40]~~

Optimal hemoglobin targets for the correction of anemia

~~From a theoretical standpoint, the different mechanisms by which ESAs and HIF-PHIs enhance erythropoiesis could warrant different therapeutic Hb targets.~~ Current targets which aim for partial correction of Hb are based on clinical trials conducted several years ago.[57-59] These trials compared higher versus lower Hb targets achieved using ESAs, in which major adverse cardiovascular events (MACE), mortality, and thrombotic events were more common among patients assigned to the higher of the Hb targets.[57-59] In addition, one trial comparing a high Hb target with placebo (and a conservative rescue strategy) in ND-CKD patients with diabetes found an increased rate of strokes.[60] However, no HIF-PHI trials to date have compared Hb normalization or

Commented [MC1]: TREAT added here

near-normalization with the currently recommended lower Hb targets ~~recommended~~ for CKD patients. A few Japanese trials using daprodustat and molidustat have targeted Hb values exceeding 12 g/dl.[20, 24, 25] Because phase 3 trials of HIF-PHIs were designed primarily for efficacy and safety evaluation and to meet criteria set forth by regulatory agencies in different geographic regions, guideline-recommended Hb targets were used resulting in some regional differences (**Tables 2-3**). Overall, the attendees felt that the available data do not provide a rationale for targeting higher Hb levels with HIF-PHIs than the currently recommended targets established using ESAs.

Implications for iron management during the correction of anemia

Iron therapy is a critical cornerstone of anemia management, and iron availability is impaired in patients with CKD.[3, 61] Although data from clinical trials suggest that HIF-PHIs may modulate iron metabolism,[62] iron parameters and iron utilization were not primary outcomes in these studies. The conference participants generally felt that the interpretation of iron-related data from these trials is impeded by significant limitations in trial design. Many aspects of iron management were not appropriately specified and were left to the discretion of the investigator and/or were based on local clinical practice patterns.[9] In some trials, iron protocols differed between treatment and comparator groups within a trial.[32, 47] Other design limitations included differences in Hb targets and achieved Hb between treatment arms, differences in the proportion of patients with baseline iron deficiency, and baseline imbalances in iron and hepcidin status and relevant co-morbidities.

Notwithstanding the limitations in trials thus far, higher serum transferrin levels in HIF-PHI treated patients, either measured directly [20, 26-28, 35, 42-45, 63-65] or indirectly by calculating total iron binding capacity (TIBC), were reported across different compounds. In contrast, the effects on serum iron, hepcidin, transferrin saturation (TSAT) and ferritin were more variable among individual trials and between compounds.[62] A summary of iron use and changes in iron parameters is shown in **Tables 4-5**.[21, 29-32,34,36-38,46-49,51]

Commented [MC2]: PIVOTAL added here

Although there is potential for a reduction in intravenous (IV) iron treatment, there was general consensus that HIF-PHI therapy will not eliminate the need for iron replacement in DD-CKD patients. The conference participants agreed that iron parameters should be monitored during treatment with HIF-PHIs, and iron deficiency should be avoided because it is associated with thromboembolic events, impaired red blood cell production,[43] lower HRQoL, higher rates of cardiovascular events, and higher mortality.[66, 67]

In summary, conference participants agreed that clinically meaningful differences in iron utilization have not so far been demonstrated using HIF-PHIs. There will likely be a continued role of iron therapy in patients with ND- and DD-CKD treated with HIF-PHIs.

Effect of HIF-PHIs on Health-Related Quality of Life (HRQoL)

Several large Phase 3 HIF-PHI trials have included assessments of QoL as exploratory or secondary endpoints.[29-31, 47] These trials have used different scoring systems which may limit comparability across trials.[29-31, 47] Numerical improvements, in particular for the SF-36 Physical Functioning subscore, were reported in the OLYMPUS trial which compared roxadustat to placebo.[31] Data from the smaller dedicated ASCEND-NHQ study in ND-CKD patients, which evaluated the effects of daprodustat versus placebo on QoL using the SF-36 Vitality score, suggested higher vitality score (fatigue) in those receiving daprodustat.[68] In general, assessment of differences in HRQoL is difficult in trials that do not have a double-blinded design.

The patient representatives in attendance felt that although HRQoL was important, a new treatment should ideally be superior to the current standard of care for both safety and efficacy. However, some patients who were not treated with hemodialysis would prefer an oral option over an injection if safety and efficacy were similar.

Safety of HIF-PHIs

Cardiovascular outcomes

Cardiovascular safety signals from clinical trials of ESAs targeting normal or near-normal Hb concentrations led to labelling changes by the US Food and Drug Administration (FDA) beginning in 2007.[69] The current FDA labels for ESAs include warnings on increased risk of death, serious adverse cardiovascular events, and stroke when ESAs are administered to target Hb levels >11 g/dl. No trial has identified an ideal target Hb level, ESA dose, or dosing strategy that does not increase these risks. Thus, for HIF-PHI approval, regulatory agencies asked manufacturers to demonstrate non-inferiority or superiority of HIF-PHIs in terms of the risk for MACE in both dialysis and non-dialysis populations within target ranges recommended for ESAs.

*CKD not requiring dialysis (non-dialysis dependent, ND-CKD) (**Table 6**)*[21,29-31,34]

Roxadustat was the first HIF-PHI to be reviewed by the FDA. Data submitted in support of the New Drug Application included 3 separate trials comparing roxadustat with placebo that were pooled for meta-analyses in the ND-CKD (n = 4270) population.[70, 71] ~~Three ND-dependent studies comparing roxadustat with placebo were pooled.[63]~~ A fourth study comparing roxadustat to darbepoetin alfa was analyzed separately.[28] The pooled analyses for roxadustat did not have prespecified non-inferiority margins that were agreed upon by the FDA.[71, 72] Comparing the upper limits of the 95% CI against the pre-specified non-inferiority margin of daprodustat and vadadustat trials (HR 1.25), roxadustat would not have met the criteria for non-inferiority in pooled analyses of MACE in the ND-CKD population when compared with placebo: HR 1.10; 95% CI: 0.96-1.27. In further on-treatment sensitivity analyses (as opposed to intention-to-treat analysis) requested by the FDA to minimize the effect of including unexposed person-times or events that may not be affected by the intervention, this risk was heightened.[72] When assessing events occurring while patients were on treatment and for one week after discontinuation (on-treatment + 7 days analyses), 277 (7.2%) events were recorded in the roxadustat arm compared with 131 (5.6%) events in the placebo arm (HR 1.38; 95% CI: 1.11-1.70). A caveat in these analyses is the higher

dropout rates in the placebo compared to roxadustat arms, with potential for bias that may have disadvantaged roxadustat.

Vadadustat ND-CKD Phase 3 trials of ESA-treated (n = 1725) and ESA-untreated (n = 1751) patients were pooled, as pre-specified, with darbepoetin alfa as the comparator arm in both trials.[34] The primary MACE analysis did not meet the pre-specified HR=1.30 non-inferiority margin (HR 1.17; 95% CI: 1.01-1.36), and showed a higher risk of MACE in the vadadustat arm. The excess risk was accounted for by nonfatal MI and death from non-cardiovascular causes. Subgroup analyses found a regional difference in the study results, with the increased MACE risk observed in non-U.S. study sites (HR 1.30; 95% CI 1.05-1.62) but no difference in risk in the U.S. study sites (HR 1.06; 95% CI 0.87-1.29).[34]

Daprodustat non-inferiority trials met the pre-specified non-inferiority margins of a HR of 1.25 in primary analyses of the ND-CKD population in a mixed population of previously ESA-treated and untreated patients (HR: 1.03; 95% CI: 0.89-1.19) in comparison to darbepoetin alfa.[21] However, in the sensitivity on-treatment MACE analysis, which censored patients at 28 days after the last dose, participants randomized to daprodustat had a higher incidence of MACE than those randomized to ESA in the ND-CKD study (14.1% vs. 10.5%, HR 1.40; 95% CI: 1.17-1.68).[21] However, differences in the dosing frequency of daprodustat versus ESAs in this trial and differences in definitions of treatment periods may have led to potential bias that disadvantaged daprodustat.[21]

There was a general view among conference participants that major clinical trials have failed to conclusively demonstrate that HIF-PHIs are non-inferior to placebo or conventional ESAs in ND-CKD patients for cardiovascular outcomes. In fact, variable results have been reported for different HIF-PHIs and in different study settings, depending on the type of analyses being performed (e.g., intention-to-treat versus on-treatment analyses). Potential explanations for the differential effects on MACE outcomes between different trials and different agents may result from ~~regional differences in event rates together with imbalances~~ imbalances in patent characteristics

or geographic location at baseline, or from non-matching intervals of follow-up assessment after the last study drug dose in different randomized groups.[73]

Dialysis-dependent (DD-CKD) population

In contrast to the ND-CKD trial results, there was consensus that HIF-PHIs in general met non-inferiority criteria for MACE in cardiovascular outcome trials in DD-CKD populations (**Table 7**)[36-38, 42-51] although controversies surrounding interpretation of the data were discussed. Moreover, in most clinical trials, efficacy and safety of HIF-PHIs was similar in incident and prevalent dialysis populations.

Three studies of roxadustat involving dialysis patients (N=3880) were meta-analyzed in a report submitted to the FDA.[70] All trials included in this report compared roxadustat to ESA. The analyses of the effect of roxadustat for MACE were discordant based on the analytical approach: in the primary, on-treatment + 7 day analyses, the risk of MACE was similar in the roxadustat and ESA groups: HR 1.02; 95% CI: 0.88-1.20. In the sensitivity, on-treatment analysis, the HR for the risk of MACE in patients treated with roxadustat versus ESA was 1.14; 95% CI: 1.00-1.30, a difference that just missed statistical significance for non-inferiority. A fourth trial conducted in Europe and not included in the pooled meta-analysis due to differences in study design demonstrated a higher risk of death in roxadustat vs. ESA-treated patients (8.9 per 100 patient years (PY) vs. 6.3 per 100 PY; HR 1.54, 95% CI 1.04-2.28).[70] In a published analysis of the four roxadustat trials in the DD-CKD population,[74] MACE and MACE+ (a composite of MACE plus unstable angina or congestive heart failure requiring hospitalization) in the on-treatment plus 7 day analyses showed different results in incident vs. prevalent dialysis patients, with the hazard ratio suggesting benefit in incident patients but harm in prevalent patients. In contrast to the ND-CKD studies, treatment duration was longer for the ESA group.

Vadadustat DD-CKD Phase 3 trials pooled two studies of prevalent (n = 3554) and incident (n = 369) patients, with darbepoetin alfa as the comparator group (**Table 3**).[51] Pooled results showed similar MACE rates in the two arms and met non-inferiority

(HR 0.96; 95% CI: 0.83-1.11).[51] Sensitivity analyses were not available at the time of this conference.

Daprodustat trials met the pre-specified non-inferiority margin of 1.25 in primary analyses of the DD-CKD populations (DD: 0.93; 95% CI: 0.81-1.07).[21, 37] The sensitivity on-treatment analysis of the DD-CKD population was similar to the primary analysis ~~, with confidence intervals including 1.0 and upper limit of the 95% CI equal to 1.14~~ (**Table 7**). ~~As seen in studies with ND-CKD patients, regional differences in MACE event rates between geographical regions may at least in part explain these results.[67]~~

In most clinical trials, efficacy and safety of HIF-PHI were similar in incident and prevalent dialysis populations (**Tables 3 and 7**). A pooled analysis of roxadustat studies noted similar risk of MACE (HR 0.83; 95% CI: 0.61-1.13) and nominally lower risk of MACE+ (HR 0.76; 95% CI: 0.57-1.00) among incident dialysis patients treated with roxadustat, whereas roxadustat was less favorable for MACE (HR 1.18; 95% CI: 1.00-1.38) and all-cause mortality (HR 1.23; 95% CI: 1.02-1.49) in prevalent dialysis patients.[74] However, the statistical significance of this difference between incident and prevalent dialysis patients was not reported.

Despite overall consensus that HIF-PHI met non-inferiority criteria for MACE in cardiovascular outcome trials involving DD-CKD populations, it was recognized that controversy has surrounded interpretation of the relevant data for roxadustat in this context. This has been fueled by retraction of a published pooled analysis because of post-publication recognition of deviation from the prespecified analytical plan.[75]

Thromboembolic events, including vascular access thrombosis

Administration of HIF-PHIs has been associated with a higher risk of thrombotic events compared with ESAs or placebo.[76, 77] Although the underlying mechanisms are not understood and appear to be complex, they may be related to the steeper rate of rise in Hb as suggested by a recent FDA safety review for roxadustat.[76] In addition, HIF-PHI interactions with iron metabolism, i.e., upregulation of transferrin,[78] or the

interference of HIF with the coagulation system, e.g., through increased expression of plasminogen activator inhibitor may contribute to thrombotic risk.[79]

Roxadustat showed an excess risk of thrombosis in both ND- (versus ESA) and DD-CKD (versus placebo) trials.[70] A pooled analysis of roxadustat trials showed higher risks of thromboembolic events that were associated with the rate of Hb rise.[71] It is unclear, however, whether lower doses of roxadustat, which would be expected to lead to a slower rate of Hb rise, would ameliorate thrombosis risk while maintaining efficacy. Concerns surrounding the thrombotic risk with vadadustat were raised by the FDA although these concerns were not initially noted in published data.[80] Daprodustat trials have not reported excess risk of thrombosis compared with active comparator.[21, 37]

Hypertension

Pre-clinical studies in healthy rats and rats with CKD demonstrated that HIF-PHIs generate significant dose-dependent blood-pressure lowering effects.[81-83] However, so far, no significant blood pressure effects have been reported in any HIF-PHI phase 3 programs. The results from a dedicated blood pressure study with daprodustat (ASCEND-BP) have not yet been published (NCT03029247).

Lipid metabolism

Theoretically, HIF-dependent increases in lipoprotein uptake and reductions in cholesterol synthesis via enhanced degradation of 3-hydroxy-3-methyl-glutaryl-CoA reductase may lead to lower blood cholesterol levels with HIF-PHI treatment.[84, 85] Although dedicated clinical studies specifically focused on the interactions between HIF-PHIs and lipid metabolism have not yet been conducted, significant and consistent reductions in total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels were reported in patients treated with roxadustat or daprodustat (ND- and DD-CKD).[20, 26, 29, 32, 42, 46, 47, 49, 63, 65] These reductions were not seen in patients treated with enarodustat, molidustat or vadadustat,[23, 24, 40, 53, 55, 86, 87] clearly indicating that different compounds may have different properties. To what degree cholesterol-lowering effects of daprodustat and

roxadustat might impact cardiovascular risk in patients with CKD anemia is not clear. Given the ~~simultaneous lowering of both LDL- and HDL-cholesterol and~~ lack of clear cardiovascular benefits ~~resulting from~~with the initiation of statin therapy in ~~cholesterol-lowering therapy (such as statins) in~~dialysis patients ~~advanced CKD~~,[88] HIF-PHI-mediated interactions with lipid metabolism may not necessarily translate into clinical benefits, even when considering long-term effects beyond the exposure in studies conducted so far.

Kidney disease progression

Pharmacologic HIF activation has been studied in multiple kidney disease models using pharmacologic and genetic approaches.[4] Experimental studies have consistently demonstrated renoprotective effects of HIF activation in acute kidney injury models, whereas the effects of HIF activation in models of chronic kidney injury appeared to be context-dependent and less consistent.[4] This has raised concerns that anemia therapy with HIF-PHIs may worsen CKD in certain subgroups of patients. In one trial of molidustat versus ESA, the risk of CKD progression was higher with molidustat, though whether this finding is specific to molidustat is unclear.[25]

Prespecified secondary analyses of Phase 3 trials of daprodustat and vadadustat in ND-CKD patients showed no beneficial or harmful effects of either drug on CKD outcomes, including the need for dialysis, kidney transplantation, or >40% decline in eGFR.[21, 34] A Phase 3 trial of roxadustat[31] suggested greater decline in kidney function compared with placebo. The annual rate of change in eGFR was -3.70 ml/min per 1.73 m^2 with roxadustat and -3.19 ml/min per 1.73 m^2 with placebo (difference -0.51 ml/min per 1.73 m^2; 95% CI: −1.00 - −0.01; nominal P = 0.046). Conference participants agreed that data from CKD anemia trials reported so far do not suggest any clinically relevant impact of HIF-PHIs on kidney disease progression, but also pointed out that these trials were not specifically designed to evaluate such effects.

Malignancy risk

Adaptation to regional hypoxia mediated by the HIF-pathway plays an important role in tumor progression.[89] Moreover, genetic HIF activation is a central mechanism of

tumorigenesis in patients with the von Hippel-Lindau (VHL) disease and clear cell renal carcinomas.[90] This and other evidence implies that cancer initiation and/or progression could be an adverse event associated with HIF-PHI use.

While the HIF-PHI phase 3 studies have mostly not shown any signals supporting this assumption, in the ASCEND-ND trial, cancer-related death or tumor progression or recurrence was more commonly observed in those randomized to daprodustat (72 of 1937, 3.7%) than in those randomized to darbepoetin alfa (49 of 1933, 2.5%), with relative risk of 1.47 (95% CI: 1.03- 2.10).[21] *Post hoc* analyses that accounted for differential dosing frequency attenuated this observed risk.[21] A clinical trial of molidustat also reported neoplasms in 9.8% of trial participants in the molidustat group compared with 5.3% in the darbepoetin group.[41] The conference participants agreed that there has been no consistent signal across the HIF-PHIs of an excess risk of malignancy-related adverse events, but the accrued exposure time in clinical trials and clinical practice has not been long enough to be confident of the absence of a clinically relevant risk compared with ESAs, and patients with a history of recent or active malignancy were excluded from trials. Post-marketing surveillance will be important to confirm the safety of HIF-PHIs from the standpoint of cancer risk and provide longer-term follow-up data, and avoidance of HIF-PHIs in patients with a history of malignancy is recommended.

Additional safety concerns

An approximate 2-fold increase in the risk for sepsis and septic shock was reported for roxadustat in ND-CKD patients (pooled studies).[76] No increased risk of infections has been noted in the serious adverse events of other trials.[21, 34, 37, 51]

Upregulation of vascular endothelial growth factor by the HIF pathway may increase angiogenesis and therefore in theory worsen diabetic retinopathy and age-related macular degeneration.[91, 92] All HIF-PHI trials have included individuals with diabetes at risk for diabetic retinopathy. However, to date, retinopathy has not been reported to worsen during treatment with HIF-PHIs.[93]

Although higher rates of hyperkalemia and low serum bicarbonate have been reported for HIF-PHIs in some studies,[26, 29, 42, 94-96] such data have not been reproduced by centralized laboratory analysis or in larger trials.[33, 34, 50, 51]

Central hypothyroidism has been reported in patients treated with roxadustat,[97-99] and the Japanese regulatory agency recently added central hypothyroidism as a potential complication of roxadustat in the package insert. This may be due to the structure of roxadustat, which has a molecular structure similar to triiodothyronine (T3), so that its binding to thyroid hormone receptor β may lead to the down-regulation of thyrotropin releasing hormone (TRH). There has been no report of hypothyroidism as a complication in patients treated with other HIF-PHIs according to our knowledge.

Other clinically significant adverse events may become more apparent as we gain experience with the use of HIF-PHIs in clinical practice.

Practical considerations

Dosing considerations

There have been no head-to-head trials comparing different HIF-PHIs in patients with ND- or DD-CKD. However, marked differences exist in potency, dose requirements, and presumably pharmacokinetics. Phase 3 trials generally showed good efficacy in achieving and maintaining target Hb ranges overall and in subgroups based on age, sex, race, and dialysis modality. There was consensus among conference participants that the appropriate dose depends on the drug and should follow label recommendations. There was also general consensus that the starting HIF-PHI dose should be lower for those who are ESA-naïve versus those who are not. Based on the current Hb and the achieved change in Hb (typically over a 4-week period), the dosing in phase 3 trials was maintained or changed in stepwise fashion. Treatment was temporarily discontinued when Hb exceeded 12 or 13 g/dl in most studies.[21, 22, 24-26, 31, 34, 35, 37, 39, 42, 46, 51, 54-56, 100, 101] Conference participants generally felt that in clinical routine the HIF-PHI dose should be maintained or changed in similar stepwise fashion as in trial protocols based on the current Hb and its rate of change.

Use of HIF-PHIs in subpopulations of interest

Patients hyporesponsive to ESAs

By lowering hepcidin levels, HIF-PHIs may theoretically be more effective in treating patients who are hyporesponsive to ESAs because of chronic inflammation or functional iron deficiency. Preliminary data suggest that whereas higher doses of ESAs are needed for patients with high C-reactive protein (CRP) levels, this may not be true for HIF-PHIs.[16, 45] However, CRP concentrations that were considered high in trial participants were only slightly elevated, and sicker and more inflamed patients may have been less likely to have been enrolled in trials of HIF-PHIs. Conference participants also felt that data on the effect of HIF-PHIs in ESA-hyporesponsive patients are limited.

Although the use of HIF-PHIs in combination with ESAs might theoretically be advantageous for patients who are ESA hyporesponsive, there are no data available to support this strategy in clinical practice at present.[102] As with all drugs, there is a risk for drug-drug interactions with the use of HIF-PHIs, particularly in combination with other oral agents (**Supplemental Table ~~1~~2**).

Children

Anemia is also a common complication of CKD in children and is associated with decreased quality of life, reduced neurocognitive ability, left ventricular hypertrophy, and increased risk of hospitalizations.[103] Pain has also been reported with subcutaneous injections of ESAs, making an oral formulation for anemia treatment especially attractive in the pediatric population.[104] However, participants felt that there are insufficient data supporting the use of HIF-PHIs in pediatric patients with anemia of CKD because patients under the age of 18 years were excluded from all Phase 3 trials.[105] Several new trials with roxadustat, daprodustat, and molidustat are planned in pediatric patients after completion of Phase 3 trials in adults.

Polycystic kidney disease

HIF activation occurs in polycystic kidneys in humans and rodents and activation of the HIF–pathway has been shown to enhance cyst expansion in preclinical models.[106] However, whether the use of HIF-PHIs to treat anemia may enhance cyst growth remains unclear. Nevertheless conference participants felt that these agents should not be used in patients with polycystic kidney disease until adequate safety data emerge.

Kidney transplantation

While kidney transplant recipients were excluded from Phase 3 trials of roxadustat and vadadustat, no formal exclusion of subjects with prior kidney transplant was stated in the Phase 3 trials of daprodustat.[21, 37, 107] However, whether subjects with a functioning kidney transplant at baseline were actually enrolled is currently unknown. HIF-PHIs play a role in immune cell function and therefore HIF-PHIs use could potentially promote graft rejection or increase the risk of malignancy.[108] There is limited experience of using HIF-PHIs in patients who are receiving immunosuppression, such as those with kidney allografts.

Other novel therapeutic agents

Several new agents have been introduced into clinical medicine that may be beneficial for patients with CKD anemia and might be used concurrently with ESAs or HIF-PHIs. Agents in clinical development have been discussed during the first KDIGO Controversies in Optimal Anemia Management Conference in 2019 and are not further discussed here.[3] In analogy with HIF-PHIs, SGLT2 inhibitors (SGLT2i) are also considered to stimulate endogenous EPO production.

SGLT2 inhibitors

In addition to their antidiabetic and beneficial cardiovascular and kidney effects, SGLT2i have been shown to increase Hb in patients with kidney disease and/or heart failure.[109-114] Because increased Hb in patients treated with SGLT2i appears to be independent of diuretic use and/or rate of intravascular volume depletion,[115] SGLT2i-

induced changes in Hb are no longer believed to simply reflect hemoconcentration due to diuresis.[116] In fact, SGLT2i administration was associated with transient increases in serum EPO concentrations (30-40%), an increase in reticulocyte counts, a decrease in ferritin and hepcidin, indicating erythropoietic stimulation.[117-120] It has been hypothesized that these pro-erythropoietic actions may have contributed to SGLT2i-mediated protective effects on heart failure outcomes and kidney disease progression.[109-111] Although current data suggest that SGLT2i may provide beneficial "anti-anemic" effects and delay or prevent the initiation of anemia therapy,[121] conference participants agreed that more information is needed to better understand the mechanisms of action underlying these effects and their clinical relevance.

Conclusions

In summary, HIF-PHIs are non-inferior to conventional ESAs in increasing and maintaining Hb concentrations in patients with NDD- and DD-CKD, and reduce transfusion requirements when compared with placebo. In terms of cardiovascular ~~outcomes~~safety, HIF-PHIs are ~~not superior to~~inferior, or at best, similar to conventional ESAs. Different safety signals were observed for different HIF-PHIs across large phase 3 trial programs, and concerns surrounding cardiovascular and thrombotic risks persist. The data that are currently available do not support the concept that use of HIF-PHIs will reduce the need for IV or oral iron supplementation among patients with NDD- or DD-CKD nor have superior efficacy in the correction of anemia in states of chronic inflammation. However, published trials to date were not designed to address ~~this~~ these question~~s~~, and iron was administered according to trial protocols which varied widely. Studies examining alternative iron dosing strategies in patients receiving HIF-PHIs are needed. Currently, there are insufficient data to determine whether use of HIF-PHIs improves quality of life in patients with ND-CKD. Further research recommendations are provided in **Table 8**.

DISCLOSURES

The conference was sponsored by KDIGO and was in part supported by unrestricted educational grants from 7 Elements Global, Akebia Therapeutics, Amgen, Astellas, AstraZeneca, GlaxoSmithKline, Mitsubishi Tanabe Pharma Group, Otsuka, Roche, Rockwell Medical, Torii Pharmaceutical Co., Ltd., US Renal Care, and Vifor Fresenius Medical Care Renal Pharma.

Tables

Table 1: Potential advantages and disadvantages of various CKD-anemia therapies

Table 2: Efficacy data from phase 3 HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Table 3: Efficacy data from phase 3 HIF-PHI clinical trials in patients with dialysis-dependent chronic kidney disease

Table 4: Iron parameters from phase 3 HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Table 5: Iron parameters from phase 3 HIF-PHI clinical trials in dialysis-dependent chronic kidney disease

Table 6: Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Table 7: Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in dialysis-dependent chronic kidney disease

Table 8: Research recommendations

Supplemental Table 1: Availability of HIF-PHIs (as of April 24, 2023)

Supplemental Table 2: Drug-drug interactions of HIF-PHIs

REFERENCES

1. Babitt JL, Lin HY. Mechanisms of anemia in CKD. *J Am Soc Nephrol* 2012; **23:** 1631-1634.

2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl*. 2012; 2: 279–335.

3. Babitt JL, Eisenga MF, Haase VH*, et al.* Controversies in optimal anemia management: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. *Kidney international* 2021; **99:** 1280-1295.

4. Schodel J, Ratcliffe PJ. Mechanisms of hypoxia signalling: new implications for nephrology. *Nat Rev Nephrol* 2019; **15:** 641-659.

5. Barrett TD, Palomino HL, Brondstetter TI*, et al.* Prolyl hydroxylase inhibition corrects functional iron deficiency and inflammation-induced anaemia in rats. *Br J Pharmacol* 2015; **172:** 4078-4088.

6. Rankin EB, Biju MP, Liu Q*, et al.* Hypoxia-inducible factor-2 (HIF-2) regulates hepatic erythropoietin in vivo. *J Clin Invest* 2007; **117:** 1068-1077.

7. Sun CC, Vaja V, Chen S*, et al.* A hepcidin lowering agent mobilizes iron for incorporation into red blood cells in an adenine-induced kidney disease model of anemia in rats. *Nephrol Dial Transplant* 2013; **28:** 1733-1743.

8. Haase VH. Pathophysiological Consequences of HIF Activation: HIF as a modulator of fibrosis. *Ann N Y Acad Sci* 2009; **1177:** 57-65.

9. Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease. *Kidney Int Suppl (2011)* 2021; **11:** 8-25.

10. Hanudel MR, Wong S, Jung G*, et al.* Amelioration of chronic kidney disease-associated anemia by vadadustat in mice is not dependent on erythroferrone. *Kidney international* 2021; **100:** 79-89.

11. Nicolas G, Chauvet C, Viatte L*, et al.* The gene encoding the iron regulatory peptide hepcidin is regulated by anemia, hypoxia, and inflammation. *J Clin Invest* 2002; **110:** 1037-1044.

12. Bruick RK, McKnight SL. A conserved family of prolyl-4-hydroxylases that modify HIF. *Science* 2001; **294:** 1337-1340.

13. Gupta N, Wish JB. Hypoxia-inducible factor prolyl hydroxylase inhibitors: A potential new treatment for anemia in patients with CKD. *Am J Kidney Dis* 2017; **69:** 815-826.

14. Kurata Y, Tanaka T, Nangaku M. Hypoxia-inducible factor prolyl hydroxylase inhibitor in the treatment of anemia in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2020; **29:** 414-422.

15. Sugahara M, Tanaka T, Nangaku M. Prolyl hydroxylase domain inhibitors as a novel therapeutic approach against anemia in chronic kidney disease. *Kidney international* 2017; **92:** 306-312.

16. Provenzano R, Besarab A, Wright S*, et al.* Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study. *Am J Kidney Dis* 2016; **67:** 912-924.

17. Hill P, Shukla D, Tran MG*, et al.* Inhibition of hypoxia inducible factor hydroxylases protects against renal ischemia-reperfusion injury. *J Am Soc Nephrol* 2008; **19:** 39-46.

18. Kapitsinou PP, Jaffe J, Michael M*, et al.* Preischemic targeting of HIF prolyl hydroxylation inhibits fibrosis associated with acute kidney injury. *Am J Physiol Renal Physiol* 2012; **302:** F1172-1179.

19. Natale P, Palmer SC, Jaure A*, et al.* Hypoxia-inducible factor stabilisers for the anaemia of chronic kidney disease. *Cochrane Database Syst Rev* 2022; **8:** CD013751.

20. Nangaku M, Hamano T, Akizawa T*, et al.* Daprodustat Compared with Epoetin Beta Pegol for Anemia in Japanese Patients Not on Dialysis: A 52-Week Randomized Open-Label Phase 3 Trial. *Am J Nephrol* 2021; **52:** 26-35.

21. Singh AK, Carroll K, McMurray JJV*, et al.* Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis. *N Engl J Med* 2021; **385:** 2313-2324.

22. Agrawal D, Varade D, Shah H*, et al.* Desidustat in Anemia due to Non-Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-ND). *Am J Nephrol* 2022; **53:** 352-360.

23. Akizawa T, Nangaku M, Yamaguchi T*, et al.* A Phase 3 Study of Enarodustat in Anemic Patients with CKD not Requiring Dialysis: The SYMPHONY ND Study. *Kidney Int Rep* 2021; **6:** 1840-1849.

24. Yamamoto H, Nobori K, Matsuda Y*, et al.* Efficacy and Safety of Molidustat for Anemia in ESA-Naive Nondialysis Patients: A Randomized, Phase 3 Trial. *Am J Nephrol* 2021; **52:** 871-883.

25. Yamamoto H, Nobori K, Matsuda Y*, et al.* Molidustat for Renal Anemia in Nondialysis Patients Previously Treated with Erythropoiesis-Stimulating Agents: A Randomized, Open-Label, Phase 3 Study. *Am J Nephrol* 2021; **52:** 884-893.

26. Chen N, Hao C, Peng X*, et al.* Roxadustat for anemia in patients with kidney disease not receiving dialysis. *N Engl J Med* 2019; **381:** 1001-1010.

27. Akizawa T, Yamaguchi Y, Otsuka T*, et al.* A Phase 3, Multicenter, Randomized, Two-Arm, Open-Label Study of Intermittent Oral Dosing of Roxadustat for the Treatment of Anemia in Japanese Erythropoiesis-Stimulating Agent-Naive Chronic Kidney Disease Patients Not on Dialysis. *Nephron* 2020; **144:** 372-382.

28. Akizawa T, Iwasaki M, Otsuka T*, et al.* Phase 3 Study of Roxadustat to Treat Anemia in Non-Dialysis-Dependant CKD. *Kidney Int Rep* 2021; **6:** 1810-1828.

29. Shutov E, Sulowicz W, Esposito C*, et al.* Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, double-blind, placebo-controlled study (ALPS). *Nephrol Dial Transplant* 2021; **36:** 1629-1639.

30. Coyne DW, Roger SD, Shin SK*, et al.* Roxadustat for CKD-related Anemia in Non-dialysis Patients. *Kidney Int Rep* 2021; **6:** 624-635.

31. Fishbane S, El-Shahawy MA, Pecoits-Filho R*, et al.* Roxadustat for Treating Anemia in Patients with CKD Not on Dialysis: Results from a Randomized Phase 3 Study. *J Am Soc Nephrol* 2021; **32:** 737-755.

32. Barratt J, Andric B, Tataradze A*, et al.* Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, open-label, active-controlled study (DOLOMITES). *Nephrol Dial Transplant* 2021; **36:** 1616-1628.

33. Nangaku M, Kondo K, Kokado Y*, et al.* Phase 3 Randomized Study Comparing Vadadustat with Darbepoetin Alfa for Anemia in Japanese Patients with Nondialysis-Dependent CKD. *J Am Soc Nephrol* 2021; **32:** 1779-1790.

34. Chertow GM, Pergola PE, Farag YMK*, et al.* Vadadustat in Patients with Anemia and Non-Dialysis-Dependent CKD. *N Engl J Med* 2021; **384:** 1589-1600.

35. Akizawa T, Nangaku M, Yonekawa T*, et al.* Efficacy and Safety of Daprodustat Compared with Darbepoetin Alfa in Japanese Hemodialysis Patients with Anemia: A Randomized, Double-Blind, Phase 3 Trial. *Clin J Am Soc Nephrol* 2020; **15:** 1155-1165.

36. Singh AK, Cizman B, Carroll K*, et al.* Efficacy and Safety of Daprodustat for Treatment of Anemia of Chronic Kidney Disease in Incident Dialysis Patients: A Randomized Clinical Trial. *JAMA Intern Med* 2022; **182:** 592-602.

37. Singh AK, Carroll K, Perkovic V*, et al.* Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis. *N Engl J Med* 2021; **385:** 2325-2335.

38. Coyne DW, Singh AK, Lopes RD*, et al.* Three Times Weekly Dosing of Daprodustat versus Conventional Epoetin for Treatment of Anemia in Hemodialysis Patients: ASCEND-TD: A Phase 3 Randomized, Double-Blind, Noninferiority Trial. *Clin J Am Soc Nephrol* 2022; **17:** 1325-1336.

39. Gang S, Khetan P, Varade D*, et al.* Desidustat in Anemia due to Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-D). *Am J Nephrol* 2022; **53:** 343-351.

40. Akizawa T, Nangaku M, Yamaguchi T*, et al.* A Phase 3 Study of Enarodustat (JTZ-951) in Japanese Hemodialysis Patients for Treatment of Anemia in Chronic Kidney Disease: SYMPHONY HD Study. *Kidney Dis (Basel)* 2021; **7:** 494-502.

41. Akizawa T, Yamada T, Nobori K*, et al.* Molidustat for Japanese Patients With Renal Anemia Receiving Dialysis. *Kidney Int Rep* 2021; **6:** 2604-2616.

42. Chen N, Hao C, Liu BC*, et al.* Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis. *N Engl J Med* 2019; **381:** 1011-1022.

43. Akizawa T, Ueno M, Shiga T*, et al.* Oral roxadustat three times weekly in ESA-naive and ESA-converted patients with anemia of chronic kidney disease on hemodialysis: Results from two phase 3 studies. *Ther Apher Dial* 2020; **24:** 628-641.

44. Akizawa T, Otsuka T, Reusch M*, et al.* Intermittent Oral Dosing of Roxadustat in Peritoneal Dialysis Chronic Kidney Disease Patients with Anemia: A Randomized, Phase 3, Multicenter, Open-Label Study. *Ther Apher Dial* 2020; **24:** 115-125.

45. Akizawa T, Iwasaki M, Yamaguchi Y*, et al.* Phase 3, Randomized, Double-Blind, Active-Comparator (Darbepoetin Alfa) Study of Oral Roxadustat in CKD Patients with Anemia on Hemodialysis in Japan. *J Am Soc Nephrol* 2020; **31:** 1628-1639.

46. Provenzano R, Shutov E, Eremeeva L*, et al.* Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. *Nephrol Dial Transplant* 2021; **36:** 1717-1730.

47. Csiky B, Schomig M, Esposito C*, et al.* Roxadustat for the Maintenance Treatment of Anemia in Patients with End-Stage Kidney Disease on Stable Dialysis: A European Phase 3, Randomized, Open-Label, Active-Controlled Study (PYRENEES). *Adv Ther* 2021; **38:** 5361-5380.

48. Fishbane S, Pollock CA, El-Shahawy M*, et al.* Roxadustat Versus Epoetin Alfa for Treating Anemia in Patients with Chronic Kidney Disease on Dialysis: Results from the Randomized Phase 3 ROCKIES Study. *J Am Soc Nephrol* 2022; **33:** 850-866.

49. Charytan C, Manllo-Karim R, Martin ER*, et al.* A Randomized Trial of Roxadustat in Anemia of Kidney Failure: SIERRAS Study. *Kidney Int Rep* 2021; **6:** 1829-1839.

50. Nangaku M, Kondo K, Ueta K*, et al.* Efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese anemic patients on hemodialysis: a Phase 3, multicenter, randomized, double-blind study. *Nephrol Dial Transplant* 2021; **36:** 1731-1741.

51. 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:** 1601-1612.

52. Mauri L, D'Agostino RB, Sr. Challenges in the Design and Interpretation of Noninferiority Trials. *N Engl J Med* 2017; **377:** 1357-1367.

53. Akizawa T, Nangaku M, Yamaguchi T*, et al.* A Placebo-Controlled, Randomized Trial of Enarodustat in Patients with Chronic Kidney Disease Followed by Long-Term Trial. *Am J Nephrol* 2019; **49:** 165-174.

54. Akizawa T, Nobori K, Matsuda Y*, et al.* Molidustat for anemia correction in Japanese patients undergoing hemodialysis: a single-arm, phase 3 study. *Ther Apher Dial* 2021; **25:** 917-925.

55. Macdougall IC, Akizawa T, Berns JS*, et al.* Effects of Molidustat in the Treatment of Anemia in CKD. *Clin J Am Soc Nephrol* 2019; **14:** 28-39.

56. Kanai H, Nangaku M, Nagai R*, et al.* Efficacy and safety of daprodustat in Japanese peritoneal dialysis patients. *Ther Apher Dial* 2021; **25:** 979-987.

57. Besarab A, Bolton WK, Browne JK*, et al.* The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; **339:** 584-590.

58. Drüeke TB, Locatelli F, Clyne N*, et al.* Normalization of Hemoglobin Level in Patients with Chronic Kidney Disease and Anemia. *New England Journal of Medicine* 2006; **355:** 2071-2084.

59. Singh AK, Szczech L, Tang KL*, et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355:** 2085-2098.

60. Pfeffer MA, Burdmann EA, Chen CY*, et al.* A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; **361:** 2019-2032.

61. Macdougall IC, White C, Anker SD*, et al.* Intravenous Iron in Patients Undergoing Maintenance Hemodialysis. *N Engl J Med* 2019; **380:** 447-458.

62. Agarwal AK. Iron metabolism and management: focus on chronic kidney disease. *Kidney Int Suppl (2011)* 2021; **11:** 46-58.

63. Akizawa T, Tsubakihara Y, Nangaku M*, et al.* Effects of Daprodustat, a Novel Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor on Anemia Management in Japanese Hemodialysis Subjects. *Am J Nephrol* 2017; **45:** 127-135.

64. Besarab A, Chernyavskaya E, Motylev I*, et al.* Roxadustat (FG-4592): Correction of Anemia in Incident Dialysis Patients. *J Am Soc Nephrol* 2016; **27:** 1225-1233.

65. Holdstock L, Meadowcroft AM, Maier R*, et al.* Four-Week Studies of Oral Hypoxia-Inducible Factor-Prolyl Hydroxylase Inhibitor GSK1278863 for Treatment of Anemia. *J Am Soc Nephrol* 2016; **27:** 1234-1244.

66. Guedes M, Muenz D, Zee J*, et al.* Serum biomarkers of iron stores are associated with worse physical health-related quality of life in nondialysis-dependent chronic kidney disease patients with or without anemia. *Nephrol Dial Transplant* 2021; **36:** 1694-1703.

67. Guedes M, Muenz DG, Zee J*, et al.* Serum Biomarkers of Iron Stores Are Associated with Increased Risk of All-Cause Mortality and Cardiovascular Events in Nondialysis CKD Patients, with or without Anemia. *J Am Soc Nephrol* 2021; **32:** 2020-2030.

68. Johansen KL, Cobitz AR, Singh AK, *et al*. The ASCEND-NHQ trial found positive effects of daprodustat on hemoglobin and quality of life in patients with non-dialysis-dependent

chronic kidney disease. *Kidney Int* (in press). DOI: https://doi.org/10.1016/j.kint.2023.02.019.

69. FDA. FDA Drug Safety Communication: Modified Dosing Recommendations to Improve the Safe Use of Erythropoiesis-Stimulating Agents in Chronic Kidney Disease. (http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm).

70. FDA. Cardiovascular and Renal Drugs Advisory Committee Meeting - Roxadustat. https://www.fda.gov/media/150728/download.

71. Provenzano R, Szczech L, Leong R, *et al.* Efficacy and Cardiovascular Safety of Roxadustat for Treatment of Anemia in Patients with Non-Dialysis-Dependent CKD: Pooled Results of Three Randomized Clinical Trials. *Clin J Am Soc Nephrol* 2021; **16:** 1190-1200.

72. Winkelmayer WC, Walther CP. Cardiovascular Safety of Roxadustat in CKD Anemia: A Fig Leaf Named Noninferiority. *Clin J Am Soc Nephrol* 2021; **16:** 1155-1157.

73. Mc Causland FR, Singh AK, Claggett BL, *et al.* Daprodustat and On-Treatment Cardiovascular Events in Chronic Kidney Disease. Reply. *N Engl J Med* 2022; **387:** 2482-2485.

74. Barratt J, Sulowicz W, Schomig M, *et al.* Efficacy and Cardiovascular Safety of Roxadustat in Dialysis-Dependent Chronic Kidney Disease: Pooled Analysis of Four Phase 3 Studies. *Adv Ther* 2021; **38:** 5345-5360.

75. Provenzano R, Fishbane S, Szczech L, *et al.* Retraction notice to "Pooled Analysis of Roxadustat for Anemia in Patients With Kidney Failure Incident to Dialysis." Kidney Int Rep. 2021;6:613-623. *Kidney Int Rep* 2022; **7:** 665.

76. FDA. Roxadustat for the Treatment of Anemia Due to Chronic Kidney Disease in Adult Patients not on Dialysis and on Dialysis. FDA Presentation: Cardiovascular and Renal Drugs Advisory Committee Meeting. 2021. Available at: https://www.fda.gov/media/150756/download. Accessed January 27, 2023.

77. Yap DYH, McMahon LP, Hao CM, *et al.* Recommendations by the Asian Pacific society of nephrology (APSN) on the appropriate use of HIF-PH inhibitors. *Nephrology (Carlton)* 2021; **26:** 105-118.

78. Tang X, Fang M, Cheng R, *et al.* Iron-Deficiency and Estrogen Are Associated With Ischemic Stroke by Up-Regulating Transferrin to Induce Hypercoagulability. *Circ Res* 2020; **127:** 651-663.

79. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. *Thromb Res* 2019; **181:** 77-83.

80. Akebia Therapeutics Receives Complete Response Letter from the FDA for Vadadustat for the Treatment of Anemia due to Chronic Kidney Disease in Adult Patients. Press release, March 30, 2022. https://ir.akebia.com/news-releases/news-release-details/akebia-therapeutics-receives-complete-response-letter-fda.

81. Burmakin M, Fasching A, Kobayashi H, *et al.* Pharmacological HIF-PHD inhibition reduces renovascular resistance and increases glomerular filtration by stimulating nitric oxide generation. *Acta Physiol (Oxf)* 2021; **233:** e13668.

82. Flamme I, Oehme F, Ellinghaus P, *et al.* Mimicking hypoxia to treat anemia: HIF-stabilizer BAY 85-3934 (Molidustat) stimulates erythropoietin production without hypertensive effects. *PLoS One* 2014; **9:** e111838.

83. Yu J, Wang S, Shi W, *et al.* Roxadustat prevents Ang II hypertension by targeting angiotensin receptors and eNOS. *JCI Insight* 2021; **6:** e133690.

84. Hwang S, Nguyen AD, Jo Y, *et al.* Hypoxia-inducible factor 1alpha activates insulin-induced gene 2 (Insig-2) transcription for degradation of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase in the liver. *J Biol Chem* 2017; **292:** 9382-9393.

85. Shen GM, Zhao YZ, Chen MT, *et al.* Hypoxia-inducible factor-1 (HIF-1) promotes LDL and VLDL uptake through inducing VLDLR under hypoxia. *Biochem J* 2012; **441:** 675-683.

86. Akizawa T, Nangaku M, Yamaguchi T, *et al.* Two long-term phase 3 studies of enarodustat (JTZ-951) in Japanese anemic patients with chronic kidney disease not on dialysis or on maintenance hemodialysis: SYMPHONY ND-Long and HD-Long studies. *Ther Apher Dial* 2022; **26:** 345-356.

87. Nangaku M, Farag YMK, deGoma E, *et al.* Vadadustat, an oral hypoxia-inducible factor prolyl hydroxylase inhibitor, for treatment of anemia of chronic kidney disease: two randomized Phase 2 trials in Japanese patients. *Nephrol Dial Transplant* 2020**:** gfaa060.

88. Ku E, Campese V. Is lipid management effective for all stages of CKD? *Blood Purif* 2013; **35:** 26-30.

89. Rashid M, Zadeh LR, Baradaran B, *et al.* Up-down regulation of HIF-1α in cancer progression. *Gene* 2021; **798:** 145796.

90. Haase VH. The VHL tumor suppressor: master regulator of HIF. *Curr Pharm Des* 2009; **15:** 3895-3903.

91. Barben M, Samardzija M, Grimm C. The Role of Hypoxia, Hypoxia-Inducible Factor (HIF), and VEGF in Retinal Angiomatous Proliferation. *Adv Exp Med Biol* 2018; **1074:** 177-183.

92. Zhang D, Lv FL, Wang GH. Effects of HIF-1alpha on diabetic retinopathy angiogenesis and VEGF expression. *Eur Rev Med Pharmacol Sci* 2018; **22:** 5071-5076.

93. Sepah YJ, Nguyen QD, Yamaguchi Y*, et al.* Two Phase 3 Studies on Ophthalmologic Effects of Roxadustat Versus Darbepoetin. *Kidney Int Rep* 2022; **7:** 763-775.

94. Besarab A, Provenzano R, Hertel J*, et al.* Randomized placebo-controlled dose-ranging and pharmacodynamics study of roxadustat (FG-4592) to treat anemia in nondialysis-dependent chronic kidney disease (NDD-CKD) patients. *Nephrol Dial Transplant* 2015; **30:** 1665-1673.

95. Meadowcroft AM, Cizman B, Holdstock L*, et al.* Daprodustat for anemia: a 24-week, open-label, randomized controlled trial in participants on hemodialysis. *Clin Kidney J* 2019; **12:** 139-148.

96. Pergola PE, Spinowitz BS, Hartman CS*, et al.* Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. *Kidney international* 2016; **90:** 1115-1122.

97. Ichii M, Mori K, Miyaoka D*, et al.* Suppression of thyrotropin secretion during roxadustat treatment for renal anemia in a patient undergoing hemodialysis. *BMC Nephrol* 2021; **22:** 104.

98. Tokuyama A, Kadoya H, Obata A*, et al.* Roxadustat and thyroid-stimulating hormone suppression. *Clin Kidney J* 2021; **14:** 1472-1474.

99. Cheng Y, Xiang Q, Cao T*, et al.* Suppression of thyroid profile during roxadustat treatment in chronic kidney disease patients. *Nephrol Dial Transplant* 2023.

100. Nangaku M, Kondo K, Takabe S*, et al.* Vadadustat for anemia in chronic kidney disease patients on peritoneal dialysis: A phase 3 open-label study in Japan. *Ther Apher Dial* 2021; **25:** 642-653.

101. Nangaku M, Kondo K, Takabe S, *et al.* A phase 3, open-label, single-arm study of vadadustat for anemia in chronic kidney disease for Japanese patients on hemodialysis not receiving erythropoiesis-stimulating agents. *Ther Apher Dial* 2022; **26:** 45-54.

102. Joharapurkar AA, Patel VJ, Kshirsagar SG, *et al.* Prolyl hydroxylase inhibitor desidustat improves anemia in erythropoietin hyporesponsive state. *Curr Res Pharmacol Drug Discov* 2022; **3:** 100102.

103. Atkinson MA, Martz K, Warady BA, *et al.* Risk for anemia in pediatric chronic kidney disease patients: a report of NAPRTCS. *Pediatr Nephrol* 2010; **25:** 1699-1706.

104. Schmitt CP, Nau B, Brummer C, *et al.* Increased injection pain with darbepoetin-alpha compared to epoetin-beta in paediatric dialysis patients. *Nephrol Dial Transplant* 2006; **21:** 3520-3524.

105. Kular D, Macdougall IC. HIF stabilizers in the management of renal anemia: from bench to bedside to pediatrics. *Pediatr Nephrol* 2019; **34:** 365-378.

106. Buchholz B, Eckardt KU. Role of oxygen and the HIF-pathway in polycystic kidney disease. *Cell Signal* 2020; **69:** 109524.

107. Perkovic V, Blackorby A, Cizman B, *et al.* The ASCEND-ND trial: study design and participant characteristics. *Nephrol Dial Transplant* 2022; **37:** 2157-2170.

108. Taylor CT, Doherty G, Fallon PG, *et al.* Hypoxia-dependent regulation of inflammatory pathways in immune cells. *J Clin Invest* 2016; **126:** 3716-3724.

109. Inzucchi SE, Zinman B, Fitchett D, *et al.* How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial. *Diabetes Care* 2018; **41:** 356-363.

110. Li J, Neal B, Perkovic V, *et al.* Mediators of the effects of canagliflozin on kidney protection in patients with type 2 diabetes. *Kidney international* 2020; **98:** 769-777.

111. Li J, Woodward M, Perkovic V, *et al.* Mediators of the Effects of Canagliflozin on Heart Failure in Patients With Type 2 Diabetes. *JACC Heart Fail* 2020; **8:** 57-66.

112. Marathias KP, Lambadiari VA, Markakis KP, *et al.* Competing Effects of Renin Angiotensin System Blockade and Sodium-Glucose Cotransporter-2 Inhibitors on Erythropoietin Secretion in Diabetes. *Am J Nephrol* 2020; **51:** 349-356.

113. Stefansson BV, Heerspink HJL, Wheeler DC*, et al.* Correction of anemia by dapagliflozin in patients with type 2 diabetes. *J Diabetes Complications* 2020; **34:** 107729.

114. Zinman B, Wanner C, Lachin JM*, et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015; **373:** 2117-2128.

115. Jackson AM, Dewan P, Anand IS*, et al.* Dapagliflozin and Diuretic Use in Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF. *Circulation* 2020; **142:** 1040-1054.

116. Docherty KF, Curtain JP, Anand IS*, et al.* Effect of dapagliflozin on anaemia in DAPA-HF. *Eur J Heart Fail* 2021; **23:** 617-628.

117. Ferrannini E, Baldi S, Frascerra S*, et al.* Renal Handling of Ketones in Response to Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 2 Diabetes. *Diabetes Care* 2017; **40:** 771-776.

118. Ghanim H, Abuaysheh S, Hejna J*, et al.* Dapagliflozin Suppresses Hepcidin And Increases Erythropoiesis. *J Clin Endocrinol Metab* 2020; **105**.

119. Lambers Heerspink HJ, de Zeeuw D, Wie L*, et al.* Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. *Diabetes Obes Metab* 2013; **15:** 853-862.

120. Maruyama T, Takashima H, Oguma H*, et al.* Canagliflozin Improves Erythropoiesis in Diabetes Patients with Anemia of Chronic Kidney Disease. *Diabetes Technol Ther* 2019; **21:** 713-720.

121. Oshima M, Neuen BL, Jardine MJ*, et al.* Effects of canagliflozin on anaemia in patients with type 2 diabetes and chronic kidney disease: a post-hoc analysis from the CREDENCE trial. *Lancet Diabetes Endocrinol* 2020; **8:** 903-914.

Novel Anemia Therapies in CKD: A KDIGO Controversies Conference Report

TABLES

Table 1: Potential advantages and disadvantages of various CKD-anemia therapies

Agents	Potential Advantages	Potential Disadvantages
HIF-PHIs	• Oral dosing more convenient for some patients • May facilitate anemia treatment in patients with non-dialysis dependent CKD • May improve utilization of iron for erythropoiesis, particularly oral iron • May be more effective in chronic inflammatory states (CRP >5 mg/l)	• Difficult to monitor adherence • Potential polypharmacy and drug-drug interactions • Less clinical experience • Potential risk of enhancing tumor growth • Potential risk of worsening retinopathy • Potential risk of cyst growth in ADPKD
ESAs	• Adherence can be monitored with in-clinic administration • Extensive clinical experience	• Treatment requires self-injection or regular clinic visits • Resistance in chronic inflammatory states • Risk of enhancing tumor growth • Antibody-mediated pure red cell aplasia (rare)
Iron compounds	• No serious adverse effects of oral iron	• If PO, risk of poor gastrointestinal tolerance and non-adherence to therapy • If IV, risk of allergic/anaphylactic reaction • If IV, potential risk of increasing oxidative stress • If IV, potential risk of hemosiderosis

Table 2: Efficacy data from phase 3 HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Study; Location Sponsor	Study design; No. of patients, randomization	Treatment, starting dose,[a] study duration	Primary efficacy outcomes: Differences in mean Hb and/or ΔHb from baseline to evaluation period	Hb targets and Hb response rate[b]
***Daprodustat* (GlaxoSmithKline)**				
Nangaku *et al.*, 2021[20] (NCT02791763); Japan	R, OL, AC; ESA-naïve and ESA-treated; n = 299, 1:1	DAPRO 2 and 4 mg QD[c] for ESA-naïve and 4 mg QD[c] for ESA-users vs EBP, 52 weeks	Difference in mean Hb, weeks 40-52: DAPRO: 12 g/dl EBP: 11.9 g/dl Difference: 0.1 (-0.1, 0.3) g/dl	Hb within target range (11–13 g/dl) during weeks 40–52: DAPRO: 92% EBP: 92%
ASCEND-ND[21] (NCT02876835); Global	R, OL, AC; ESA-naïve and ESA-treated; n = 3872, 1:1	DAPRO 2-4 mg QD[c] for ESA-naïve and 1-4 mg QD[d] for ESA-users vs DPO, 148 weeks	Difference in mean ΔHb, weeks 28-52: DAPRO: 0.74 g/dl DPO: 0.66 g/dl Difference: 0.08 (0.03, 0.13) g/dl	Hb target (10-11 g/dl)
***Desidustat* (Cadila Healthcare Ltd.)**				
DREAM-ND[22] (NCT04012957); India, Sri Lanka	R, OL, AC; ESA-naïve; n = 588, 1:1	DESI 100 mg TIW vs DPO, 24 weeks	Difference in mean ΔHb, weeks 16-24: DESI: 1.95 g/dl DPO: 1.83 g/dl LSMD: 0.11 (–0.12, 0.35) g/dl	Hb within target range (10–12 g/dl) during weeks 16-24: DESI: 77.78% DPO: 68.48%
***Enarodustat* (Japan Tobacco Inc.)**				
SYMPHONY ND[23] (JapicCTI-183870); Japan	R, OL, AC; ESA-naïve and ESA-treated; n = 216, 1:1	ENARO 2 mg QD vs DPO, 24 weeks	Difference in mean Hb, weeks 20–24: ENARO: 10.96 g/dl DPO: 10.87 g/dl Difference: 0.09 (–0.07, 0.26) g/dl	Hb within target range (10–12 g/dl) during weeks 4–24: ENARO: 88.6% DPO: 87.9%
***Molidustat* (Bayer Yakuhin, Ltd.)**				
MIYABI ND-C[24] (NCT03350321); Japan	R, OL, AC; ESA-naïve; n = 162, 1:1	MOLI 25 mg QD vs DPO, 52 weeks	Difference in mean Hb, weeks 30-36: MOLI: 11.28 g/dl DPO: 11.70 g/dl Difference in mean ΔHb, weeks 30-36: MOLI: 1.32 g/dl DPO: 1.69 g/dl LSMD: –0.38 (–0.67, –0.08) g/dl	Hb within target range (11–13 g/dl), responder rate during weeks 30–36: MOLI: 59.8% DPO: 82.5%

MIYABI ND-M[25] (NCT03350347); Japan	R, OL, AC; ESA-treated; n = 164, 1:1	MOLI 25 mg or 50 mg QD[d] vs DPO, 52 weeks	Difference in mean Hb, weeks 30-36: MOLI: 11.67 g/dl DPO: 11.53 g/dl Difference in mean ΔHb, weeks 30-36: MOLI: 0.36 g/dl DPO: 0.24 g/dl LSMD: 0.13 (–0.15, 0.40) g/dl	Hb within target range (11–13 g/dl), responder rate during weeks 30–36: MOLI: 72.0% DPO: 76.8%
***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
Chen *et al*., 2019[26] (NCT02652819); China FibroGen, Inc.	R, DB, PC; ESA-naïve; n = 154, 2:1, n = 152 (safety population)	ROXA 70 or 100 mg TIW[e] vs PBO, 8 weeks DB, then 18 weeks OL	Difference in mean ΔHb, weeks 7–9: ROXA: 1.9 g/dl PBO: -0.4 g/dl Difference: 2.2 (1.9, 2.6) g/dl*	Hb target: 10-12 g/dl; pts with >10 g/dl and increase in ΔHb of 1-2 g/dl at week 9: ROXA: 75% PBO: 0%
Akizawa *et al*., 2020[27] (NCT02964936); Japan Astellas Pharma, Inc.	R, OL, NC; ESA-naïve; n = 99	ROXA 50 or 70 mg TIW[c], 24 weeks	Difference in mean ΔHb, weeks 18-24: ROXA 50 mg: 1.34 g/dl ROXA 70 mg: 1.30 g/dl	Hb target: 10-12 g/dl; Hb ≥ 10 g/dl and ΔHb of ≥1 g/dl at EOT: ROXA 50 mg: 97.0% ROXA 70 mg: 100.0% for Hb ≥ 10.5 g/dl: ROXA 50 mg: 94.9% ROXA 70 mg: 98.0%
Akizawa *et al*., 2021[28] (NCT02988973); Japan Astellas Pharma, Inc.	R, OL, AC; ESA-treated (DPO and EBP); n = 334, 1:1,	ROXA 70 or 100 mg TIW[d] vs DPO, 52 weeks	Difference in mean ΔHb, weeks 18-24: ROXA: 0.15 g/dl DPO: 0.22 g/dl LSMD: -0.07 g/ (-0.23, 0.10) g/dl	Hb within target range (10–12 g/dl), maintenance rate during weeks 18-24: ROXA: 77.1% PBO: 85.5%
ALPS[29] (NCT01887600); Europe Astellas Pharma, Inc.	R, DB, PC; ESA-naïve; n = 594, 2:1	ROXA 70 or 100 mg TIW[f] vs PBO, 104 weeks	EMA endpoint,[g] first 24 weeks: ROXA: 79.2% PBO: 9.9% Odds ratio: 34.74 (20.48, 58.93) %* FDA endpoint,[h] weeks 28-52: ROXA: 1.99 g/dl PBO: 0.3 g/dl LSMD: 1.69 (1.52, 1.86) g/dl*	Hb target: 10-12 g/dl, maint.; Mean ΔHb without rescue therapy, weeks 28-36: ROXA: 2.01 g/dl (iron-replete) [i] PBO: 0.26 g/dl (iron-replete) [i] ROXA: 2.01 g/dl (non-replete) [i] PBO: 0.493 g/dl (non-replete) [i]
ANDES[30] (NCT01750190); Global (no European sites) FibroGen Inc.	R, DB, PC; ESA-naïve; n = 922, 2:1	ROXA 70 or 100 mg TIW[f] vs PBO, 52 weeks	EMA endpoint,[g] first 24 weeks: ROXA: 86.0% PBO: 6.6% Odds ratio: 77.6 (44.7, 134.5) %* FDA endpoint,[h] weeks 28-52: ROXA: 2.00 g/dl PBO: 0.16 g/dl	Hb target: 10–12 g/dl, maint.; Mean ΔHb without rescue therapy, weeks 28-36 (exploratory): ROXA: 2.02 g/dl PBO: 0.20 g/dl LSMD: 1.88 (1.73, 2.04) g/dl*

			LSMD: 1.85 (1.74, 1.97) g/dl*	
OLYMPUS[31] (NCT02174627); Global AstraZeneca	R, DB, PC; ESA-naïve; n = 2781, 1:1	ROXA 70 mg TIW vs PBO, 164 weeks	FDA endpoint,[h] weeks 28-52: ROXA: 1.75 g/dl PBO: 0.4 g/dl LSMD: 1.35 (1.27, 1.43) g/dl*	Hb target: 10-12 g/dl, maint.; EMA endpoint,[g] first 24 weeks: ROXA: 77% PBO: 8.5% Odds ratio: 9.12 (7.63, 10.89)*, comparable results in iron-replete versus non-replete groups [i]
DOLOMITES[32] (NCT02021318); Europe Astellas Pharma, Inc.	R, OL, AC; ESA-naïve; n = 616, 1:1	ROXA 70 or 100 mg TIW[f] vs DPO, 104 weeks	EMA endpoint,[g] first 24 weeks: ROXA: 89.5% DPO: 78.0% Difference: 11.51 (5.66, 17.36) %	Hb target: 10-12 g/dl, maint.; EMA endpoint,[g] first 24 weeks: ROXA: 96.4% (iron-replete) [i] DPO: 84.3% (iron-replete) [i] ROXA: 80.2% (non-replete) [i] DPO: 71.4% (non-replete) [i]
Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)				
Nangaku *et al*., 2021[33] (NCT03329196); Japan	R, OL, AC; ESA-naïve and ESA-treated; n = 304, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 52 weeks	Difference in mean Hb, weeks 20 and 24: VADA: 11.66 g/dl DPO: 11.93 g/dl LSMD: -0.26 (-0.50, -0.02) g/dl	Hb within target range (11–13 g/dl) at week 52 (ESA-naïve | ESA-treated) VADA: 71.4% | 79.2% DPO: 84.5% | 76.6%
PRO_2TECT[34] (NCT02648347); Global	R, OL, AC; ESA-naïve; n = 1751, 1:1	VADA 300mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 168 weeks	Difference in mean ΔHb, weeks 24-36: VADA: 1.43 g/dl DPO: 1.38 g/dl LMSD: 0.05 (-0.04, 0.15) g/dl Difference in mean ΔHb, weeks 40-52 [k]: VADA: 1.52 g/dl DPO: 1.48 g/dl LSMD: 0.04 (-0.06, 0.14) g/dl	Hb target range: US, 10-11 g/dl / non-US, 10-12 g/dl; Hb at target, weeks 24-36: VADA: 50.4% DPO: 50.2% Hb at target, weeks 40-52: VADA: 43.1% DPO: 43.5%
PRO_2TECT[34] (NCT02680574); Global	R, OL, AC; ESA-treated; n = 1725, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 168 weeks	Difference in mean ΔHb, weeks 24-36: VADA: 0.41 g/dl DPO: 0.42 g/dl LSMD: -0.01 (-0.09, 0.07) g/dl Difference in mean ΔHb, weeks 40-52 [k]: VADA: 0.43 g/dl DPO: 0.44 g/dl LSMD: 0.00 (-0.10, 0.09) g/dl	Hb target range: US, 10-11 g/dl / non-US, 10-12 g/dl; Hb at target, weeks 24-36: VADA: 60.1% DPO: 60.7% Hb at target, weeks 40-52: VADA: 50.7% DPO: 49.0%

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% confidence intervals are shown in brackets.
AC, active-controlled; DAPRO, daprodustat; DB, double-blind; DESI, desidustat; DPO, darbepoetin alfa; EBP, epoetin beta pegol; ENARO, enarodustat; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; LSMD, least-squares mean difference; maint., maintenance; MOLI, molidustat; NC, non-

comparative; NR, not reported; OL, open-label; PBO, placebo; PC, placebo-controlled; QD, once daily; R, randomized; ROXA, roxadustat; TIW, three times weekly; VADA, vadadustat. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

[a] starting dose, then titrated to maintain target Hb levels (right column).
[b] proportion of patients with Hb in target range reported as secondary outcomes in most studies.
[c] starting dose based on baseline Hb level; for NCT02964936, Akizawa *et al*., 2020,[27] starting dose is based on an algorithm that included 2 baseline Hb levels, weight and eGFR.
[d] starting dose based on prior ESA dose.
[e] weight-based dosing: 70 mg for patients weighing 40 to < 60 kg or 100 mg for ≥ 60 kg.
[f] weight-based dosing: 70 mg for weight of 45 to <70 kg; 100 mg for ≥70 kg.
[g] EMA: For the European Union's European Medicines Agency (EMA), the primary efficacy endpoint was Hb response defined as Hb ≥ 11.0 g/dl and an Hb increase from baseline by ≥1.0 g/dl in any patient with baseline Hb >8.0 g/dl, or an increase from baseline by ≥ 2.0 g/dl in any patient with baseline Hb ≤ 8.0 g/dl at two consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA or IV iron administration) prior to Hb response.
[h] FDA: For the US Food and Drug Administration (FDA), the primary efficacy endpoint was the mean change in Hb from baseline to the average Hb level during the evaluation period (defined as Weeks 28–52), regardless of rescue therapy.
[i] iron status: iron replete, transferrin saturation (TSAT) ≥ 20% and ferritin ≥ 100 ng/ml; non-replete, TSAT ≤ 20% and ferritin ≤ 100 ng/ml.
[j] key secondary endpoint.
* Statistical significance reported.

Table 3: Efficacy data from phase 3 HIF-PHI clinical trials in patients with dialysis-dependent chronic kidney disease

Study; Location	Study design; No. of pts, randomization	Treatment: Starting dose,[a] study duration	Primary efficacy outcomes: Differences in mean Hb and/or ΔHb from baseline to evaluation period	Hb targets and Hb response rate[b]
***Daprodustat* (GlaxoSmithKline)**				
Akizawa *et al*., 2020[35] (NCT02969655); Japan	R, DB, AC; ESA-treated, M-HD; n = 271, 1:1	DAPRO 4 mg QD vs DPO, 52 weeks	Difference in mean Hb, weeks 40–52: DAPRO: 10.9 g/dl DPO: 10.8 g/dl Adjusted difference: 0.1 (–0.1, 0.2) g/dl	Hb at target (10–12 g/dl) during weeks 40–52: DAPRO: 88% DPO: 90%
ASCEND-ID[36] (NCT03029208); Global	R, OL, AC; ESA-naïve and ESA-treated (limited exposure <6 weeks), I-DD; n = 312, 1:1	DAPRO 1-4 mg QD[c] vs DPO, 52 weeks	Difference in mean ΔHb, weeks 28–52: DAPRO: 1.02 g/dl DPO: 1.12 g/dl Difference: 0.10 (-0.34, 0.14) g/dl	Hb target: 10-11 g/dl.
ASCEND-D[37] (NCT02879305); Global	R, OL, AC; ESA-treated, M-DD; n = 2964, 1:1	DAPRO 4-12 mg QD[d] vs ESA (epoetin alfa for HD, DPO for PD, 52 weeks	Difference in mean ΔHb, weeks 28-52: DAPRO: 0.28 g/dl ESA: 0.10 g/dl Difference: 0.18 (0.12, 0.24) g/dl	Hb target: 10-11 g/dl
ASCEND-TD[38] (NCT03400033); Global	R, DB, AC; ESA-treated, M-DD; n = 407, 2:1	DAPRO 8-24 mg TIW[d] adjusted to dose range of 2-48 mg TIW vs epoetin alfa, 52 weeks	Difference in mean ΔHb, weeks 28-52: DAPRO: -0.04 g/dl Epoetin alfa: 0.02 g/dl Difference: -0.05 (-0.21, 0.10) g/dl	Hb target 10-11 g/dl Hb within analysis range of 10–11.5 g/dl during weeks 28-52: DAPRO: 80% Epoetin alfa: 64%*
***Desidustat* (Cadila Healthcare Ltd.)**				
DREAM-D[39] (NCT04215120); (CTRI/2019/12/022312) India	R, OL, AC; ESA-naïve (n = 50) and ESA-treated, M-HD (2 or 3 x week); n = 392, 1:1	DESI 100 mg TIW (ESA-naïve); 100, 125 or 150 mg TIW[d] (ESA-treated) vs epoetin alfa, 24 weeks	Difference in mean ΔHb, weeks 16–24: DESI: 0.95 g/dl Epoetin alfa: 0.80 g/dl LSM difference: 0.14 (–0.13, 0.42) g/dl	Hb within target range (10–12 g/dl) during weeks 16–24: DESI: 59.2% Epoetin alfa: 48.4%
***Enarodustat* (Japan Tobacco Inc.)**				
SYMPHONY-HD[40] (JapicCTI-183938) Japan	R, DB, AC; ESA-treated; M-HD; n = 173, 1:1; FAS: n = 172	ENARO 4 mg QD vs DPO; 24 weeks.	Difference in mean Hb, weeks 20–24: ENARO: 10.73 g/dl DPO: 10.85 g/dl Difference: –0.12 (–0.33, +0.10) g/dl	Hb within target range (10–12 g/dl) during EOT period: ENARO: 77.9% DPO: 88.4%

***Molidustat* (Bayer Yakuhin, Ltd.)**				
MIYABI HD-M[41] (NCT03543657); Japan	R, DB, AC; ESA-treated, M-HD; n = 229, 2:1	MOLI 75 mg QD vs DPO; 52 weeks	Difference in mean Hb, weeks 33-36: MOLI: 10.63 d/dl DPO: 10.77 g/dl Difference in mean ΔHb, weeks 33-36: MOLI: -0.14 g/dl DPO: -0.07 g/dl LSMD: -0.13 (-0.46, 0.19) g/dl	Hb within target range (10-12 g/dl): MOLI: 61.2-77.8% during weeks 18-52 DPO: 68.7-88.7% during weeks 2-52.
***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
Chen *et al*., 2019[42] (NCT02652806); China FibroGen, Inc.	R, OL, AC; ESA-treated; M-DD; n = 304, 2:1	ROXA 100 or 120 mg TIW[e] vs epoetin alfa, 26 weeks	Difference in mean ΔHb, weeks 23–27: ROXA: 0.7 g/dl Epoetin alfa: 0.5 g/dl Difference: 0.2 (-0.02, 0.5) g/dl	Hb target: 10–12 g/dl Hb of ≥ 10 g/dl, weeks 23-27: ROXA: 87.0% Epoetin alfa: 88.5%
Akizawa *et al*., 2020[43] (NCT02779764, NCT02780141); Japan Astellas Pharma, Inc.	R, OL, NC; I-HD (ESA-naïve, n = 75) and M-HD (>12 weeks, ESA-treated); n = 239	ESA-naïve: ROXA 50 or 70 mg TIW[c], 24 weeks ESA-treated: ROXA 70 or 100 mg TIW[d], 52 weeks	Difference in mean ΔHb, weeks 18-24: ESA-naïve: 2.26 g/dl ESA-treated: -0.03 g/dl During weeks 46–52: ESA-treated: 0.12 g/dl	Hb within target range (10–12 g/dl) [f]: ESA-naïve: 73% at weeks 18-24 ESA-treated: 79.1% at weeks 18-24 and 71.2% at weeks 46-52
Akizawa *et al*., 2020[44] (NCT02780726); Japan Astellas Pharma, Inc.	R, OL, NC; ESA-naïve (n = 13) and ESA-treated, PD (> 4 weeks); n = 56	ROXA 50 or 70 mg TIW[c] (ESA-naïve) or ROXA 70 or 100 mg TIW[d] (ESA-treated), 24 weeks	Difference in mean Hb, weeks 18–24: ESA-naïve: 1.69 g/dl ESA-treated: 0.14 g/dl	Hb within target range (10–12 g/dl) during weeks 18-24: ESA-naïve: 92.3% ESA-treated: 74.4%
Akizawa *et al*., 2020[45] (NCT02952092); Japan Astellas Pharma, Inc.	R, DB, AC; ESA-treated, M-HD; n = 303, 1:1	ROXA 70 or 100 mg TIW[d] vs DPO QW, 24 weeks	Difference in mean Hb, weeks 18–24: ROXA: -0.04 g/dl DPO: -0.03 g/dl Difference: -0.02 (-0.18, 0.15) g/dl	Hb within target range (10–12 g/dl) during weeks 18–24 [f]: ROXA: 79.3% DPO: 83.4%
HIMALAYAS[46] (NCT02052310); Global FibroGen, Inc.	R, OL, AC, ESA-naïve and ESA-limited use (≤3 weeks), I-DD; n = 1043, 1:1	ROXA 70-100mg TIW[g, j] vs epoetin alfa, 52 weeks	EMA endpoint,[h] first 24 weeks: ROXA: 88.2% Epoetin alfa: 84.4% Difference: 3.5 (-0.7, 7.7)% FDA endpoint,[i] weeks 28-52: ROXA: 2.57 g/dl Epoetin alfa: 2.36 g/dl LSMD: 1.18 (0.08, 0.29) g/dl*	Hb at target (10-12 g/dl), first 24 weeks (US second. endpoint): ROXA: 84.3% Epoetin alfa: 79.5% ΔHb, weeks 28-52 (EU second. endpoint): ROXA: 2.62 g/dl Epoetin alfa: 2.44 g/dl*
PYRENEES[47] (NCT02278341);	R, OL, AC, ESA-treated, M-DD;	ROXA 100-200 mg TIW[d] vs ESA (epoetin alfa or	Difference in mean ΔHb, weeks 28-36: ROXA: 0.43 g/dl	Hb within target range (10-12 g/dl) at weeks 28 to 36:

Europe Astellas Pharma, Inc.	n = 838 (836 treated), 1:1	DPO), 52–104 weeks	ESA: 0.19. g/dl LSMD: 0.23 (0.13, 0.34) g/dl* Difference in mean ΔHb, weeks 28-52: ROXA: 0.36 g/dl ESA: 0.19 g/dl LSMD: 0.17 (0.082, 0.261) g/dl*	ROXA: 84.2% Epoetin alfa: 82.4%
ROCKIES[48] (NCT02174731); Global AstraZeneca	R, OL, AC; ESA-naïve and ESA-treated, M-DD and I-DD (n = 416); n = 2133, 1:1	ROXA 70-200 mg TIW[d, j] for ESA-treated and 70 or 100 mg TIW[g] for ESA-naïve vs epoetin alfa, 52-164 weeks	Difference in mean ΔHb, weeks 28-52: ROXA: 0.77 g/dl Epoetin alfa: 0.68 g/dl LSMD: 0.09 (0.01, 0.18) g/dl*	Proportion of time with Hb ≥ 10 g/dl during weeks 28–52: ROXA: 79% Epoetin alfa: 76%
SIERRAS[49] (NCT02273726); United States FibroGen, Inc.	R, OL, AC; ESA-treated, M-DD and I-DD (n=71); total n = 741, 1:1	ROXA 70-200 mg TIW[j, d] vs epoetin alfa, 52 weeks	Difference in mean ΔHb, weeks 28-52: ROXA: 0.39 g/dl Epoetin alfa: -0.09 g/dl LSMD: 0.48 (0.37, 0.59) g/dl*	Hb target range: 10-12 g/dl Hb ≥10 g/dl, weeks 28-52: ROXA: 66.1% Epoetin alfa: 58.6%
***Vadadustat* (Akebia Therapeutics; Otsuka Pharmaceuticals)**				
Nangaku *et al*., 2021[50] (NCT03439137); Japan	R, DB, AC; ESA-treated, M-HD; n = 323. 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 52 weeks	Difference in mean Hb, weeks 20-24: VADA: 10.61 g/dl DPO: 10.65 g/dl LSMD: -0.05 g/dl (-0.26 to 0.17)	Hb within target range (10–12 g/dl) at weeks 24 and 52: VADA: 75.4 and 75.7% DPO: 75.7 and 86.5%
INNO$_2$VATE[51] (NCT02865850); Global	R, DB, AC; ESA-naïve and ESA-treated; I-DD; n = 369, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg vs DPO, 116 weeks	Difference in mean ΔHb, weeks 24-36: VADA: 1.26 g/dl DPO: 1.58 g/dl LMSD: g/dl -0.31 (-0.53, -0.10) Difference in mean ΔHb, weeks 40-52 [k]: VADA: 1.42 g/dl DPO: 1.50 g/dl LSMD: -0.07 (-0.34, 0.19) g/dl	Hb target range: US, 10-11 g/dl / non-US, 10-12 g/dl; Hb at target, weeks 24-36: VADA: 43.6% DPO: 56.9% Hb at target, weeks 40-52: VADA: 39.8% DPO: 41.0%
INNO$_2$VATE[51] (NCT02892149); Global	R, DB, AC; ESA-naïve and ESA-treated; M-DD; n = 3554, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg vs DPO, 116 weeks	Difference in mean ΔHb, weeks 24-36: VADA: 0.19 g/dl DPO: 0.36 g/dl LSMD: - 0.17 (-0.23, -0.10) g/dl Difference in mean ΔHb, weeks 40-52 [k]: VADA: 0.23 g/dl DPO: 0.41 g/dl LSMD: -0.18 (-0.25, -0.12) g/dl	Hb target range: US, 10-11 g/dl / non-US, 10-12 g/dl; Hb at target, weeks 24-36: VADA: 49.2% DPO: 53.2% Hb at target, weeks 40-52: VADA: 44.3% DPO: 50.9%

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% confidence intervals are shown in brackets.
AC, active-controlled; DAPRO, daprodustat; DB, double-blind; DESI, desidustat; DPO, darbepoetin alfa; ENARO, enarodustat; EOT, end of treatment; ESA, erythropoietin-stimulating agent; FAS, full analysis set; Hb, hemoglobin; HD, hemodialysis; I-DD, incident dialysis (HD and PD); I-HD, incident hemodialysis; M-DD, maintenance/stable dialysis (HD and PD); M-HD, maintenance/stable hemodialysis; MOLI, molidustat; LSMD, least-squares mean difference; NC, non-

comparative; NR, not reported; OL, open-label; PBO, placebo; PC, placebo-controlled; PD, peritoneal dialysis; QD, once daily; QW, once weekly; R, randomized, ROXA, roxadustat; TIW, three times weekly; VADA, vadadustat. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

[a] starting dose, then titrated to maintain target Hb levels (right column).
[b] proportion of patients with Hb in target range reported as secondary outcomes in most studies.
[c] depending on study, starting dose is based on either recent Hb measurements or weight or both.
[d] initial dose according to prior ESA dose.
[e] Weight-based dosing (100 mg for > 45 to 60 or120 mg for ≥ 60 kg), adjusted to maintain Hb levels of 10–12 g/dl.
[f] all patients, full analysis set.
[g] dosed at 70 mg for weight of 45 to 70 kg; 100 mg for weight of >70-160.
[h] EMA: For the European Union's European Medicines Agency (EMA), the primary efficacy endpoint was Hb response defined as Hb ≥ 11.0 g/dl and an Hb increase from baseline by ≥1.0 g/dl in any patient with baseline Hb >8.0 g/dl, or an increase from baseline by ≥ 2.0 g/dl in any patient with baseline Hb ≤ 8.0 g/dl at two consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA or IV iron administration) prior to Hb response.
[i] FDA: For the US Food and Drug Administration (FDA), the primary efficacy endpoint was the mean change in Hb from baseline to the average Hb level during the evaluation period (defined as Weeks 28–52), regardless of rescue therapy.
[j] titrated to achieve a Hb level of 11 g/dl and to maintain Hb levels of 10–12 g/dl.
[k] key secondary endpoint.

Table 4: Iron parameters from phase 3 HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Study; Location	Entry criteria	Iron strategy	Iron utilization	Changes in markers of iron metabolism
***Daprodustat* (GlaxoSmithKline)**				
ASCEND-ND[21] (NCT02876835); Global N=3872	ESA naïve and Hb 8-10 g/dl or ESA treated and Hb 8-11 g/dl eGFR <60 ml/min/1.73 m^2 Hb <10 g/dl Ferritin >100 ng/ml TSAT >20%	Iron starting criteria: ferritin ≤100 ng/ml or TSAT ≤20% Iron stopping criteria: ferritin ≥800 ng/ml and TSAT ≥20% or TSAT ≥40% Route of iron administration based on local clinical practice	*IV iron* 13% in HIF-PHI vs. 11% in ESA between weeks 36-48	Hepcidin: decreased from median (IQR) 105.6 (61.7-165.9) to 82.7 (43.0-142.4) ng/ml in HIF-PHI vs. 105.3 (61.2-169.8) to 120.1 (66.5-201.1) ng/ml in ESA TSAT: 30.0% (24.0-37.0) to 29.0 (22.0-35.0) in HIF-PHI vs. 29.0% (23.0-36.0) to 32.0 (24.0-41.0) in ESA Ferritin: Median (IQR) 267.0 (164.0-456.0) to 240.0 (135.0-425.0) ng/ml in HIF-PHI vs. 275.0 (171.0-449.0) to 262.0 (150.5-447.5) ng/ml in ESA TIBC: 45.0 (40.0-50.0) to 50.0 (45.0-55.0) mmol/l in HIF-PHI vs. 44.0 (40.0-49.0) to 44.0 (39.0-49.0) mmol/l in ESA Iron: 13.0 (10.0-16.0) to 14.0 (11.0-17.0) mmol/l in HIF-PHI vs. 13.0 (10.0-16.0) to 14.0 (11.0-18.0) mmol/l in ESA
***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
ALPS[29] (NCT01887600); Europe Astellas Pharma, Inc. N=594	eGFR <60 ml/min/1.73 m^2 ESA naïve Ferritin ≥30 ng/ml TSAT ≥5%	Oral iron recommended IV iron as rescue if Hb <8.5 g/dl and ferritin <100 ng/ml or TSAT <20%	Not reported	Hepcidin: decreased from 37.9 (36.6) to 24.6 (30.1) mg/l in HIF-PHI and from 41.2 (37.6) to 39.4 (37.8) mg/l in placebo Ferritin: 112.6 ng/ml (IQR 76.8-198.6 to 82.8 ng/ml (IQR 48.0-170.1) in HIF-PHI and from 111.6 ng/ml (IQR 78.2-205.3) to 100.2 ng/ml (IQR 66.5-182.1) in ESA TIBC: increased in HIF-PHI but not ESA
ANDES[30] (NCT01750190); Global (no European sites) FibroGen Inc. N=922	ESA naïve eGFR <60 ml/min/1.73 m^2 Hb ≤10 g/dl Ferritin ≥30 ng/ml TSAT ≥5%	Oral iron encouraged IV iron rescue	*% receiving IV iron* 2.5% HIF-PHI vs. 4.9% placebo; HR 0.39 (95% CI 0.15-0.81)	Hepcidin: -22.1 (80.9) mg/l in HIF-PHI and 3.9 (80.9) mg/l in placebo; LSM difference of -25.7 µg/l (95% CI -38.5 to -12.9). TIBC: increased in HIF-PHI and decreased in placebo; LSM difference 38.65 µg/dl (95% CI 31.9-45.5) TSAT: LSM difference -0.1%, 95% CI (-2.0, 1.7) Iron: LSM difference 8.3 mg/l (95% CI 2.9, 13.6)

				Ferritin: LSM difference -57.5 ng/ml (95% CI -92.8, -22.3)
OLYMPUS[31] (NCT02174627); Global AstraZeneca N=2781	ESA naïve eGFR <60 ml/min/1.73 m^2 Mean of 2 recent Hb ≤10 g/dl Ferritin ≥50 ng/ml TSAT ≥15%	Oral iron allowed without restriction and recommended IV iron if patients intolerant or unresponsive to oral iron and Hb <8.5 g/dl and ferritin <100 µg/l or TSAT <20%	*Receipt of IV iron* 4.3% HIF-PHI, 7.9% placebo; HR 0.41 (95% CI 0.29, 0.56) *Receipt of oral iron* 46.5% HIF-PHI vs. 46.5% placebo	Hepcidin: LSM difference -45.4 ng/ml (95% CI 56.2, 34.5) Ferritin: difference -54.6 mg/l (95% CI -71.7, -37.4) TSAT: difference -0.6% (95% CI -1.3, 0.2) TIBC: difference 34,6 µg/dl (95% CI 31.3, 37.9) Iron: difference 7.7 mg/dl (95% CI 5.8, 9.6)
DOLOMITES[32] (NCT02021318); Europe Astellas Pharma, Inc N=616	ESA naïve eGFR <60 ml/min/1.7 $3m^2$ Mean of 2 recent Hb ≤10.5 g/dl	Oral iron recommended in HIF-PHI and IV iron allowed if inadequate Hb response after at least 2 dose increases or maximum dose limit reached and iron deficiency or intolerance to oral iron Oral or IV iron required if ferritin <100 ng/ml or TSAT <20% in ESA	*IV iron* 6.2% HIF-PHI, 12.7% ESA Monthly dose 34.7 (30.0) mg HIF-PHI and 69.6 (67.3) ESA (among those receiving) *Oral iron* Bivalent: 43.7% HIF-PHI, 49.8% ESA; Trivalent: 35.3% HIF-PHI, 44.7% ESA	Ferritin: change from baseline at week 52: -93.1 (521.4) pmol/l HIF-PHI vs. -72.4 (459.3) pmol/l ESA TSAT: 1.3% (11.8) HIF-PHI vs. 5.2 (13.2) Iron: 1.1 (5.9) mmol/l HIF-PHI vs. 2.2 (6.8) pmol/l ESA
Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)				
PRO_2TECT[34] (NCT02648347); Global N=1751	ESA naïve eGFR ≤60 ml/min/1.73 m^2 Hb <10 g/dl Ferritin ≥100 ng/ml TSAT ≥20%	Iron supplementation encouraged to maintain ferritin ≥100 ng/ml or TSAT ≥20%	Not reported	Not reported
PRO_2TECT[34] (NCT02648347); Global N=1725	ESA treated eGFR ≤60 ml/min/1.73 m^2 Hb 8-11 g/dl in US or 9-12 non-US Ferritin ≥100 ng/ml TSAT ≥20%	Iron supplementation encouraged to maintain ferritin ≥100 ng/mL or TSAT ≥20%	Not reported	Not reported

Table 5: Iron parameters from phase 3 HIF-PHI clinical trials in dialysis-dependent chronic kidney disease

Study; Location	Entry criteria	Iron strategy	Iron utilization	Changes in markers of iron metabolism
***Daprodustat* (GlaxoSmithKline)**				
ASCEND-D[37] (NCT02879305); Global Prevalent dialysis N=2964	ESA users ferritin >100 ng/ml TSAT >20%	Iron supplementation protocol to maintain ferritin 100-800 ng/ml and TSAT 20-40%	*Mean monthly IV dose* 139.2 (171.1) to 90.8 (SE 3.3) mg HIF-PHI vs. 137.4 (174.7) to 99.9 (SE 3.3) mg ESA Difference: -9.1 mg (95% CI -18.4, 0.2)	Hepcidin: decreased more in HIF-PHI than ESA TIBC: increased more in HIF-PHI than ESA Ferritin: slight decrease in both groups TSAT: decreased slightly in both groups
ASCEND-ID[36] (NCT03029208); Global Incident Dialysis N=312	ESA naïve ferritin >100 ng/ml TSAT >20%	Iron starting criteria: ferritin ≤100 ng/ml or TSAT ≤20% Iron stopping criteria: ferritin ≥800 ng/ml and TSAT ≥20% or TSAT ≥40% Route of iron administration based on local clinical practice	159.3 (207.1) to 142 (161) mg HIF-PHI vs. 180.1 (209.9) to 128 (137) mg ESA Difference: 19.4 mg/mo (95% CI -11.0, 49.9)	Hepcidin: decreased from 112.6 ng/ml (IQR 76.8-198.6) to 82.8 ng/ml (IQR 48.0-170.1) in HIF-PHI and from 111.6 ng/ml (IQR 78.2-205.3) to 100.2 ng/ml (IQR 66.5-182.1) in ESA TIBC: increased in HIF-PHI but not ESA Ferritin: decreased in both groups TSAT: decreased in both groups Iron: stable in both groups
ASCEND-TD[38] (NCT03400033); Global Prevalent HD N=407	ESA treated Hb 8-11.5 g/dl Ferritin >100 ng/ml TSAT >20%	Iron was administered if ferritin ≤100 ng/ml or TSAT ≤20% Iron was stopped if: ferritin >800 ng/ml and TSAT >20% or TSAT >40%	*% receiving IV iron* Weeks 28-52: 38% in HIF-PHI vs. 40% in ESA Weeks 1-52: 51% HIF-PHI vs. 51% ESA *Mean monthly dose* Weeks 28-52: 104.9 (222.5) mg HIF-PHI vs. 103.1 (244.7) mg ESA Weeks 1-52: 99.0 (187.1) HIF-PHI vs. 104.4 (210.8) ESA Mean treatment difference: -8.1 (95% CI -45.7, 29.4)	Hepcidin: declined at a similar rate in both arms during the trial. TIBC: increased in HIF-PHI by week 4 and remained higher than ESA throughout the trial. Ferritin: declined at a similar rate in both arms during the trial. TSAT: similar between groups throughout the trial Iron: increased in HIF-PHI by week 4 and remained higher than ESA throughout the trial.

***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
HIMALAYAS[46] (NCT02052310); Global FibroGen, Inc Incident dialysis N=1043	ESA use for ≤3 weeks Mean of last 2 Hb ≤10 g/dl ferritin ≥100 ng/ml TSAT ≥20%	Oral iron encouraged; IV iron allowed if Hb response inadequate and ferritin ≤100 ng/ml and TSAT <20%	*% receiving IV iron* Weeks 28-52: 83.7% HIF-PHI vs. 85.4% ESA *Mean monthly IV dose* Difference -4.4 (95% CI -20.7, 12.0) mg Mean monthly oral dose 290.7 (95% CI -463.2, 1044.5) mg	Hepcidin: -64.8 (95% CI -74.3, -55.3) mg/l HIF-PHI vs. -54.1 (95% CI -63.4, -44.7) mg/l ESA; difference -10.7 (95% CI -23.2, 1.77) mg/l Ferritin: -191.3 (95% CI -234.4, -148.2) ng/ml HIF-PHI vs. -130.0 (95% CI -172.9, -87.2) ng/ml ESA; difference-61.3 (95% CI -117.0, -5.6) ng/ml TSAT: -2.7% (95% CI -3.9, -1.5) HIF-PHI vs. -2.2% (95% CI -3.4, -1.1) ESA; difference -0.5% (95% CI -2.0, 1.1) TIBC: 37.7 (95% CI 33.3, 42.1) mg/dl HIF-PHI vs. 1.7 (95% CI -2.7, 6.0) mg/dl ESA; difference 36.1 (95% CI 30.2, 41.9) mg/dl Iron: 2.1 (95% CI -1.2, 5.5) mg/dl HIF-PHI vs. -4.7 (95% CI -8.0, -1.5) mg/dl ESA; difference 6.9 (95% CI 2.4, 11.3) mg/dl
PYRENEES[47] (NCT02278341); Europe Astellas Pharma, Inc. Prevalent HD N=3188	ESA users ferritin ≥100 ng/ml TSAT ≥20%	For patients on HIF-PHI, oral iron was permitted. IV iron was allowed only if Hb did not respond adequately after 2 consecutive dose increase or if the maximum dose was reached and ferritin <100 ng/ml or TSAT <20% or the patient was intolerant to oral iron	*Mean monthly IV dose* HIF-PHI: 21.6 mg ESA: 53.5 mg Difference: -31.9 (95% CI -41.4, -22.4)	Hepcidin: -32.7 (42.3) HIF-PHI vs. -17.5 (47.3) ESA at week 52 Ferritin: lower in HIF-PHI and TSAT levels similar; exact changes not reported TIBC: 10.0 (8.8) mmol/l HIF-PHI vs. 2.7 (6.4) mmol/l ESA Iron: -0.3 (7.4) mmol/l HIF-PHI vs. -1.2 (6.3) mmol/l ESA
ROCKIES[48] (NCT02174731); Global AstraZeneca Prevalent dialysis N=2133	ESA naïve and Hb <10 g/dl or ESA user and Hb <12 g/dl Ferritin ≥100 ng/ml TSAT ≥20%	Oral iron permitted in both groups. In HIF-PHI, IV iron permitted if Hb did not increase sufficiently after ≥2 doses and ferritin <100 ng/ml or TSAT <20%	*Mean monthly IV dose* 58.7 HIF-PHI vs. 91.4 mg ESA *Oral iron use* 20.7% HIF-PHI vs. 18.0% ESA	Hepcidin: -45.0 (95% CI -57.5, -32.5) ng/ml HIF-PHI vs. -16.8 (95% CI -29.2, -4.4) ng/ml ESA; difference: -18.2 (95% CI -42.0, -14.5) ng/ml TSAT: -1.9% (95% CI -2.8, -1.1) HIF-PHI vs. -2.4% (95% CI -3.3, -1.6) ESA; difference: 0.5% (95% CI -0.4, 1.5) Ferritin: -104.5 (95% CI -126.2, -82.8) mg/l HIF-PHI vs. -41.2 (95% CI -62.1, -20.3) ESA; difference -63.3 (95% CI -87.4, -39.2) TIBC: 35.0 (95% CI 31.8, 38.2) mg/dl HIF-PHI vs. -2.4 (95% CI -5.5, 0.7) mg/dl ESA;

				difference 37.4 (95% CI 33.8, 41.0) Iron: 6.6 (95% CI 4.5, 8.7) mg/dl HIF-PHI vs. -5.5 (95% CI -7.6, -3.5) mg/dl ESA; difference 12.1 (95% CI 9.8, 14.5) mg/dl
SIERRAS[49] (NCT02273726); United States FibroGen, Inc. Prevalent HD N=741	ESA users Ferritin ≥100 ng/ml TSAT ≥20%	Oral iron encouraged IV iron if oral not tolerated or if iron deficient	*Mean monthly IV dose* 17.1 (53.4) mg HIF-PHI vs. 37.0 (106.8) mg ESA Difference: -20.1 (95% CI -33.8, -6.45)	Hepcidin: decreased in both groups; difference: -19.12 (95% CI -39.52, 1.28) Ferritin: decreased in both groups; difference: -41.71 (95% CI -96.51, 13.09) ng/ml Iron: increased in roxadustat; difference: 6.33 (95% CI 2.20, 10.45) mg/dl TSAT: decreased in both groups; difference: 2.18% (95% CI 0.16, 4.20)
Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)				
INNO$_2$VATE[51] (NCT02865850); Global Prevalent dialysis N=3554	ESA users and ESA-naïve Hb 8-11 mg/dl in US or 9-12 mg/dl in non-US ferritin ≥100 ng/ml	Encouraged iron supplementation to maintain ferritin ≥100 ng/ml or TSAT ≥20%	Not reported	Hepcidin: 193.9 (140.1) ng/ml to 137.4 (119.9) ng/ml in HIF-PHI vs. 190.4 (135.9) to 158.2 (123.4) in ESA Ferritin: 846.8 (562.7) to 787.3 (550.2) ng/ml in HIF-PHI vs. 840.7 (538.5) to 828.9 (565.8) ng/ml in ESA TSAT: 38.1% (13.5) to 34.1% (21.4) in HIF-PHI vs. 37.6% (13.2) to 36.6% (14.3) in ESA
INNO$_2$VATE[51] (NCT02865850); Global Incident dialysis N=369	Hb 8-11 mg/dl ferritin ≥100 ng/ml TSAT ≥20%	Encouraged iron supplementation to maintain ferritin ≥100 ng/ml or TSAT ≥20%	Not reported	*Changes from baseline to weeks 40-52* Hepcidin: 122.4 (109.5) to 95.7 (72.1) ng/ml in HIF-PHI vs. 126.9 (111.2) to 101.1 (95.6) in ESA Ferritin: 469.7 (316.9) to 555.5 (453.2) ng/ml in HIF-PHI vs. 527.8 (401.1) to 559.4 (458.5) ng/ml in ESA TSAT: 31.3% (9.5) to 33.1% (12.0) in HIF-PHI vs. 34.2% (12.7) to 35.6% (13.8) in ESA

Table 6: Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Study; Location Sponsor	Study design; No. of patients, randomization	Treatment, starting dose,[a] study duration	Primary outcome hazard ratio; non-inferiority margin (95% confidence interval)	Other outcome hazard ratios (95% confidence interval)
***Daprodustat* (GlaxoSmithKline)**				
ASCEND-ND[21] (NCT02876835); Global	R, OL, AC; ESA-naïve and ESA-treated; n = 3872, 1:1	DAPRO 2-4 mg QD[b] for ESA-naïve and 1-4 mg QD[c] for ESA-users vs DPO, 148 weeks	First occurrence of adjudicated MACE (composite of death, nonfatal myocardial infarction, or nonfatal stroke): HR 1.03, 95% CI 0.89-1.19 Noninferiority margin: HR 1.25	On-treatment MACE: HR 1.40, 95% CI 1.17-1.68 MACE or hospitalization for heart failure: HR 1.09, 95% CI 0.95-1.24 MACE or thromboembolic event: HR 1.06, 95% CI 0.93-1.22 All-cause death: HR 1.03, 95% CI 0.87-1.20
***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
ALPS[29] (NCT01887600); Europe Astellas Pharma, Inc.	R, DB, PC; ESA-naïve; n = 594, 2:1	ROXA 70 or 100 mg TIW[d] vs PBO, 104 weeks	Pooled analysis of ALPS, ANDES, OLYMPUS: time to first MACE (composite of death, nonfatal myocardial infarction, or nonfatal stroke): HR 1.10, 95% CI 0.96-1.27 Noninferiority margin: HR 1.30	MACE+ (composite of death, nonfatal myocardial infarction, nonfatal stroke, unstable angina and hospitalization for heart failure): HR 1.07, 95% CI 0.93-1.21 MACE, on treatment + 7d: HR 1.38, 95% CI 1.11-1.70) Myocardial infarction: HR 1.29, 95% CI 0.90-1.85 Stroke: HR 1.25, 95% CI 0.82-1.90 Unstable angina: HR 0.56, 95% CI 0.22-1.42 Congestive heart failure: HR 0.93, 95% CI 0.75-1.16 All-cause death: HR 1.08, 95% CI 0.93-1.26
ANDES[30] (NCT01750190); Global (no European sites) FibroGen Inc.	R, DB, PC; ESA-naïve; n = 922, 2:1	ROXA 70 or 100 mg TIW[d] vs PBO, 52 weeks		
OLYMPUS[31] (NCT02174627); Global AstraZeneca	R, DB, PC; ESA-naïve; n = 2781, 1:1	ROXA 70 mg TIW vs PBO, 164 weeks		

Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)				
PRO_2TECT[34] (NCT02648347); Global	R, OL, AC; ESA-naïve; n = 1751, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 168 weeks	(Pooled analysis of ESA-naive and ESA-treated subjects) Time to first MACE (composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke): HR 1.17 (1.01 to 1.36) Noninferiority margin: HR 1.25 (USA) and HR 1.30 (EMA)	MACE plus hospitalization for either heart failure or a thromboembolic event HR 1.11, 95% CI 0.97 -1.27 Death from cardiovascular causes: HR 1.01, 95% CI 0.79-1.29 Death from any cause: HR 1.09, 95% CI 0.93-1.27 Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: HR 1.16, 95% CI 0.95-1.42
PRO_2TECT[34] (NCT02680574); Global	R, OL, AC; ESA-treated; n = 1725, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 168 weeks		

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% confidence intervals are shown in brackets.
AC, active-controlled; DAPRO, daprodustat; DB, double-blind; DPO, darbepoetin alfa; EBP, epoetin beta pegol; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HR, hazard ratio; LSMD, least-squares mean difference; maint., maintenance; NC, non-comparative; NR, not reported; OL, open-label; PBO, placebo; PC, placebo-controlled; QD, once daily; R, randomized; ROXA, roxadustat; TIW, three times weekly; VADA, vadadustat. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

[a] starting dose, then titrated to maintain target Hb levels (right column).
[b] starting dose based on baseline Hb level; for NCT02964936, Akizawa *et al*., 2020,8 starting dose is based on an algorithm that included 2 baseline Hb levels, weight and eGFR.
[c] starting dose based on prior ESA dose.
[d] weight-based dosing: 70 mg for weight of 45 to <70 kg; 100 mg for ≥70 kg.

Table 7: Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in dialysis-dependent chronic kidney disease

Study; Location Sponsor	Study design; No. of patients, randomization	Treatment, starting dose,[a] study duration	Primary outcome hazard ratio; non-inferiority margin (95% confidence interval)	Other outcome hazard ratios (95% confidence interval)
***Daprodustat* (GlaxoSmithKline)**				
ASCEND-ID[36] (NCT03029208); Global	R, OL, AC; ESA-naïve and ESA-treated (limited exposure <6 weeks), I-DD; n = 312, 1:1	DAPRO 1-4 mg QD[b] vs DPO, 52 weeks	Exploratory analysis: first occurrence of adjudicated MACE (composite of death from any cause, non-fatal myocardial infarction or non-fatal stroke): n=19 (12%) DAPRO vs n=15 (10%) DPO -- absolute rate difference/100 PYs 2.41 (95% CI−4.61 to 9.43) Non-inferiority margin: N/A (not designed or powered as a non-inferiority trial)	The first occurrence of MACE or a hospitalization for heart failure: n=24 (15%) DPO vs. n=18 (12%) DPO Adjusted mean difference in systolic BP: −0.09 mm Hg (95% CI, −4.72 to 4.53); diastolic BP: 1.99 mm Hg (95%CI, −0.85 to 4.82)
ASCEND-D[37] (NCT02879305); Global	R, OL, AC; ESA-treated, M-DD; n = 2964, 1:1	DAPRO 4-12 mg QD[c] vs ESA (epoetin alfa for HD, DPO for PD, 52 weeks	Adjudicated MACE (composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke): HR 0.93, 95% CI 0.81-1.07 Non-inferiority margin: HR 1.25	MACE or thromboembolic event: HR 0.88, 95% CI 0.78-1.00 MACE or hospitalization for heart failure: HR 0.97, 95% CI 0.85-1.11
ASCEND-TD[38] (NCT03400033); Global	R, DB, AC; ESA-treated, M-DD; n = 407, 2:1	DAPRO 8-24 mg TIW[c] adjusted to dose range of 2-48 mg TIW vs epoetin alfa, 52 weeks	First occurrence of adjudicated MACE: Absolute rate difference per 100 person-years (95% CI) 2.3 (-4.4, to 9.0)	Worsening hypertension (*post-hoc*): DAPRO vs. Epoetin: Relative risk 0.83 (0.50 to 1.39)
***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
Chen *et al*., 2019[42] (NCT02652806); China FibroGen, Inc.	R, OL, AC; ESA-treated; M-DD; n = 304, 2:1	ROXA 100 or 120 mg TIW[d] vs epoetin alfa, 26 weeks	Cardiac disorders: ROXA n=5 (2.5%) and epoetin alfa n=1 (1.0%)	Vascular disorders: ROXA n=2 (1.0%) and epoetin alfa n=0

Akizawa *et al*., 2020[43] (NCT02779764, NCT02780141); Japan Astellas Pharma, Inc.	R, OL, NC; I-HD (ESA-naïve, n = 75) and M-HD (>12 weeks, ESA-treated); n = 239	ESA-naïve: ROXA 50 or 70 mg TIW[b], 24 weeks ESA-treated: ROXA 70 or 100 mg TIW[c], 52 weeks	MACE – not reported	
Akizawa *et al*., 2020[44] (NCT02780726); Japan Astellas Pharma, Inc.	R, OL, NC; ESA-naïve (n = 13) and ESA-treated, PD (> 4 weeks); n = 56	ROXA 50 or 70 mg TIW[b] (ESA-naïve) or ROXA 70 or 100 mg TIW[c] (ESA-treated), 24 weeks	MACE – not reported	
Akizawa *et al*., 2020[45] (NCT02952092); Japan Astellas Pharma, Inc.	R, DB, AC; ESA-treated, M-HD; n = 303, 1:1	ROXA 70 or 100 mg TIW[c] vs DPO QW, 24 weeks	Cardiac disorders: ROXA n=5 (3.3%), DPO n=4 (2.6%)	Vascular disorders: ROXA n=5 (3.3%), DPO n=1 (0.7%)
HIMALAYAS[46] (NCT02052310); Global FibroGen, Inc.	R, OL, AC, ESA-naïve and ESA-limited use (≤3 weeks), I-DD; n = 1043, 1:1	ROXA 70-100 mg TIW[e, f] vs epoetin alfa, 52 weeks	Pooled analysis of HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS MACE (myocardial infarction, stroke, and all-cause mortality) HR 1.09, 95% CI 0.95–1.26; Noninferiority margin: HR 1.30	Arteriovenous fistula thrombosis: ROXA n=39 (7.5%) vs n=21 (4.1%) Pooled analysis of HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS: MACE plus congestive heart failure or unstable angina requiring hospitalization: HR 0.98, 95% CI 0.86–1.11 All-cause mortality: HR 1.13, 95% CI 0.95–1.34
PYRENEES[47] (NCT02278341); Europe Astellas Pharma, Inc.	R, OL, AC, ESA-treated, M-DD; n = 838 (836 treated), 1:1	ROXA 100-200 mg TIW[c] vs ESA (epoetin alfa or DPO), 52–104 weeks		
ROCKIES[48] (NCT02174731); Global AstraZeneca	R, OL, AC; ESA-naïve and ESA-treated, M-DD and I-DD (n = 416); n = 2133, 1:1	ROXA 70-200 mg TIW[c, f] for ESA-treated and 70 or 100 mg TIW[e] for ESA-naïve vs epoetin alfa, 52-164 weeks		
SIERRAS[49] (NCT02273726); United States FibroGen, Inc.	R, OL, AC; ESA-treated, M-DD and I-DD (n=71); total n = 741, 1:1	ROXA 70-200 mg TIW[c, f] vs epoetin alfa, 52 weeks		

***Vadadustat* (Akebia Therapeutics; Otsuka Pharmaceuticals)**				
Nangaku *et al*., 2021[50] (NCT03439137); Japan	R, DB, AC; ESA-treated, M-HD; n = 323. 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 52 weeks	Cardiovascular event, cardiac failure VADA: 13 (8.0%), DPO 15 (9.3%)	Retinal disorder: VADA 21 (13.0%), DPO 16 (9.9%)
INNO$_2$VATE[51] (NCT02865850); Global	R, DB, AC; ESA-naïve and ESA-treated; I-DD; n = 369, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg vs DPO, 116 weeks	Pooled analysis of I-DD and M-DD trials MACE (myocardial infarction, stroke, and all-cause mortality): HR 0.96, 95% CI 0.83 – 1.11	MACE plus hospitalization for heart failure or thromboembolic event: HR 0.96; 95% CI, 0.84 to 1.10. Death from cardiovascular causes: HR 0.96; 95% CI, 0.77 to 1.20. All-cause death: HR 0.95; 95% CI, 0.81 to 1.12. Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: HR 0.95; 95% CI, 0.80 to 1.14.
INNO$_2$VATE[51] (NCT02892149); Global	R, DB, AC; ESA-naïve and ESA-treated; M-DD; n = 3554, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg vs DPO, 116 weeks	Non-inferiority margin: HR 1.25	

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% confidence intervals are shown in brackets.
AC, active-controlled; DAPRO, daprodustat; DB, double-blind; DESI, desidustat; DPO, darbepoetin alfa; ENARO, enarodustat; EOT: end of treatment; ESA, erythropoietin-stimulating agent; FAS, full analysis set; Hb, hemoglobin; HD, hemodialysis; HR, hazard ratio; I-DD, incident dialysis (HD and PD); I-HD, incident hemodialysis; M-DD, maintenance/stable dialysis (HD and PD); M-HD, maintenance/stable hemodialysis; MOLI, molidustat; LSMD, least-squares mean difference; NC, non-comparative; NR, not reported; OL, open-label; PBO, placebo; PC, placebo-controlled; PD, peritoneal dialysis; QD, once daily; QW, once weekly; R, randomized, ROXA, roxadustat; TIW, three times weekly; VADA, vadadustat. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

[a] starting dose, then titrated to maintain target Hb levels (right column).
[b] depending on study, starting dose is based on either recent Hb measurements or weight or both.
[c] initial dose according to prior ESA dose.
[d] Weight-based dosing (100 mg for > 45 to 60 or120 mg for ≥ 60 kg), adjusted to maintain Hb levels of 10–12 g/dl.
[e] dosed at 70 mg for weight of 45 to 70 kg; 100 mg for weight of >70-160.
[f] titrated to achieve a Hb level of 11 g/dl and to maintain Hb levels of 10–12 g/dl.

Table 8: Research recommendations

- Determine whether HIF-PHIs have an impact on progression of CKD based on severity of baseline disease, presence of proteinuria/albuminuria, or the cause of CKD
- Understand if hemoglobin targets should be the same when using HIF-PHIs versus ESAs for patients with ND-CKD and DD-CKD
- Conduct of additional trials to understand the need for iron supplementation and the appropriate iron dosing strategy with the use of HIF-PHIs, along with identification of iron targets during treatment
- Assess long-term safety for specific populations such as children, older adults, kidney transplant recipients, patients with PKD or acute kidney injury in future HIF-PHI studies
- Identification of novel biomarkers that can be used to monitor the safety of HIF-PHIs
- Ascertain variability in the risk of MACE and thrombosis with respect to region of the world, patients characteristics/subpopulations, Hb target, or rate of Hb correction
- Perform future studies to understand the effect of HIF-PHIs on HRQoL and patient-centered outcomes
- Determine whether HIF-PHIs are effective in patients with ESA hyporesponsiveness or in immunosuppressed populations, including those with kidney transplants
- Obtain longer term safety data (e.g., post-market surveillance) for HIF-PHI on risk for *de novo* cancer or progression of malignancy, retinopathy, and other potential adverse effects
- In regions where HIF-PHIs are available, comparative cost-effectiveness analysis should be conducted between these agents and ESAs

REFERENCES

9. Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease. Kidney Int Suppl (2011) 2021; 11: 8-25.

20. Nangaku M, Hamano T, Akizawa T, et al. Daprodustat Compared with Epoetin Beta Pegol for Anemia in Japanese Patients Not on Dialysis: A 52-Week Randomized Open-Label Phase 3 Trial. Am J Nephrol 2021; 52: 26-35.

21. Singh AK, Carroll K, McMurray JJV, et al. Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis. N Engl J Med 2021; 385: 2313-2324.

22. Agrawal D, Varade D, Shah H, et al. Desidustat in Anemia due to Non-Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-ND). Am J Nephrol 2022; 53: 352-360.

23. Akizawa T, Nangaku M, Yamaguchi T, et al. A Phase 3 Study of Enarodustat in Anemic Patients with CKD not Requiring Dialysis: The SYMPHONY ND Study. Kidney Int Rep 2021; 6: 1840-1849.

24. Yamamoto H, Nobori K, Matsuda Y, et al. Efficacy and Safety of Molidustat for Anemia in ESA-Naive Nondialysis Patients: A Randomized, Phase 3 Trial. Am J Nephrol 2021; 52: 871-883.

25. Yamamoto H, Nobori K, Matsuda Y, et al. Molidustat for Renal Anemia in Nondialysis Patients Previously Treated with Erythropoiesis-Stimulating Agents: A Randomized, Open-Label, Phase 3 Study. Am J Nephrol 2021; 52: 884-893.

26. Chen N, Hao C, Peng X, et al. Roxadustat for anemia in patients with kidney disease not receiving dialysis. N Engl J Med 2019; 381: 1001-1010.

27. Akizawa T, Yamaguchi Y, Otsuka T, et al. A Phase 3, Multicenter, Randomized, Two-Arm, Open-Label Study of Intermittent Oral Dosing of Roxadustat for the Treatment of Anemia in Japanese Erythropoiesis-Stimulating Agent-Naive Chronic Kidney Disease Patients Not on Dialysis. Nephron 2020; 144: 372-382.

28. Akizawa T, Iwasaki M, Otsuka T, et al. Phase 3 Study of Roxadustat to Treat Anemia in Non-Dialysis-Dependant CKD. Kidney Int Rep 2021; 6: 1810-1828.

29. Shutov E, Sulowicz W, Esposito C, et al. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, double-blind, placebo-controlled study (ALPS). Nephrol Dial Transplant 2021; 36: 1629-1639.

30. Coyne DW, Roger SD, Shin SK, et al. Roxadustat for CKD-related Anemia in Non-dialysis Patients. Kidney Int Rep 2021; 6: 624-635.

31. Fishbane S, El-Shahawy MA, Pecoits-Filho R, et al. Roxadustat for Treating Anemia in Patients with CKD Not on Dialysis: Results from a Randomized Phase 3 Study. J Am Soc Nephrol 2021; 32: 737-755.

32. Barratt J, Andric B, Tataradze A, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, open-label, active-controlled study (DOLOMITES). Nephrol Dial Transplant 2021; 36: 1616-1628.

33. Nangaku M, Kondo K, Kokado Y, et al. Phase 3 Randomized Study Comparing Vadadustat with Darbepoetin Alfa for Anemia in Japanese Patients with Nondialysis-Dependent CKD. J Am Soc Nephrol 2021; 32: 1779-1790.

34. Chertow GM, Pergola PE, Farag YMK, et al. Vadadustat in Patients with Anemia and Non-Dialysis-Dependent CKD. N Engl J Med 2021; 384: 1589-1600.

35. Akizawa T, Nangaku M, Yonekawa T, et al. Efficacy and Safety of Daprodustat Compared with Darbepoetin Alfa in Japanese Hemodialysis Patients with Anemia: A Randomized, Double-Blind, Phase 3 Trial. Clin J Am Soc Nephrol 2020; 15: 1155-1165.

36. Singh AK, Cizman B, Carroll K, et al. Efficacy and Safety of Daprodustat for Treatment of Anemia of Chronic Kidney Disease in Incident Dialysis Patients: A Randomized Clinical Trial. JAMA Intern Med 2022; 182: 592-602.

37. Singh AK, Carroll K, Perkovic V, et al. Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis. N Engl J Med 2021; 385: 2325-2335.

38. Coyne DW, Singh AK, Lopes RD, et al. Three Times Weekly Dosing of Daprodustat versus Conventional Epoetin for Treatment of Anemia in Hemodialysis Patients: ASCEND-TD: A Phase 3 Randomized, Double-Blind, Noninferiority Trial. Clin J Am Soc Nephrol 2022; 17: 1325-1336.

39. Gang S, Khetan P, Varade D, et al. Desidustat in Anemia due to Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-D). Am J Nephrol 2022; 53: 343-351.

40. Akizawa T, Nangaku M, Yamaguchi T, et al. A Phase 3 Study of Enarodustat (JTZ-951) in Japanese Hemodialysis Patients for Treatment of Anemia in Chronic Kidney Disease: SYMPHONY HD Study. Kidney Dis (Basel) 2021; 7: 494-502.

41. Akizawa T, Yamada T, Nobori K, et al. Molidustat for Japanese Patients With Renal Anemia Receiving Dialysis. Kidney Int Rep 2021; 6: 2604-2616.

42. Chen N, Hao C, Liu BC, et al. Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis. N Engl J Med 2019; 381: 1011-1022.

43. Akizawa T, Ueno M, Shiga T, et al. Oral roxadustat three times weekly in ESA-naive and ESA-converted patients with anemia of chronic kidney disease on hemodialysis: Results from two phase 3 studies. Ther Apher Dial 2020; 24: 628-641.

44. Akizawa T, Otsuka T, Reusch M, et al. Intermittent Oral Dosing of Roxadustat in Peritoneal Dialysis Chronic Kidney Disease Patients with Anemia: A Randomized, Phase 3, Multicenter, Open-Label Study. Ther Apher Dial 2020; 24: 115-125.

45. Akizawa T, Iwasaki M, Yamaguchi Y, et al. Phase 3, Randomized, Double-Blind, Active-Comparator (Darbepoetin Alfa) Study of Oral Roxadustat in CKD Patients with Anemia on Hemodialysis in Japan. J Am Soc Nephrol 2020; 31: 1628-1639.

46. Provenzano R, Shutov E, Eremeeva L, et al. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. Nephrol Dial Transplant 2021; 36: 1717-1730.

47. Csiky B, Schomig M, Esposito C, et al. Roxadustat for the Maintenance Treatment of Anemia in Patients with End-Stage Kidney Disease on Stable Dialysis: A European Phase 3, Randomized, Open-Label, Active-Controlled Study (PYRENEES). Adv Ther 2021; 38: 5361-5380.

48. Fishbane S, Pollock CA, El-Shahawy M, et al. Roxadustat Versus Epoetin Alfa for Treating Anemia in Patients with Chronic Kidney Disease on Dialysis: Results from the Randomized Phase 3 ROCKIES Study. J Am Soc Nephrol 2022; 33: 850-866.

49. Charytan C, Manllo-Karim R, Martin ER, et al. A Randomized Trial of Roxadustat in Anemia of Kidney Failure: SIERRAS Study. Kidney Int Rep 2021; 6: 1829-1839.

50. Nangaku M, Kondo K, Ueta K, et al. Efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese anemic patients on hemodialysis: a Phase 3, multicenter, randomized, double-blind study. Nephrol Dial Transplant 2021; 36: 1731-1741.

51. 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: 1601-1612.

Novel Anemia Therapies in CKD: A KDIGO Controversies Conference Report

TABLES

Table 1: Potential advantages and disadvantages of various CKD-anemia therapies

Agents	Potential Advantages	Potential Disadvantages
HIF-PHIs	• Oral dosing more convenient for some patients • May facilitate anemia treatment in patients with non-dialysis dependent CKD • ~~Suppression of hepcidin may~~May improve utilization of iron for erythropoiesis, particularly oral iron • May be more effective in chronic inflammatory states (CRP >5 mg/l)	• Difficult to monitor adherence • Potential polypharmacy and drug-drug interactions • Less clinical experience • Potential risk of enhancing tumor growth • Potential risk of worsening retinopathy • Potential risk of cyst growth in ADPKD
ESAs	• Adherence can be monitored with in-clinic administration • Extensive clinical experience	• Treatment requires self-injection or regular clinic visits • Resistance in chronic inflammatory states • Risk of enhancing tumor growth • Antibody-mediated pure red cell aplasia (rare)
Iron compounds	• No serious adverse effects of oral iron	• If PO, risk of poor gastrointestinal tolerance and non-adherence to therapy • If IV, risk of allergic/anaphylactic reaction • If IV, potential risk of increasing oxidative stress • If IV, potential risk of hemosiderosis

Table 2: Efficacy data from phase 3 HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Study; Location Sponsor	Study design; No. of patients, randomization	Treatment, starting dose,[a] study duration	Primary efficacy outcomes: Differences in mean Hb and/or ΔHb from baseline to evaluation period	Hb targets and Hb response rate[b]
***Daprodustat* (GlaxoSmithKline)**				
Nangaku *et al.*, 2021[20] (NCT02791763); Japan	R, OL, AC; ESA-naïve and ESA-treated; n = 299, 1:1	DAPRO 2 and 4 mg QD[c] for ESA-naïve and 4 mg QD[c] for ESA-users vs EBP, 52 weeks	Difference in mean Hb, weeks 40-52: DAPRO: 12 g/dl EBP: 11.9 g/dl Difference: 0.1 (-0.1, 0.3) g/dl	Hb within target range (11–13 g/dl) during weeks 40–52: DAPRO: 92% EBP: 92%
ASCEND-ND[21] (NCT02876835); Global	R, OL, AC; ESA-naïve and ESA-treated; n = 3872, 1:1	DAPRO 2-4 mg QD[c] for ESA-naïve and 1-4 mg QD[d] for ESA-users vs DPO, 148 weeks	Difference in mean ΔHb, weeks 28-52: DAPRO: 0.74 g/dl DPO: 0.66 g/dl Difference: 0.08 (0.03, 0.13) g/dl	Hb target (10-11 g/dl)
***Desidustat* (Cadila Healthcare Ltd.)**				
DREAM-ND[22] (NCT04012957); India, Sri Lanka	R, OL, AC; ESA-naïve; n = 588, 1:1	DESI 100 mg TIW vs DPO, 24 weeks	Difference in mean ΔHb, weeks 16-24: DESI: 1.95 g/dl DPO: 1.83 g/dl LSMD: 0.11 (–0.12, 0.35) g/dl	Hb within target range (10–12 g/dl) during weeks 16-24: DESI: 77.78% DPO: 68.48%
***Enarodustat* (Japan Tobacco Inc.)**				
SYMPHONY ND[23] (JapicCTI-183870); Japan	R, OL, AC; ESA-naïve and ESA-treated; n = 216, 1:1	ENARO 2 mg QD vs DPO, 24 weeks	Difference in mean Hb, weeks 20–24: ENARO: 10.96 g/dl DPO: 10.87 g/dl Difference: 0.09 (–0.07, 0.26) g/dl	Hb within target range (10–12 g/dl) during weeks 4–24: ENARO: 88.6% DPO: 87.9%
***Molidustat* (Bayer Yakuhin, Ltd.)**				
MIYABI ND-C[24] (NCT03350321); Japan	R, OL, AC; ESA-naïve; n = 162, 1:1	MOLI 25 mg QD vs DPO, 52 weeks	Difference in mean Hb, weeks 30-36: MOLI: 11.28 g/dl DPO: 11.70 g/dl Difference in mean ΔHb, weeks 30-36: MOLI: 1.32 g/dl DPO: 1.69 g/dl LSMD: –0.38 (–0.67, –0.08) g/dl	Hb within target range (11–13 g/dl), responder rate during weeks 30–36: MOLI: 59.8% DPO: 82.5%

MIYABI ND-M[25] (NCT03350347); Japan	R, OL, AC; ESA-treated; n = 164, 1:1	MOLI 25 mg or 50 mg QD[d] vs DPO, 52 weeks	Difference in mean Hb, weeks 30-36: MOLI: 11.67 g/dl DPO: 11.53 g/dl Difference in mean ΔHb, weeks 30-36: MOLI: 0.36 g/dl DPO: 0.24 g/dl LSMD: 0.13 (–0.15, 0.40) g/dl	Hb within target range (11–13 g/dl), responder rate during weeks 30–36: MOLI: 72.0% DPO: 76.8%
***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
Chen *et al*., 2019[26] (NCT02652819); China FibroGen, Inc.	R, DB, PC; ESA-naïve; n = 154, 2:1, n = 152 (safety population)	ROXA 70 or 100 mg TIW[e] vs PBO, 8 weeks DB, then 18 weeks OL	Difference in mean ΔHb, weeks 7–9: ROXA: 1.9 g/dl PBO: -0.4 g/dl Difference: 2.2 (1.9, 2.6) g/dl*	Hb target: 10-12 g/dl; pts with >10 g/dl and increase in ΔHb of 1-2 g/dl at week 9: ROXA: 75% PBO: 0%
Akizawa *et al*., 2020[27] (NCT02964936); Japan Astellas Pharma, Inc.	R, OL, NC; ESA-naïve; n = 99	ROXA 50 or 70 mg TIW[c], 24 weeks	Difference in mean ΔHb, weeks 18-24: ROXA 50 mg: 1.34 g/dl ROXA 70 mg: 1.30 g/dl	Hb target: 10-12 g/dl; Hb ≥ 10 g/dl and ΔHb of ≥1 g/dl at EOT: ROXA 50 mg: 97.0% ROXA 70 mg: 100.0% for Hb ≥ 10.5 g/dl: ROXA 50 mg: 94.9% ROXA 70 mg: 98.0%
Akizawa *et al*., 2021[28] (NCT02988973); Japan Astellas Pharma, Inc.	R, OL, AC; ESA-treated (DPO and EBP); n = 334, 1:1,	ROXA 70 or 100 mg TIW[d] vs DPO, 52 weeks	Difference in mean ΔHb, weeks 18-24: ROXA: 0.15 g/dl DPO: 0.22 g/dl LSMD: -0.07 g/ (-0.23, 0.10) g/dl	Hb within target range (10–12 g/dl), maintenance rate during weeks 18-24: ROXA: 77.1% PBO: 85.5%
ALPS[29] (NCT01887600); Europe Astellas Pharma, Inc.	R, DB, PC; ESA-naïve; n = 594, 2:1	ROXA 70 or 100 mg TIW[f] vs PBO, 104 weeks	EMA endpoint,[g] first 24 weeks: ROXA: 79.2% PBO: 9.9% Odds ratio: 34.74 (20.48, 58.93) %* FDA endpoint,[h] weeks 28-52: ROXA: 1.99 g/dl PBO: 0.3 g/dl LSMD: 1.69 (1.52, 1.86) g/dl*	Hb target: 10-12 g/dl, maint.; Mean ΔHb without rescue therapy, weeks 28-36: ROXA: 2.01 g/dl (iron-replete) [i] PBO: 0.26 g/dl (iron-replete) [i] ROXA: 2.01 g/dl (non-replete) [i] PBO: 0.493 g/dl (non-replete) [i]
ANDES[30] (NCT01750190); Global (no European sites) FibroGen Inc.	R, DB, PC; ESA-naïve; n = 922, 2:1	ROXA 70 or 100 mg TIW[f] vs PBO, 52 weeks	EMA endpoint,[g] first 24 weeks: ROXA: 86.0% PBO: 6.6% Odds ratio: 77.6 (44.7, 134.5) %* FDA endpoint,[h] weeks 28-52: ROXA: 2.00 g/dl PBO: 0.16 g/dl	Hb target: 10–12 g/dl, maint.; Mean ΔHb without rescue therapy, weeks 28-36 (exploratory): ROXA: 2.02 g/dl PBO: 0.20 g/dl LSMD: 1.88 (1.73, 2.04) g/dl*

			LSMD: 1.85 (1.74, 1.97) g/dl*	
OLYMPUS[31] (NCT02174627); Global AstraZeneca	R, DB, PC; ESA-naïve; n = 2781, 1:1	ROXA 70 mg TIW vs PBO, 164 weeks	FDA endpoint,[h] weeks 28-52: ROXA: 1.75 g/dl PBO: 0.4 g/dl LSMD: 1.35 (1.27, 1.43) g/dl*	Hb target: 10-12 g/dl, maint.; EMA endpoint,[g] first 24 weeks: ROXA: 77% PBO: 8.5% Odds ratio: 9.12 (7.63, 10.89)*, comparable results in iron-replete versus non-replete groups [i]
DOLOMITES[32] (NCT02021318); Europe Astellas Pharma, Inc.	R, OL, AC; ESA-naïve; n = 616, 1:1	ROXA 70 or 100 mg TIW[f] vs DPO, 104 weeks	EMA endpoint,[g] first 24 weeks: ROXA: 89.5% DPO: 78.0% Difference: 11.51 (5.66, 17.36) %	Hb target: 10-12 g/dl, maint.; EMA endpoint,[g] first 24 weeks: ROXA: 96.4% (iron-replete) [i] DPO: 84.3% (iron-replete) [i] ROXA: 80.2% (non-replete) [i] DPO: 71.4% (non-replete) [i]
Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)				
Nangaku *et al*., 2021[33] (NCT03329196); Japan	R, OL, AC; ESA-naïve and ESA-treated; n = 304, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 52 weeks	Difference in mean Hb, weeks 20 and 24: VADA: 11.66 g/dl DPO: 11.93 g/dl LSMD: -0.26 (-0.50, -0.02) g/dl	Hb within target range (11–13 g/dl) at week 52 (ESA-naïve | ESA-treated) VADA: 71.4% | 79.2% DPO: 84.5% | 76.6%
PRO_2TECT[34] (NCT02648347); Global	R, OL, AC; ESA-naïve; n = 1751, 1:1	VADA 300mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 168 weeks	Difference in mean ΔHb, weeks 24-36: VADA: 1.43 g/dl DPO: 1.38 g/dl LMSD: 0.05 (-0.04, 0.15) g/dl Difference in mean ΔHb, weeks 40-52 [k]: VADA: 1.52 g/dl DPO: 1.48 g/dl LSMD: 0.04 (-0.06, 0.14) g/dl	Hb target range: US, 10-11 g/dl / non-US, 10-12 g/dl; Hb at target, weeks 24-36: VADA: 50.4% DPO: 50.2% Hb at target, weeks 40-52: VADA: 43.1% DPO: 43.5%
PRO_2TECT[34] (NCT02680574); Global	R, OL, AC; ESA-treated; n = 1725, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 168 weeks	Difference in mean ΔHb, weeks 24-36: VADA: 0.41 g/dl DPO: 0.42 g/dl LSMD: -0.01 (-0.09, 0.07) g/dl Difference in mean ΔHb, weeks 40-52 [k]: VADA: 0.43 g/dl DPO: 0.44 g/dl LSMD: 0.00 (-0.10, 0.09) g/dl	Hb target range: US, 10-11 g/dl / non-US, 10-12 g/dl; Hb at target, weeks 24-36: VADA: 60.1% DPO: 60.7% Hb at target, weeks 40-52: VADA: 50.7% DPO: 49.0%

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% confidence intervals are shown in brackets.
AC, active-controlled; DAPRO, daprodustat; DB, double-blind; DESI, desidustat; DPO, darbepoetin alfa; EBP, epoetin beta pegol; ENARO, enarodustat; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; LSMD, least-squares mean difference; maint., maintenance; MOLI, molidustat; NC, non-

comparative; NR, not reported; OL, open-label; PBO, placebo; PC, placebo-controlled; QD, once daily; R, randomized; ROXA, roxadustat; TIW, three times weekly; VADA, vadadustat. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

[a] starting dose, then titrated to maintain target Hb levels (right column).
[b] proportion of patients with Hb in target range reported as secondary outcomes in most studies.
[c] starting dose based on baseline Hb level; for NCT02964936, Akizawa *et al*., 2020,[27] starting dose is based on an algorithm that included 2 baseline Hb levels, weight and eGFR.
[d] starting dose based on prior ESA dose.
[e] weight-based dosing: 70 mg for patients weighing 40 to < 60 kg or 100 mg for ≥ 60 kg.
[f] weight-based dosing: 70 mg for weight of 45 to <70 kg; 100 mg for ≥70 kg.
[g] EMA: For the European Union's European Medicines Agency (EMA), the primary efficacy endpoint was Hb response defined as Hb ≥ 11.0 g/dl and an Hb increase from baseline by ≥1.0 g/dl in any patient with baseline Hb >8.0 g/dl, or an increase from baseline by ≥ 2.0 g/dl in any patient with baseline Hb ≤ 8.0 g/dl at two consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA or IV iron administration) prior to Hb response.
[h] FDA: For the US Food and Drug Administration (FDA), the primary efficacy endpoint was the mean change in Hb from baseline to the average Hb level during the evaluation period (defined as Weeks 28–52), regardless of rescue therapy.
[i] iron status: iron replete, transferrin saturation (TSAT) ≥ 20% and ferritin ≥ 100 ng/ml; non-replete, TSAT ≤ 20% and ferritin ≤ 100 ng/ml.
[j] key secondary endpoint.
* Statistical significance reported.

Table 3: Efficacy data from phase 3 HIF-PHI clinical trials in patients with dialysis-dependent chronic kidney disease

Study; Location	Study design; No. of pts, randomization	Treatment: Starting dose,[a] study duration	Primary efficacy outcomes: Differences in mean Hb and/or ΔHb from baseline to evaluation period	Hb targets and Hb response rate[b]
***Daprodustat* (GlaxoSmithKline)**				
Akizawa *et al*., 2020[35] (NCT02969655); Japan	R, DB, AC; ESA-treated, M-HD; n = 271, 1:1	DAPRO 4 mg QD vs DPO, 52 weeks	Difference in mean Hb, weeks 40–52: DAPRO: 10.9 g/dl DPO: 10.8 g/dl Adjusted difference: 0.1 (–0.1, 0.2) g/dl	Hb at target (10–12 g/dl) during weeks 40–52: DAPRO: 88% DPO: 90%
ASCEND-ID[36] (NCT03029208); Global	R, OL, AC; ESA-naïve and ESA-treated (limited exposure <6 weeks), I-DD; n = 312, 1:1	DAPRO 1-4 mg QD[c] vs DPO, 52 weeks	Difference in mean ΔHb, weeks 28–52: DAPRO: 1.02 g/dl DPO: 1.12 g/dl Difference: 0.10 (-0.34, 0.14) g/dl	Hb target: 10-11 g/dl.
ASCEND-D[37] (NCT02879305); Global	R, OL, AC; ESA-treated, M-DD; n = 2964, 1:1	DAPRO 4-12 mg QD[d] vs ESA (epoetin alfa for HD, DPO for PD, 52 weeks	Difference in mean ΔHb, weeks 28-52: DAPRO: 0.28 g/dl ESA: 0.10 g/dl Difference: 0.18 (0.12, 0.24) g/dl	Hb target: 10-11 g/dl
ASCEND-TD[38] (NCT03400033); Global	R, DB, AC; ESA-treated, M-DD; n = 407, 2:1	DAPRO 8-24 mg TIW[d] adjusted to dose range of 2-48 mg TIW vs epoetin alfa, 52 weeks	Difference in mean ΔHb, weeks 28-52: DAPRO: -0.04 g/dl Epoetin alfa: 0.02 g/dl Difference: -0.05 (-0.21, 0.10) g/dl	Hb target 10-11 g/dl Hb within analysis range of 10–11.5 g/dl during weeks 28-52: DAPRO: 80% Epoetin alfa: 64%*
***Desidustat* (Cadila Healthcare Ltd.)**				
DREAM-D[39] (NCT04215120); (CTRI/2019/12/022312) India	R, OL, AC; ESA-naïve (n = 50) and ESA-treated, M-HD (2 or 3 x week); n = 392, 1:1	DESI 100 mg TIW (ESA-naïve); 100, 125 or 150 mg TIW[d] (ESA-treated) vs epoetin alfa, 24 weeks	Difference in mean ΔHb, weeks 16–24: DESI: 0.95 g/dl Epoetin alfa: 0.80 g/dl LSM difference: 0.14 (–0.13, 0.42) g/dl	Hb within target range (10–12 g/dl) during weeks 16–24: DESI: 59.2% Epoetin alfa: 48.4%
***Enarodustat* (Japan Tobacco Inc.)**				
SYMPHONY-HD[40] (JapicCTI-183938) Japan	R, DB, AC; ESA-treated; M-HD; n = 173, 1:1; FAS: n = 172	ENARO 4 mg QD vs DPO; 24 weeks.	Difference in mean Hb, weeks 20–24: ENARO: 10.73 g/dl DPO: 10.85 g/dl Difference: –0.12 (–0.33, +0.10) g/dl	Hb within target range (10–12 g/dl) during EOT period: ENARO: 77.9% DPO: 88.4%

***Molidustat* (Bayer Yakuhin, Ltd.)**				
MIYABI HD-M[41] (NCT03543657); Japan	R, DB, AC; ESA-treated, M-HD; n = 229, 2:1	MOLI 75 mg QD vs DPO; 52 weeks	Difference in mean Hb, weeks 33-36: MOLI: 10.63 d/dl DPO: 10.77 g/dl Difference in mean ΔHb, weeks 33-36: MOLI: -0.14 g/dl DPO: -0.07 g/dl LSMD: -0.13 (-0.46, 0.19) g/dl	Hb within target range (10-12 g/dl): MOLI: 61.2-77.8% during weeks 18-52 DPO: 68.7-88.7% during weeks 2-52.
***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
Chen *et al*., 2019[42] (NCT02652806); China FibroGen, Inc.	R, OL, AC; ESA-treated; M-DD; n = 304, 2:1	ROXA 100 or 120 mg TIW[e] vs epoetin alfa, 26 weeks	Difference in mean ΔHb, weeks 23–27: ROXA: 0.7 g/dl Epoetin alfa: 0.5 g/dl Difference: 0.2 (-0.02, 0.5) g/dl	Hb target: 10–12 g/dl Hb of ≥ 10 g/dl, weeks 23-27: ROXA: 87.0% Epoetin alfa: 88.5%
Akizawa *et al*., 2020[43] (NCT02779764, NCT02780141); Japan Astellas Pharma, Inc.	R, OL, NC; I-HD (ESA-naïve, n = 75) and M-HD (>12 weeks, ESA-treated); n = 239	ESA-naïve: ROXA 50 or 70 mg TIW[c], 24 weeks ESA-treated: ROXA 70 or 100 mg TIW[d], 52 weeks	Difference in mean ΔHb, weeks 18-24: ESA-naïve: 2.26 g/dl ESA-treated: -0.03 g/dl During weeks 46–52: ESA-treated: 0.12 g/dl	Hb within target range (10–12 g/dl) [f]: ESA-naïve: 73% at weeks 18-24 ESA-treated: 79.1% at weeks 18-24 and 71.2% at weeks 46-52
Akizawa *et al*., 2020[44] (NCT02780726); Japan Astellas Pharma, Inc.	R, OL, NC; ESA-naïve (n = 13) and ESA-treated, PD (> 4 weeks); n = 56	ROXA 50 or 70 mg TIW[c] (ESA-naïve) or ROXA 70 or 100 mg TIW[d] (ESA-treated), 24 weeks	Difference in mean Hb, weeks 18–24: ESA-naïve: 1.69 g/dl ESA-treated: 0.14 g/dl	Hb within target range (10–12 g/dl) during weeks 18-24: ESA-naïve: 92.3% ESA-treated: 74.4%
Akizawa *et al*., 2020[45] (NCT02952092); Japan Astellas Pharma, Inc.	R, DB, AC; ESA-treated, M-HD; n = 303, 1:1	ROXA 70 or 100 mg TIW[d] vs DPO QW, 24 weeks	Difference in mean Hb, weeks 18–24: ROXA: -0.04 g/dl DPO: -0.03 g/dl Difference: -0.02 (-0.18, 0.15) g/dl	Hb within target range (10–12 g/dl) during weeks 18–24 [f]: ROXA: 79.3% DPO: 83.4%
HIMALAYAS[46] (NCT02052310); Global FibroGen, Inc.	R, OL, AC, ESA-naïve and ESA-limited use (≤3 weeks), I-DD; n = 1043, 1:1	ROXA 70-100mg TIW[g, j] vs epoetin alfa, 52 weeks	EMA endpoint,[h] first 24 weeks: ROXA: 88.2% Epoetin alfa: 84.4% Difference: 3.5 (-0.7, 7.7)% FDA endpoint,[i] weeks 28-52: ROXA: 2.57 g/dl Epoetin alfa: 2.36 g/dl LSMD: 1.18 (0.08, 0.29) g/dl*	Hb at target (10-12 g/dl), first 24 weeks (US second. endpoint): ROXA: 84.3% Epoetin alfa: 79.5% ΔHb, weeks 28-52 (EU second. endpoint): ROXA: 2.62 g/dl Epoetin alfa: 2.44 g/dl*
PYRENEES[47] (NCT02278341);	R, OL, AC, ESA-treated, M-DD;	ROXA 100-200 mg TIW[d] vs ESA (epoetin alfa or	Difference in mean ΔHb, weeks 28-36: ROXA: 0.43 g/dl	Hb within target range (10-12 g/dl) at weeks 28 to 36:

Europe Astellas Pharma, Inc.	n = 838 (836 treated), 1:1	DPO), 52–104 weeks	ESA: 0.19. g/dl LSMD: 0.23 (0.13, 0.34) g/dl* Difference in mean ΔHb, weeks 28-52: ROXA: 0.36 g/dl ESA: 0.19 g/dl LSMD: 0.17 (0.082, 0.261) g/dl*	ROXA: 84.2% Epoetin alfa: 82.4%
ROCKIES[48] (NCT02174731); Global AstraZeneca	R, OL, AC; ESA-naïve and ESA-treated, M-DD and I-DD (n = 416); n = 2133, 1:1	ROXA 70-200 mg TIW[d, j] for ESA-treated and 70 or 100 mg TIW[g] for ESA-naïve vs epoetin alfa, 52-164 weeks	Difference in mean ΔHb, weeks 28-52: ROXA: 0.77 g/dl Epoetin alfa: 0.68 g/dl LSMD: 0.09 (0.01, 0.18) g/dl*	Proportion of time with Hb ≥ 10 g/dl during weeks 28–52: ROXA: 79% Epoetin alfa: 76%
SIERRAS[49] (NCT02273726); United States FibroGen, Inc.	R, OL, AC; ESA-treated, M-DD and I-DD (n=71); total n = 741, 1:1	ROXA 70-200 mg TIW[j, d] vs epoetin alfa, 52 weeks	Difference in mean ΔHb, weeks 28-52: ROXA: 0.39 g/dl Epoetin alfa: -0.09 g/dl LSMD: 0.48 (0.37, 0.59) g/dl*	Hb target range: 10-12 g/dl Hb ≥10 g/dl, weeks 28-52: ROXA: 66.1% Epoetin alfa: 58.6%
***Vadadustat* (Akebia Therapeutics; Otsuka Pharmaceuticals)**				
Nangaku *et al*., 2021[50] (NCT03439137); Japan	R, DB, AC; ESA-treated, M-HD; n = 323. 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 52 weeks	Difference in mean Hb, weeks 20-24: VADA: 10.61 g/dl DPO: 10.65 g/dl LSMD: -0.05 g/dl (-0.26 to 0.17)	Hb within target range (10–12 g/dl) at weeks 24 and 52: VADA: 75.4 and 75.7% DPO: 75.7 and 86.5%
INNO$_2$VATE[51] (NCT02865850); Global	R, DB, AC; ESA-naïve and ESA-treated; I-DD; n = 369, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg vs DPO, 116 weeks	Difference in mean ΔHb, weeks 24-36: VADA: 1.26 g/dl DPO: 1.58 g/dl LMSD: g/dl -0.31 (-0.53, -0.10) Difference in mean ΔHb, weeks 40-52 [k]: VADA: 1.42 g/dl DPO: 1.50 g/dl LSMD: -0.07 (-0.34, 0.19) g/dl	Hb target range: US, 10-11 g/dl / non-US, 10-12 g/dl; Hb at target, weeks 24-36: VADA: 43.6% DPO: 56.9% Hb at target, weeks 40-52: VADA: 39.8% DPO: 41.0%
INNO$_2$VATE[51] (NCT02892149); Global	R, DB, AC; ESA-naïve and ESA-treated; M-DD; n = 3554, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg vs DPO, 116 weeks	Difference in mean ΔHb, weeks 24-36: VADA: 0.19 g/dl DPO: 0.36 g/dl LSMD: - 0.17 (-0.23, -0.10) g/dl Difference in mean ΔHb, weeks 40-52 [k]: VADA: 0.23 g/dl DPO: 0.41 g/dl LSMD: -0.18 (-0.25, -0.12) g/dl	Hb target range: US, 10-11 g/dl / non-US, 10-12 g/dl; Hb at target, weeks 24-36: VADA: 49.2% DPO: 53.2% Hb at target, weeks 40-52: VADA: 44.3% DPO: 50.9%

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% confidence intervals are shown in brackets.
AC, active-controlled; DAPRO, daprodustat; DB, double-blind; DESI, desidustat; DPO, darbepoetin alfa; ENARO, enarodustat; EOT, end of treatment; ESA, erythropoietin-stimulating agent; FAS, full analysis set; Hb, hemoglobin; HD, hemodialysis; I-DD, incident dialysis (HD and PD); I-HD, incident hemodialysis; M-DD, maintenance/stable dialysis (HD and PD); M-HD, maintenance/stable hemodialysis; MOLI, molidustat; LSMD, least-squares mean difference; NC, non-

comparative; NR, not reported; OL, open-label; PBO, placebo; PC, placebo-controlled; PD, peritoneal dialysis; QD, once daily; QW, once weekly; R, randomized, ROXA, roxadustat; TIW, three times weekly; VADA, vadadustat. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

[a] starting dose, then titrated to maintain target Hb levels (right column).
[b] proportion of patients with Hb in target range reported as secondary outcomes in most studies.
[c] depending on study, starting dose is based on either recent Hb measurements or weight or both.
[d] initial dose according to prior ESA dose.
[e] Weight-based dosing (100 mg for > 45 to 60 or120 mg for ≥ 60 kg), adjusted to maintain Hb levels of 10–12 g/dl.
[f] all patients, full analysis set.
[g] dosed at 70 mg for weight of 45 to 70 kg; 100 mg for weight of >70-160.
[h] EMA: For the European Union's European Medicines Agency (EMA), the primary efficacy endpoint was Hb response defined as Hb ≥ 11.0 g/dl and an Hb increase from baseline by ≥1.0 g/dl in any patient with baseline Hb >8.0 g/dl, or an increase from baseline by ≥ 2.0 g/dl in any patient with baseline Hb ≤ 8.0 g/dl at two consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA or IV iron administration) prior to Hb response.
[i] FDA: For the US Food and Drug Administration (FDA), the primary efficacy endpoint was the mean change in Hb from baseline to the average Hb level during the evaluation period (defined as Weeks 28–52), regardless of rescue therapy.
[j] titrated to achieve a Hb level of 11 g/dl and to maintain Hb levels of 10–12 g/dl.
[k] key secondary endpoint.

Table 4: Iron parameters from phase 3 HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Study; Location	Entry criteria	Iron strategy	Iron utilization	Changes in markers of iron metabolism
***Daprodustat* (GlaxoSmithKline)**				
ASCEND-ND[21] (NCT02876835); Global N=3872	ESA naïve and Hb 8-10 g/dl or ESA treated and Hb 8-11 g/dl eGFR <60 ml/min/1.73 m^2 Hb <10 g/dl Ferritin >100 ng/ml TSAT >20%	Iron starting criteria: ferritin ≤100 ng/ml or TSAT ≤20% Iron stopping criteria: ferritin ≥800 ng/ml and TSAT ≥20% or TSAT ≥40% Route of iron administration based on local clinical practice	*IV iron* 13% in HIF-PHI vs. 11% in ESA between weeks 36-48	Hepcidin: decreased from median (IQR) 105.6 (61.7-165.9) to 82.7 (43.0-142.4) ng/ml in HIF-PHI vs. 105.3 (61.2-169.8) to 120.1 (66.5-201.1) ng/ml in ESA TSAT: 30.0% (24.0-37.0) to 29.0 (22.0-35.0) in HIF-PHI vs. 29.0% (23.0-36.0) to 32.0 (24.0-41.0) in ESA Ferritin: Median (IQR) 267.0 (164.0-456.0) to 240.0 (135.0-425.0) ng/ml in HIF-PHI vs. 275.0 (171.0-449.0) to 262.0 (150.5-447.5) ng/ml in ESA TIBC: 45.0 (40.0-50.0) to 50.0 (45.0-55.0) mmol/l in HIF-PHI vs. 44.0 (40.0-49.0) to 44.0 (39.0-49.0) mmol/l in ESA Iron: 13.0 (10.0-16.0) to 14.0 (11.0-17.0) mmol/l in HIF-PHI vs. 13.0 (10.0-16.0) to 14.0 (11.0-18.0) mmol/l in ESA
***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
ALPS[29] (NCT01887600); Europe Astellas Pharma, Inc. N=594	eGFR <60 ml/min/1.73 m^2 ESA naïve Ferritin ≥30 ng/ml TSAT ≥5%	Oral iron recommended IV iron as rescue if Hb <8.5 g/dl and ferritin <100 ng/ml or TSAT <20%	Not reported	Hepcidin: decreased from 37.9 (36.6) to 24.6 (30.1) mg/l in HIF-PHI and from 41.2 (37.6) to 39.4 (37.8) mg/l in placebo Ferritin: 112.6 ng/ml (IQR 76.8-198.6 to 82.8 ng/ml (IQR 48.0-170.1) in HIF-PHI and from 111.6 ng/ml (IQR 78.2-205.3) to 100.2 ng/ml (IQR 66.5-182.1) in ESA TIBC: increased in HIF-PHI but not ESA
ANDES[30] (NCT01750190); Global (no European sites) FibroGen Inc. N=922	ESA naïve eGFR <60 ml/min/1.73 m^2 Hb ≤10 g/dl Ferritin ≥30 ng/ml TSAT ≥5%	Oral iron encouraged IV iron rescue	*% receiving IV iron* 2.5% HIF-PHI vs. 4.9% placebo; HR 0.39 (95% CI 0.15-0.81)	Hepcidin: -22.1 (80.9) mg/l in HIF-PHI and 3.9 (80.9) mg/l in placebo; LSM difference of -25.7 µg/l (95% CI -38.5 to -12.9). TIBC: increased in HIF-PHI and decreased in placebo; LSM difference 38.65 µg/dl (95% CI 31.9-45.5) TSAT: LSM difference -0.1%, 95% CI (-2.0, 1.7) Iron: LSM difference 8.3 mg/l (95% CI 2.9, 13.6)

				Ferritin: LSM difference -57.5 ng/ml (95% CI -92.8, -22.3)
OLYMPUS[31] (NCT02174627); Global AstraZeneca N=2781	ESA naïve eGFR <60 ml/min/1.73 m^2 Mean of 2 recent Hb ≤10 g/dl Ferritin ≥50 ng/ml TSAT ≥15%	Oral iron allowed without restriction and recommended IV iron if patients intolerant or unresponsive to oral iron and Hb <8.5 g/dl and ferritin <100 µg/l or TSAT <20%	*Receipt of IV iron* 4.3% HIF-PHI, 7.9% placebo; HR 0.41 (95% CI 0.29, 0.56) *Receipt of oral iron* 46.5% HIF-PHI vs. 46.5% placebo	Hepcidin: LSM difference -45.4 ng/ml (95% CI 56.2, 34.5) Ferritin: difference -54.6 mg/l (95% CI -71.7, -37.4) TSAT: difference -0.6% (95% CI -1.3, 0.2) TIBC: difference 34,6 µg/dl (95% CI 31.3, 37.9) Iron: difference 7.7 mg/dl (95% CI 5.8, 9.6)
DOLOMITES[32] (NCT02021318); Europe Astellas Pharma, Inc N=616	ESA naïve eGFR <60 ml/min/1.7 3m^2 Mean of 2 recent Hb ≤10.5 g/dl	Oral iron recommended in HIF-PHI and IV iron allowed if inadequate Hb response after at least 2 dose increases or maximum dose limit reached and iron deficiency or intolerance to oral iron Oral or IV iron required if ferritin <100 ng/ml or TSAT <20% in ESA	*IV iron* 6.2% HIF-PHI, 12.7% ESA Monthly dose 34.7 (30.0) mg HIF-PHI and 69.6 (67.3) ESA (among those receiving) *Oral iron* Bivalent: 43.7% HIF-PHI, 49.8% ESA; Trivalent: 35.3% HIF-PHI, 44.7% ESA	Ferritin: change from baseline at week 52: -93.1 (521.4) pmol/l HIF-PHI vs. -72.4 (459.3) pmol/l ESA TSAT: 1.3% (11.8) HIF-PHI vs. 5.2 (13.2) Iron: 1.1 (5.9) mmol/l HIF-PHI vs. 2.2 (6.8) pmol/l ESA
Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)				
PRO_2TECT[34] (NCT02648347); Global N=1751	ESA naïve eGFR ≤60 ml/min/1.73 m^2 Hb <10 g/dl Ferritin ≥100 ng/ml TSAT ≥20%	Iron supplementation encouraged to maintain ferritin ≥100 ng/ml or TSAT ≥20%	Not reported	Not reported
PRO_2TECT[34] (NCT02648347); Global N=1725	ESA treated eGFR ≤60 ml/min/1.73 m^2 Hb 8-11 g/dl in US or 9-12 non-US Ferritin ≥100 ng/ml TSAT ≥20%	Iron supplementation encouraged to maintain ferritin ≥100 ng/mL or TSAT ≥20%	Not reported	Not reported

Table 5: Iron parameters from phase 3 HIF-PHI clinical trials in dialysis-dependent chronic kidney disease

Study; Location	Entry criteria	Iron strategy	Iron utilization	Changes in markers of iron metabolism
***Daprodustat* (GlaxoSmithKline)**				
ASCEND-D[37] (NCT02879305); Global Prevalent dialysis N=2964	ESA users ferritin >100 ng/ml TSAT >20%	Iron supplementation protocol to maintain ferritin 100-800 ng/ml and TSAT 20-40%	*Mean monthly IV dose* 139.2 (171.1) to 90.8 (SE 3.3) mg HIF-PHI vs. 137.4 (174.7) to 99.9 (SE 3.3) mg ESA Difference: -9.1 mg (95% CI -18.4, 0.2)	Hepcidin: decreased more in HIF-PHI than ESA TIBC: increased more in HIF-PHI than ESA Ferritin: slight decrease in both groups TSAT: decreased slightly in both groups
ASCEND-ID[36] (NCT03029208); Global Incident Dialysis N=312	ESA naïve ferritin >100 ng/ml TSAT >20%	Iron starting criteria: ferritin ≤100 ng/ml or TSAT ≤20% Iron stopping criteria: ferritin ≥800 ng/ml and TSAT ≥20% or TSAT ≥40% Route of iron administration based on local clinical practice	159.3 (207.1) to 142 (161) mg HIF-PHI vs. 180.1 (209.9) to 128 (137) mg ESA Difference: 19.4 mg/mo (95% CI -11.0, 49.9)	Hepcidin: decreased from 112.6 ng/ml (IQR 76.8-198.6) to 82.8 ng/ml (IQR 48.0-170.1) in HIF-PHI and from 111.6 ng/ml (IQR 78.2-205.3) to 100.2 ng/ml (IQR 66.5-182.1) in ESA TIBC: increased in HIF-PHI but not ESA Ferritin: decreased in both groups TSAT: decreased in both groups Iron: stable in both groups
ASCEND-TD[38] (NCT03400033); Global Prevalent HD N=407	ESA treated Hb 8-11.5 g/dl Ferritin >100 ng/ml TSAT >20%	Iron was administered if ferritin ≤100 ng/ml or TSAT ≤20% Iron was stopped if: ferritin >800 ng/ml and TSAT >20% or TSAT >40%	*% receiving IV iron* Weeks 28-52: 38% in HIF-PHI vs. 40% in ESA Weeks 1-52: 51% HIF-PHI vs. 51% ESA *Mean monthly dose* Weeks 28-52: 104.9 (222.5) mg HIF-PHI vs. 103.1 (244.7) mg ESA Weeks 1-52: 99.0 (187.1) HIF-PHI vs. 104.4 (210.8) ESA Mean treatment difference: -8.1 (95% CI -45.7, 29.4)	Hepcidin: declined at a similar rate in both arms during the trial. TIBC: increased in HIF-PHI by week 4 and remained higher than ESA throughout the trial. Ferritin: declined at a similar rate in both arms during the trial. TSAT: similar between groups throughout the trial Iron: increased in HIF-PHI by week 4 and remained higher than ESA throughout the trial.

***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
HIMALAYAS[46] (NCT02052310); Global FibroGen, Inc Incident dialysis N=1043	ESA use for ≤3 weeks Mean of last 2 Hb ≤10 g/dl ferritin ≥100 ng/ml TSAT ≥20%	Oral iron encouraged; IV iron allowed if Hb response inadequate and ferritin ≤100 ng/ml and TSAT <20%	*% receiving IV iron* Weeks 28-52: 83.7% HIF-PHI vs. 85.4% ESA *Mean monthly IV dose* Difference -4.4 (95% CI -20.7, 12.0) mg Mean monthly oral dose 290.7 (95% CI -463.2, 1044.5) mg	Hepcidin: -64.8 (95% CI -74.3, -55.3) mg/l HIF-PHI vs. -54.1 (95% CI -63.4, -44.7) mg/l ESA; difference -10.7 (95% CI -23.2, 1.77) mg/l Ferritin: -191.3 (95% CI -234.4, -148.2) ng/ml HIF-PHI vs. -130.0 (95% CI -172.9, -87.2) ng/ml ESA; difference-61.3 (95% CI -117.0, -5.6) ng/ml TSAT: -2.7% (95% CI -3.9, -1.5) HIF-PHI vs. -2.2% (95% CI -3.4, -1.1) ESA; difference -0.5% (95% CI -2.0, 1.1) TIBC: 37.7 (95% CI 33.3, 42.1) mg/dl HIF-PHI vs. 1.7 (95% CI -2.7, 6.0) mg/dl ESA; difference 36.1 (95% CI 30.2, 41.9) mg/dl Iron: 2.1 (95% CI -1.2, 5.5) mg/dl HIF-PHI vs. -4.7 (95% CI -8.0, -1.5) mg/dl ESA; difference 6.9 (95% CI 2.4, 11.3) mg/dl
PYRENEES[47] (NCT02278341); Europe Astellas Pharma, Inc. Prevalent HD N=3188	ESA users ferritin ≥100 ng/ml TSAT ≥20%	For patients on HIF-PHI, oral iron was permitted. IV iron was allowed only if Hb did not respond adequately after 2 consecutive dose increase or if the maximum dose was reached and ferritin <100 ng/ml or TSAT <20% or the patient was intolerant to oral iron	*Mean monthly IV dose* HIF-PHI: 21.6 mg ESA: 53.5 mg Difference: -31.9 (95% CI -41.4, -22.4)	Hepcidin: -32.7 (42.3) HIF-PHI vs. -17.5 (47.3) ESA at week 52 Ferritin: lower in HIF-PHI and TSAT levels similar; exact changes not reported TIBC: 10.0 (8.8) mmol/l HIF-PHI vs. 2.7 (6.4) mmol/l ESA Iron: -0.3 (7.4) mmol/l HIF-PHI vs. -1.2 (6.3) mmol/l ESA
ROCKIES[48] (NCT02174731); Global AstraZeneca Prevalent dialysis N=2133	ESA naïve and Hb <10 g/dl or ESA user and Hb <12 g/dl Ferritin ≥100 ng/ml TSAT ≥20%	Oral iron permitted in both groups. In HIF-PHI, IV iron permitted if Hb did not increase sufficiently after ≥2 doses and ferritin <100 ng/ml or TSAT <20%	*Mean monthly IV dose* 58.7 HIF-PHI vs. 91.4 mg ESA *Oral iron use* 20.7% HIF-PHI vs. 18.0% ESA	Hepcidin: -45.0 (95% CI -57.5, -32.5) ng/ml HIF-PHI vs. -16.8 (95% CI -29.2, -4.4) ng/ml ESA; difference: -18.2 (95% CI -42.0, -14.5) ng/ml TSAT: -1.9% (95% CI -2.8, -1.1) HIF-PHI vs. -2.4% (95% CI -3.3, -1.6) ESA; difference: 0.5% (95% CI -0.4, 1.5) Ferritin: -104.5 (95% CI -126.2, -82.8) mg/l HIF-PHI vs. -41.2 (95% CI -62.1, -20.3) ESA; difference -63.3 (95% CI -87.4, -39.2) TIBC: 35.0 (95% CI 31.8, 38.2) mg/dl HIF-PHI vs. -2.4 (95% CI -5.5, 0.7) mg/dl ESA;

				difference 37.4 (95% CI 33.8, 41.0) Iron: 6.6 (95% CI 4.5, 8.7) mg/dl HIF-PHI vs. -5.5 (95% CI -7.6, -3.5) mg/dl ESA; difference 12.1 (95% CI 9.8, 14.5) mg/dl
SIERRAS[49] (NCT02273726); United States FibroGen, Inc. Prevalent HD N=741	ESA users Ferritin ≥100 ng/ml TSAT ≥20%	Oral iron encouraged IV iron if oral not tolerated or if iron deficient	*Mean monthly IV dose* 17.1 (53.4) mg HIF-PHI vs. 37.0 (106.8) mg ESA Difference: -20.1 (95% CI -33.8, -6.45)	Hepcidin: decreased in both groups; difference: -19.12 (95% CI -39.52, 1.28) Ferritin: decreased in both groups; difference: -41.71 (95% CI -96.51, 13.09) ng/ml Iron: increased in roxadustat; difference: 6.33 (95% CI 2.20, 10.45) mg/dl TSAT: decreased in both groups; difference: 2.18% (95% CI 0.16, 4.20)
Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)				
$INNO_2VATE$[51] (NCT02865850); Global Prevalent dialysis N=3554	ESA users and ESA-naïve Hb 8-11 mg/dl in US or 9-12 mg/dl in non-US ferritin ≥100 ng/ml	Encouraged iron supplementation to maintain ferritin ≥100 ng/ml or TSAT ≥20%	Not reported	Hepcidin: 193.9 (140.1) ng/ml to 137.4 (119.9) ng/ml in HIF-PHI vs. 190.4 (135.9) to 158.2 (123.4) in ESA Ferritin: 846.8 (562.7) to 787.3 (550.2) ng/ml in HIF-PHI vs. 840.7 (538.5) to 828.9 (565.8) ng/ml in ESA TSAT: 38.1% (13.5) to 34.1% (21.4) in HIF-PHI vs. 37.6% (13.2) to 36.6% (14.3) in ESA
$INNO_2VATE$[51] (NCT02865850); Global Incident dialysis N=369	Hb 8-11 mg/dl ferritin ≥100 ng/ml TSAT ≥20%	Encouraged iron supplementation to maintain ferritin ≥100 ng/ml or TSAT ≥20%	Not reported	*Changes from baseline to weeks 40-52* Hepcidin: 122.4 (109.5) to 95.7 (72.1) ng/ml in HIF-PHI vs. 126.9 (111.2) to 101.1 (95.6) in ESA Ferritin: 469.7 (316.9) to 555.5 (453.2) ng/ml in HIF-PHI vs. 527.8 (401.1) to 559.4 (458.5) ng/ml in ESA TSAT: 31.3% (9.5) to 33.1% (12.0) in HIF-PHI vs. 34.2% (12.7) to 35.6% (13.8) in ESA

Table 6: Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in non-dialysis-dependent chronic kidney disease

Study; Location Sponsor	Study design; No. of patients, randomization	Treatment, starting dose,[a] study duration	Primary outcome hazard ratio; non-inferiority margin (95% confidence interval)	Other outcome hazard ratios (95% confidence interval)
***Daprodustat* (GlaxoSmithKline)**				
ASCEND-ND[21] (NCT02876835); Global	R, OL, AC; ESA-naïve and ESA-treated; n = 3872, 1:1	DAPRO 2-4 mg QD[b] for ESA-naïve and 1-4 mg QD[c] for ESA-users vs DPO, 148 weeks	First occurrence of adjudicated MACE (composite of death, nonfatal myocardial infarction, or nonfatal stroke): HR 1.03, 95% CI 0.89-1.19 Noninferiority margin: HR 1.25	On-treatment MACE: HR 1.40, 95% CI 1.17-1.68 MACE or hospitalization for heart failure: HR 1.09, 95% CI 0.95-1.24 MACE or thromboembolic event: HR 1.06, 95% CI 0.93-1.22 All-cause death: HR 1.03, 95% CI 0.87-1.20
***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
ALPS[29] (NCT01887600); Europe Astellas Pharma, Inc.	R, DB, PC; ESA-naïve; n = 594, 2:1	ROXA 70 or 100 mg TIW[d] vs PBO, 104 weeks	Pooled analysis of ALPS, ANDES, OLYMPUS: time to first MACE (composite of death, nonfatal myocardial infarction, or nonfatal stroke): HR 1.10, 95% CI 0.96-1.27 Noninferiority margin: HR 1.30	MACE+ (composite of death, nonfatal myocardial infarction, nonfatal stroke, unstable angina and hospitalization for heart failure): HR 1.07, 95% CI 0.93-1.21 MACE, on treatment + 7d: HR 1.38, 95% CI 1.11-1.70) Myocardial infarction: HR 1.29, 95% CI 0.90-1.85 Stroke: HR 1.25, 95% CI 0.82-1.90 Unstable angina: HR 0.56, 95% CI 0.22-1.42 Congestive heart failure: HR 0.93, 95% CI 0.75-1.16 All-cause death: HR 1.08, 95% CI 0.93-1.26
ANDES[30] (NCT01750190); Global (no European sites) FibroGen Inc.	R, DB, PC; ESA-naïve; n = 922, 2:1	ROXA 70 or 100 mg TIW[d] vs PBO, 52 weeks		
OLYMPUS[31] (NCT02174627); Global AstraZeneca	R, DB, PC; ESA-naïve; n = 2781, 1:1	ROXA 70 mg TIW vs PBO, 164 weeks		

Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)				
PRO_2TECT[34] (NCT02648347); Global	R, OL, AC; ESA-naïve; n = 1751, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 168 weeks	(Pooled analysis of ESA-naive and ESA-treated subjects) Time to first MACE (composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke): HR 1.17 (1.01 to 1.36) Noninferiority margin: HR 1.25 (USA) and HR 1.30 (EMA)	MACE plus hospitalization for either heart failure or a thromboembolic event HR 1.11, 95% CI 0.97 -1.27 Death from cardiovascular causes: HR 1.01, 95% CI 0.79-1.29 Death from any cause: HR 1.09, 95% CI 0.93-1.27 Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: HR 1.16, 95% CI 0.95-1.42
PRO_2TECT[34] (NCT02680574); Global	R, OL, AC; ESA-treated; n = 1725, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 168 weeks		

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% confidence intervals are shown in brackets.
AC, active-controlled; DAPRO, daprodustat; DB, double-blind; DPO, darbepoetin alfa; EBP, epoetin beta pegol; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HR, hazard ratio; LSMD, least-squares mean difference; maint., maintenance; NC, non-comparative; NR, not reported; OL, open-label; PBO, placebo; PC, placebo-controlled; QD, once daily; R, randomized; ROXA, roxadustat; TIW, three times weekly; VADA, vadadustat. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

[a] starting dose, then titrated to maintain target Hb levels (right column).
[b] starting dose based on baseline Hb level; for NCT02964936, Akizawa *et al*., 2020,8 starting dose is based on an algorithm that included 2 baseline Hb levels, weight and eGFR.
[c] starting dose based on prior ESA dose.
[d] weight-based dosing: 70 mg for weight of 45 to <70 kg; 100 mg for ≥70 kg.

Table 7: Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in dialysis-dependent chronic kidney disease

Study; Location Sponsor	Study design; No. of patients, randomization	Treatment, starting dose,[a] study duration	Primary outcome hazard ratio; non-inferiority margin (95% confidence interval)	Other outcome hazard ratios (95% confidence interval)
***Daprodustat* (GlaxoSmithKline)**				
ASCEND-ID[36] (NCT03029208); Global	R, OL, AC; ESA-naïve and ESA-treated (limited exposure <6 weeks), I-DD; n = 312, 1:1	DAPRO 1-4 mg QD[b] vs DPO, 52 weeks	Exploratory analysis: first occurrence of adjudicated MACE (composite of death from any cause, non-fatal myocardial infarction or non-fatal stroke): n=19 (12%) DAPRO vs n=15 (10%) DPO -- absolute rate difference/100 PYs 2.41 (95% CI−4.61 to 9.43) Non-inferiority margin: N/A (not designed or powered as a non-inferiority trial)	The first occurrence of MACE or a hospitalization for heart failure: n=24 (15%) DPO vs. n=18 (12%) DPO Adjusted mean difference in systolic BP: −0.09 mm Hg (95% CI, −4.72 to 4.53); diastolic BP: 1.99 mm Hg (95%CI, −0.85 to 4.82)
ASCEND-D[37] (NCT02879305); Global	R, OL, AC; ESA-treated, M-DD; n = 2964, 1:1	DAPRO 4-12 mg QD[c] vs ESA (epoetin alfa for HD, DPO for PD, 52 weeks	Adjudicated MACE (composite of death from any cause, nonfatal myocardial infarction, or nonfatal stroke): HR 0.93, 95% CI 0.81-1.07 Non-inferiority margin: HR 1.25	MACE or thromboembolic event: HR 0.88, 95% CI 0.78-1.00 MACE or hospitalization for heart failure: HR 0.97, 95% CI 0.85-1.11
ASCEND-TD[38] (NCT03400033); Global	R, DB, AC; ESA-treated, M-DD; n = 407, 2:1	DAPRO 8-24 mg TIW[c] adjusted to dose range of 2-48 mg TIW vs epoetin alfa, 52 weeks	First occurrence of adjudicated MACE: Absolute rate difference per 100 person-years (95% CI) 2.3 (-4.4, to 9.0)	Worsening hypertension (*post-hoc*): DAPRO vs. Epoetin: Relative risk 0.83 (0.50 to 1.39)
***Roxadustat* (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)**				
Chen *et al*., 2019[42] (NCT02652806); China FibroGen, Inc.	R, OL, AC; ESA-treated; M-DD; n = 304, 2:1	ROXA 100 or 120 mg TIW[d] vs epoetin alfa, 26 weeks	Cardiac disorders: ROXA n=5 (2.5%) and epoetin alfa n=1 (1.0%)	Vascular disorders: ROXA n=2 (1.0%) and epoetin alfa n=0

Akizawa *et al*., 2020[43] (NCT02779764, NCT02780141); Japan Astellas Pharma, Inc.	R, OL, NC; I-HD (ESA-naïve, n = 75) and M-HD (>12 weeks, ESA-treated); n = 239	ESA-naïve: ROXA 50 or 70 mg TIW[b], 24 weeks ESA-treated: ROXA 70 or 100 mg TIW[c], 52 weeks	MACE – not reported	
Akizawa *et al*., 2020[44] (NCT02780726); Japan Astellas Pharma, Inc.	R, OL, NC; ESA-naïve (n = 13) and ESA-treated, PD (> 4 weeks); n = 56	ROXA 50 or 70 mg TIW[b] (ESA-naïve) or ROXA 70 or 100 mg TIW[c] (ESA-treated), 24 weeks	MACE – not reported	
Akizawa *et al*., 2020[45] (NCT02952092); Japan Astellas Pharma, Inc.	R, DB, AC; ESA-treated, M-HD; n = 303, 1:1	ROXA 70 or 100 mg TIW[c] vs DPO QW, 24 weeks	Cardiac disorders: ROXA n=5 (3.3%), DPO n=4 (2.6%)	Vascular disorders: ROXA n=5 (3.3%), DPO n=1 (0.7%)
HIMALAYAS[46] (NCT02052310); Global FibroGen, Inc.	R, OL, AC, ESA-naïve and ESA-limited use (≤3 weeks), I-DD; n = 1043, 1:1	ROXA 70-100 mg TIW[e, f] vs epoetin alfa, 52 weeks	Pooled analysis of HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS MACE (myocardial infarction, stroke, and all-cause mortality) HR 1.09, 95% CI 0.95–1.26; Noninferiority margin: HR 1.30	Arteriovenous fistula thrombosis: ROXA n=39 (7.5%) vs n=21 (4.1%) Pooled analysis of HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS: MACE plus congestive heart failure or unstable angina requiring hospitalization: HR 0.98, 95% CI 0.86–1.11 All-cause mortality: HR 1.13, 95% CI 0.95–1.34
PYRENEES[47] (NCT02278341); Europe Astellas Pharma, Inc.	R, OL, AC, ESA-treated, M-DD; n = 838 (836 treated), 1:1	ROXA 100-200 mg TIW[c] vs ESA (epoetin alfa or DPO), 52–104 weeks		
ROCKIES[48] (NCT02174731); Global AstraZeneca	R, OL, AC; ESA-naïve and ESA-treated, M-DD and I-DD (n = 416); n = 2133, 1:1	ROXA 70-200 mg TIW[c, f] for ESA-treated and 70 or 100 mg TIW[e] for ESA-naïve vs epoetin alfa, 52-164 weeks		
SIERRAS[49] (NCT02273726); United States FibroGen, Inc.	R, OL, AC; ESA-treated, M-DD and I-DD (n=71); total n = 741, 1:1	ROXA 70-200 mg TIW[c, f] vs epoetin alfa, 52 weeks		

***Vadadustat* (Akebia Therapeutics; Otsuka Pharmaceuticals)**				
Nangaku *et al*., 2021[50] (NCT03439137); Japan	R, DB, AC; ESA-treated, M-HD; n = 323. 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg QD vs DPO, 52 weeks	Cardiovascular event, cardiac failure VADA: 13 (8.0%), DPO 15 (9.3%)	Retinal disorder: VADA 21 (13.0%), DPO 16 (9.9%)
INNO$_2$VATE[51] (NCT02865850); Global	R, DB, AC; ESA-naïve and ESA-treated; I-DD; n = 369, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg vs DPO, 116 weeks	Pooled analysis of I-DD and M-DD trials MACE (myocardial infarction, stroke, and all-cause mortality): HR 0.96, 95% CI 0.83 – 1.11 Non-inferiority margin: HR 1.25	MACE plus hospitalization for heart failure or thromboembolic event: HR 0.96; 95% CI, 0.84 to 1.10. Death from cardiovascular causes: HR 0.96; 95% CI, 0.77 to 1.20. All-cause death: HR 0.95; 95% CI, 0.81 to 1.12. Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: HR 0.95; 95% CI, 0.80 to 1.14.
INNO$_2$VATE[51] (NCT02892149); Global	R, DB, AC; ESA-naïve and ESA-treated; M-DD; n = 3554, 1:1	VADA 300 mg QD, then adjusted to 150, 450 or 600 mg vs DPO, 116 weeks		

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% confidence intervals are shown in brackets.
AC, active-controlled; DAPRO, daprodustat; DB, double-blind; DESI, desidustat; DPO, darbepoetin alfa; ENARO, enarodustat; EOT: end of treatment; ESA, erythropoietin-stimulating agent; FAS, full analysis set; Hb, hemoglobin; HD, hemodialysis; HR, hazard ratio; I-DD, incident dialysis (HD and PD); I-HD, incident hemodialysis; M-DD, maintenance/stable dialysis (HD and PD); M-HD, maintenance/stable hemodialysis; MOLI, molidustat; LSMD, least-squares mean difference; NC, non-comparative; NR, not reported; OL, open-label; PBO, placebo; PC, placebo-controlled; PD, peritoneal dialysis; QD, once daily; QW, once weekly; R, randomized, ROXA, roxadustat; TIW, three times weekly; VADA, vadadustat. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

[a] starting dose, then titrated to maintain target Hb levels (right column).
[b] depending on study, starting dose is based on either recent Hb measurements or weight or both.
[c] initial dose according to prior ESA dose.
[d] Weight-based dosing (100 mg for > 45 to 60 or120 mg for ≥ 60 kg), adjusted to maintain Hb levels of 10–12 g/dl.
[e] dosed at 70 mg for weight of 45 to 70 kg; 100 mg for weight of >70-160.
[f] titrated to achieve a Hb level of 11 g/dl and to maintain Hb levels of 10–12 g/dl.

Table 8: Research recommendations

- Determine whether HIF-PHIs have an impact on progression of CKD based on severity of baseline disease, presence of proteinuria/albuminuria, or the cause of CKD
- Understand if hemoglobin targets should be the same when using HIF-PHIs versus ESAs for patients with ND-CKD and DD-CKD
- Conduct of additional trials to understand the need for iron supplementation and the appropriate iron dosing strategy with the use of HIF-PHIs, along with identification of iron targets during treatment
- Assess long-term safety for specific populations such as children, older adults, kidney transplant recipients, patients with PKD or acute kidney injury in future HIF-PHI studies
- Identification of novel biomarkers that can be used to monitor the safety of HIF-PHIs
- Ascertain variability in the risk of MACE and thrombosis with respect to region of the world, patients characteristics/subpopulations, Hb target, or rate of Hb correction
- Perform future studies to understand the effect of HIF-PHIs on HRQoL and patient-centered outcomes
- Determine whether HIF-PHIs are effective in patients with ESA hyporesponsiveness or in immunosuppressed populations, including those with kidney transplants
- Obtain longer term safety data (e.g., post-market surveillance) for HIF-PHI on risk for *de novo* cancer or progression of malignancy, retinopathy, and other potential adverse effects
- In regions where HIF-PHIs are available, comparative cost-effectiveness analysis should be conducted between these agents and ESAs

REFERENCES

9. Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease. Kidney Int Suppl (2011) 2021; 11: 8-25.

20. Nangaku M, Hamano T, Akizawa T, et al. Daprodustat Compared with Epoetin Beta Pegol for Anemia in Japanese Patients Not on Dialysis: A 52-Week Randomized Open-Label Phase 3 Trial. Am J Nephrol 2021; 52: 26-35.

21. Singh AK, Carroll K, McMurray JJV, et al. Daprodustat for the Treatment of Anemia in Patients Not Undergoing Dialysis. N Engl J Med 2021; 385: 2313-2324.

22. Agrawal D, Varade D, Shah H, et al. Desidustat in Anemia due to Non-Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-ND). Am J Nephrol 2022; 53: 352-360.

23. Akizawa T, Nangaku M, Yamaguchi T, et al. A Phase 3 Study of Enarodustat in Anemic Patients with CKD not Requiring Dialysis: The SYMPHONY ND Study. Kidney Int Rep 2021; 6: 1840-1849.

24. Yamamoto H, Nobori K, Matsuda Y, et al. Efficacy and Safety of Molidustat for Anemia in ESA-Naive Nondialysis Patients: A Randomized, Phase 3 Trial. Am J Nephrol 2021; 52: 871-883.

25. Yamamoto H, Nobori K, Matsuda Y, et al. Molidustat for Renal Anemia in Nondialysis Patients Previously Treated with Erythropoiesis-Stimulating Agents: A Randomized, Open-Label, Phase 3 Study. Am J Nephrol 2021; 52: 884-893.

26. Chen N, Hao C, Peng X, et al. Roxadustat for anemia in patients with kidney disease not receiving dialysis. N Engl J Med 2019; 381: 1001-1010.

27. Akizawa T, Yamaguchi Y, Otsuka T, et al. A Phase 3, Multicenter, Randomized, Two-Arm, Open-Label Study of Intermittent Oral Dosing of Roxadustat for the Treatment of Anemia in Japanese Erythropoiesis-Stimulating Agent-Naive Chronic Kidney Disease Patients Not on Dialysis. Nephron 2020; 144: 372-382.

28. Akizawa T, Iwasaki M, Otsuka T, et al. Phase 3 Study of Roxadustat to Treat Anemia in Non-Dialysis-Dependant CKD. Kidney Int Rep 2021; 6: 1810-1828.

29. Shutov E, Sulowicz W, Esposito C, et al. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, double-blind, placebo-controlled study (ALPS). Nephrol Dial Transplant 2021; 36: 1629-1639.

30. Coyne DW, Roger SD, Shin SK, et al. Roxadustat for CKD-related Anemia in Non-dialysis Patients. Kidney Int Rep 2021; 6: 624-635.

31. Fishbane S, El-Shahawy MA, Pecoits-Filho R, et al. Roxadustat for Treating Anemia in Patients with CKD Not on Dialysis: Results from a Randomized Phase 3 Study. J Am Soc Nephrol 2021; 32: 737-755.

32. Barratt J, Andric B, Tataradze A, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, open-label, active-controlled study (DOLOMITES). Nephrol Dial Transplant 2021; 36: 1616-1628.

33. Nangaku M, Kondo K, Kokado Y, et al. Phase 3 Randomized Study Comparing Vadadustat with Darbepoetin Alfa for Anemia in Japanese Patients with Nondialysis-Dependent CKD. J Am Soc Nephrol 2021; 32: 1779-1790.

34. Chertow GM, Pergola PE, Farag YMK, et al. Vadadustat in Patients with Anemia and Non-Dialysis-Dependent CKD. N Engl J Med 2021; 384: 1589-1600.

35. Akizawa T, Nangaku M, Yonekawa T, et al. Efficacy and Safety of Daprodustat Compared with Darbepoetin Alfa in Japanese Hemodialysis Patients with Anemia: A Randomized, Double-Blind, Phase 3 Trial. Clin J Am Soc Nephrol 2020; 15: 1155-1165.

36. Singh AK, Cizman B, Carroll K, et al. Efficacy and Safety of Daprodustat for Treatment of Anemia of Chronic Kidney Disease in Incident Dialysis Patients: A Randomized Clinical Trial. JAMA Intern Med 2022; 182: 592-602.

37. Singh AK, Carroll K, Perkovic V, et al. Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis. N Engl J Med 2021; 385: 2325-2335.

38. Coyne DW, Singh AK, Lopes RD, et al. Three Times Weekly Dosing of Daprodustat versus Conventional Epoetin for Treatment of Anemia in Hemodialysis Patients: ASCEND-TD: A Phase 3 Randomized, Double-Blind, Noninferiority Trial. Clin J Am Soc Nephrol 2022; 17: 1325-1336.

39. Gang S, Khetan P, Varade D, et al. Desidustat in Anemia due to Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study (DREAM-D). Am J Nephrol 2022; 53: 343-351.

40. Akizawa T, Nangaku M, Yamaguchi T, et al. A Phase 3 Study of Enarodustat (JTZ-951) in Japanese Hemodialysis Patients for Treatment of Anemia in Chronic Kidney Disease: SYMPHONY HD Study. Kidney Dis (Basel) 2021; 7: 494-502.

41. Akizawa T, Yamada T, Nobori K, et al. Molidustat for Japanese Patients With Renal Anemia Receiving Dialysis. Kidney Int Rep 2021; 6: 2604-2616.

42. Chen N, Hao C, Liu BC, et al. Roxadustat Treatment for Anemia in Patients Undergoing Long-Term Dialysis. N Engl J Med 2019; 381: 1011-1022.

43. Akizawa T, Ueno M, Shiga T, et al. Oral roxadustat three times weekly in ESA-naive and ESA-converted patients with anemia of chronic kidney disease on hemodialysis: Results from two phase 3 studies. Ther Apher Dial 2020; 24: 628-641.

44. Akizawa T, Otsuka T, Reusch M, et al. Intermittent Oral Dosing of Roxadustat in Peritoneal Dialysis Chronic Kidney Disease Patients with Anemia: A Randomized, Phase 3, Multicenter, Open-Label Study. Ther Apher Dial 2020; 24: 115-125.

45. Akizawa T, Iwasaki M, Yamaguchi Y, et al. Phase 3, Randomized, Double-Blind, Active-Comparator (Darbepoetin Alfa) Study of Oral Roxadustat in CKD Patients with Anemia on Hemodialysis in Japan. J Am Soc Nephrol 2020; 31: 1628-1639.

46. Provenzano R, Shutov E, Eremeeva L, et al. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. Nephrol Dial Transplant 2021; 36: 1717-1730.

47. Csiky B, Schomig M, Esposito C, et al. Roxadustat for the Maintenance Treatment of Anemia in Patients with End-Stage Kidney Disease on Stable Dialysis: A European Phase 3, Randomized, Open-Label, Active-Controlled Study (PYRENEES). Adv Ther 2021; 38: 5361-5380.

48. Fishbane S, Pollock CA, El-Shahawy M, et al. Roxadustat Versus Epoetin Alfa for Treating Anemia in Patients with Chronic Kidney Disease on Dialysis: Results from the Randomized Phase 3 ROCKIES Study. J Am Soc Nephrol 2022; 33: 850-866.

49. Charytan C, Manllo-Karim R, Martin ER, et al. A Randomized Trial of Roxadustat in Anemia of Kidney Failure: SIERRAS Study. Kidney Int Rep 2021; 6: 1829-1839.

50. Nangaku M, Kondo K, Ueta K, et al. Efficacy and safety of vadadustat compared with darbepoetin alfa in Japanese anemic patients on hemodialysis: a Phase 3, multicenter, randomized, double-blind study. Nephrol Dial Transplant 2021; 36: 1731-1741.

51. 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: 1601-1612.

Supplemental Table 1: Availability of HIF-PHIs (as of April 25, 2023)

HIF-PHI	Approval status by countries/regions
Daprodustat	Japan, United States
Desidustat	India
Enarodustat	Japan
Molidustat	Japan
Roxadustat	China, Chile, Egypt, European Union, Japan, Kuwait, Saudi Arabia, South Africa, South Korea, Turkey, United Arab Emirates, United Kingdom
Vadadustat	European Union, Japan, Korea

Supplemental Table 2: Drug-drug interactions of HIF-PHIs

HIF and interacting agents	Effects
Daprodustat (metabolized mainly by CYP2C8)	
CYP2C8 inhibitors • Clopidogrel • Trimethoprim	These drugs increase circulating levels of daprodustat by inhibition of CYP2C8.
Rifampicin	Rifampicin decreases circulating levels of daprodustat by induction of CYP2C8.
Enarodustat	
Phosphate binders • Sevelamer • Bixalomer • Lanthanum carbonate Drugs containing polycations (e.g., drugs containing calcium, iron, magnesium, aluminum etc.)	These drugs decrease absorption of enarodustat.
Molidustat	
HIV protease inhibitors • Atazanavir • Ritonavir • Lopinavir and ritonavir Tyrosine kinase inhibitors • Sorafenib • Erlotinib • Nilotinib Tranilast	These drugs increase circulating levels of molidustat by inhibition of UGT1A1.
Drugs containing polycations (e.g., drugs containing calcium, iron, magnesium, aluminum etc.)	These drugs decrease absorption of molidustat.
Roxadustat (substrate of CYP2C8, UGT1A9, BCRP, OATP1B1, OAT1 and OAT; roxadustat inhibits BCRP and OATP1B1)	
Phosphate binders • Sevelamer • Bixalomer Drugs containing polycations (e.g., drugs containing calcium, iron, magnesium, aluminum etc.)	These drugs decrease absorption of roxadustat.
HMG-CoA reductase inhibitors • Simvastatin • Rosuvastatin • Atorvastatin, etc.	Roxadustat increases circulating levels of HMG-CoA reductase inhibitors by inhibition of OATP1B1/BCRP.
Probenecid (UGT, OAT1/OAT3 inhibitor)	Probenecid increases circulating levels of roxadustat by inhibition of UGT/OAT. Other UGT or OAT inhibitors include: teriflunomide (OAT1/OAT3), valproate (UGT). Rifampicin is an UGT inducer.
Gemfibrozil (CYP2C8, OATP1B1 inhibitor)	Gemfibrozil increases circulating levels of roxadustat by inhibition of CYP2C8/OATP1B1. Other CYP2C8 or OATP1B1 inhibitors include: cyclosporin (OATP1B1), clopidogrel (CYP2C8). Rifampicin is a CYP2C8 inducer.

Vadadustat (substrate of OAT1 and OAT3; vadadustat inhibits BCRP and OAT3)	
Drugs containing polycations (e.g., drugs containing calcium, iron, magnesium, aluminum etc.)	These drugs decrease absorption of vadadustat.
Probenecid	Probenecid increases circulating levels of vadadustat by inhibition of OAT1/OAT3.
Drugs that serve as substrates of BCRP • Simvastatin • Rosuvastatin • Atorvastatin • Salazosulfapyridine	Vadadustat increases circulating levels of these drugs by inhibition of BCRP.
Drugs that serve as substrates of OAT3 • Furosemide • Methotrexate	Vadadustat increases circulating levels of these drugs by inhibition of OAT3.

Supplemental Table 1: Availability of HIF-PHIs (as of April 25, 2023)

HIF-PHI	Approval status by countries/regions
Daprodustat	Japan, United States
Desidustat	India
Enarodustat	Japan
Molidustat	Japan
Roxadustat	China, Chile, Egypt, European Union, Japan, Kuwait, Saudi Arabia, South Africa, South Korea, Turkey, United Arab Emirates, United Kingdom
Vadadustat	European Union, Japan, Korea

Supplemental Table 21: Drug-drug interactions of HIF-PHIs

HIF and interacting agents	Effects
Daprodustat (metabolized mainly by CYP2C8)	
CYP2C8 inhibitors • Clopidogrel • Trimethoprim	These drugs increase circulating levels of daprodustat by inhibition of CYP2C8.
Rifampicin	Rifampicin decreases circulating levels of daprodustat by induction of CYP2C8.
Enarodustat	
Phosphate binders • Sevelamer • Bixalomer • Lanthanum carbonate Drugs containing polycations (e.g., drugs containing calcium, iron, magnesium, aluminum etc.)	These drugs decrease absorption of enarodustat.
Molidustat	
HIV protease inhibitors • Atazanavir • Ritonavir • Lopinavir and ritonavir Tyrosine kinase inhibitors • Sorafenib • Erlotinib • Nilotinib Tranilast	These drugs increase circulating levels of molidustat by inhibition of UGT1A1.
Drugs containing polycations (e.g., drugs containing calcium, iron, magnesium, aluminum etc.)	These drugs decrease absorption of molidustat.
Roxadustat (substrate of CYP2C8, UGT1A9, BCRP, OATP1B1, OAT1 and OAT; roxadustat inhibits BCRP and OATP1B1)	
Phosphate binders • Sevelamer • Bixalomer Drugs containing polycations (e.g., drugs containing calcium, iron, magnesium, aluminum etc.)	These drugs decrease absorption of roxadustat.
HMG-CoA reductase inhibitors • Simvastatin • Rosuvastatin • Atorvastatin, etc.	Roxadustat increases circulating levels of HMG-CoA reductase inhibitors by inhibition of OATP1B1/BCRP.
Probenecid (UGT, OAT1/OAT3 inhibitor)	Probenecid increases circulating levels of roxadustat by inhibition of UGT/OAT. Other UGT or OAT inhibitors include: teriflunomide (OAT1/OAT3), valproate (UGT). Rifampicin is an UGT inducer.
Gemfibrozil (CYP2C8, OATP1B1 inhibitor)	Gemfibrozil increases circulating levels of roxadustat by inhibition of CYP2C8/OATP1B1. Other CYP2C8 or OATP1B1 inhibitors include: cyclosporin (OATP1B1), clopidogrel (CYP2C8). Rifampicin is a CYP2C8 inducer.

Vadadustat (substrate of OAT1 and OAT3; vadadustat inhibits BCRP and OAT3)	
Drugs containing polycations (e.g., drugs containing calcium, iron, magnesium, aluminum etc.)	These drugs decrease absorption of vadadustat.
Probenecid	Probenecid increases circulating levels of vadadustat by inhibition of OAT1/OAT3.
Drugs that serve as substrates of BCRP • Simvastatin • Rosuvastatin • Atorvastatin • Salazosulfapyridine	Vadadustat increases circulating levels of these drugs by inhibition of BCRP.
Drugs that serve as substrates of OAT3 • Furosemide • Methotrexate	Vadadustat increases circulating levels of these drugs by inhibition of OAT3.